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2013 ACCF/AHA Guideline for the Management of Heart Failure

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2013 ACCF/AHA Guideline for the Management of Heart Failure

A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines

Developed in Collaboration With the Heart Rhythm Society

Endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation

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Preamble

The medical profession should play a central role in evaluating the evidence related to drugs, devices, and procedures for the detection, management, and prevention of disease. When properly applied, expert analysis of available data on the benefits and risks of these therapies and procedures can improve the quality of care, optimize patient outcomes, and favorably affect costs by focusing resources on the most effective strategies. An organized and directed approach to a thorough review of evidence has resulted in the production of clinical practice guidelines that assist clinicians in selecting the best management strategy for an individual patient. Moreover, clinical practice guidelines can provide a foundation for other applications, such as performance measures, appropriate use criteria, and both quality improvement and clinical decision support tools.

The American College of Cardiology Foundation (ACCF) and the American Heart Association (AHA) have jointly produced guidelines in the area of cardiovascular disease since 1980. The ACCF/AHA Task Force on Practice Guidelines (Task Force), charged with developing, updating, and revising practice guidelines for cardiovascular diseases and procedures, directs and oversees this effort. Writing committees are charged with regularly reviewing and evaluating all available evidence to develop balanced, patient-centric recommendations for clinical practice.

Experts in the subject under consideration are selected by the ACCF and AHA to examine subject-specific data and write guidelines in partnership with representatives from other medical organizations and specialty groups. Writing committees are asked to perform a literature review; weigh the strength of evidence for or against particular tests, treatments, or procedures; and include estimates of expected outcomes where such data exist. Patient-specific modifiers, comorbidities, and issues of patient preference that may influence the choice of tests or therapies are considered. When available, information from studies on cost is considered, but data on efficacy and outcomes constitute the primary basis for the recommendations contained herein.

In analyzing the data and developing recommendations and supporting text, the writing committee uses evidence-based methodologies developed by the Task Force (1). The Class of Recommendation (COR) is an estimate of the size of the treatment effect considering risks versus benefits in addition to evidence and/or agreement that a given treatment or procedure is or is not useful/effective or in some situations may cause harm. The Level of Evidence (LOE) is an estimate of the certainty or precision of the treatment effect. The writing committee reviews and ranks evidence supporting each recommendation with the weight of evidence ranked as LOE A, B, or C according to specific definitions that are included in Table 1. Studies are identified as observational, retrospective, prospective, or randomized where appropriate. For certain conditions for which inadequate data are available, recommendations are based on expert consensus and clinical experience and are ranked as LOE C. When recommendations at LOE C are supported by historical clinical data, appropriate references (including clinical reviews) are cited if available. For issues for which sparse data are available, a survey of current practice among the clinicians on the writing committee is the basis for LOE C

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recommendations and no references are cited. The schema for COR and LOE are summarized in Table 1, which also provides suggested phrases for writing recommendations within each COR. A new addition to this methodology is separation of the Class III recommendations to delineate whether the recommendation is determined to be of "no benefit" or is associated with "harm" to the patient. In addition, in view of the increasing number of comparative effectiveness studies, comparator verbs and suggested phrases for writing recommendations for the comparative effectiveness of one treatment or strategy versus another have been added for COR I and IIa, LOE A or B only.

In view of the advances in medical therapy across the spectrum of cardiovascular diseases, the Task Force has designated the term *guideline-directed medical therapy (GDMT)* to represent optimal medical therapy as defined by ACCF/AHA guideline−recommended therapies (primarily Class I). This new term, *GDMT*, will be used herein and throughout all future guidelines.

Because the ACCF/AHA practice guidelines address patient populations (and clinicians) residing in North America, drugs that are not currently available in North America are discussed in the text without a specific COR. For studies performed in large numbers of subjects outside North America, each writing committee reviews the potential influence of different practice patterns and patient populations on the treatment effect and relevance to the ACCF/AHA target population to determine whether the findings should inform a specific recommendation.

The ACCF/AHA practice guidelines are intended to assist clinicians in clinical decision making by describing a range of generally acceptable approaches to the diagnosis, management, and prevention of specific diseases or conditions. The guidelines attempt to define practices that meet the needs of most patients in most circumstances. The ultimate judgment regarding care of a particular patient must be made by the clinician and patient in light of all the circumstances presented by that patient. As a result, situations may arise for which deviations from these guidelines may be appropriate. Clinical decision making should involve consideration of the quality and availability of expertise in the area where care is provided. When these guidelines are used as the basis for regulatory or payer decisions, the goal should be improvement in quality of care. The Task Force recognizes that situations arise in which additional data are needed to inform patient care more effectively; these areas will be identified within each respective guideline when appropriate.

Prescribed courses of treatment in accordance with these recommendations are effective only if followed. Because lack of patient understanding and adherence may adversely affect outcomes, clinicians should make every effort to engage the patient's active participation in prescribed medical regimens and lifestyles. In addition, patients should be informed of the risks, benefits, and alternatives to a particular treatment and be involved in shared decision making whenever feasible, particularly for COR IIa and IIb, for which the benefit-to-risk ratio may be lower.

The Task Force makes every effort to avoid actual, potential, or perceived conflicts of interest that may arise as a result of industry relationships or personal interests among the members of the writing committee. All

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writing committee members and peer reviewers of the guideline are required to disclose all current healthcare-related relationships, including those existing 12 months before initiation of the writing effort. In December 2009, the ACCF and AHA implemented a new policy for relationship with industry and other entities (RWI) that requires the writing committee chair plus a minimum of 50% of the writing committee to have no *relevant* RWI (Appendix 1 for the ACCF/AHA definition of relevance). These statements are reviewed by the Task Force and all members during each conference call and/or meeting of the writing committee and are updated as changes occur. All guideline recommendations require a confidential vote by the writing committee and must be approved by a consensus of the voting members. Members are not permitted to draft or vote on any text or recommendations pertaining to their RWI. Members who recused themselves from voting are indicated in the list of writing committee members, and specific section recusals are noted in Appendix 1. Authors' and peer reviewers' RWI pertinent to this guideline are disclosed in Appendixes 1 and 2, respectively. Additionally, to ensure complete transparency, writing committee members' comprehensive disclosure information—including RWI not pertinent to this document—is available as an online supplement (http://jaccjacc.cardiosource.com/DataSupp/ACCF/2013_HFGL_Comprehensive_RWI_Table.pdf). Comprehensive disclosure information for the Task Force is also available online at http://www.cardiosource.org/en/ACC/About-ACC/Who-We-Are/Leadership/Guidelines-and-Documents-Task-Forces.aspx. The work of writing committees is supported exclusively by the ACCF and AHA without commercial support. Writing committee members volunteered their time for this activity.

In an effort to maintain relevance at the point of care for practicing clinicians, the Task Force continues to oversee an ongoing process improvement initiative. As a result, in response to pilot projects, several changes to these guidelines will be apparent, including limited narrative text, a focus on summary and evidence tables (with references linked to abstracts in PubMed), and more liberal use of summary recommendation tables (with references that support LOE) to serve as a quick reference.

In April 2011, the Institute of Medicine released 2 reports: *Clinical Practice Guidelines We Can Trust* and *Finding What Works in Health Care: Standards for Systematic Reviews* (2, 3). It is noteworthy that the ACCF/AHA practice guidelines are cited as being compliant with many of the proposed standards. A thorough review of these reports and of our current methodology is under way, with further enhancements anticipated.

The recommendations in this guideline are considered current until they are superseded by a focused update or the full-text guideline is revised. Guidelines are official policy of both the ACCF and AHA.

Jeffrey L. Anderson, MD, FACC, FAHA
Chair, ACCF/AHA Task Force on Practice Guidelines

1. Introduction

1.1. Methodology and Evidence Review

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The recommendations listed in this document are, whenever possible, evidence based. An extensive evidence review was conducted through October 2011 and selected other references through April 2013. Searches were extended to studies, reviews, and other evidence conducted in human subjects and that were published in English from PubMed, EMBASE, Cochrane, Agency for Healthcare Research and Quality Reports, and other selected databases relevant to this guideline. Key search words included but were not limited to the following: *heart failure, cardiomyopathy, quality of life, mortality, hospitalizations, prevention, biomarkers, hypertension, dyslipidemia, imaging, cardiac catheterization, endomyocardial biopsy, angiotensin-converting enzyme inhibitors, angiotensin-receptor antagonists/blockers, beta blockers, cardiac, cardiac resynchronization therapy, defibrillator, device-based therapy, implantable cardioverter-defibrillator, device implantation, medical therapy, acute decompensated heart failure, preserved ejection fraction, terminal care and transplantation, quality measures,* and *performance measures*. Additionally, the committee reviewed documents related to the subject matter previously published by the ACCF and AHA. References selected and published in this document are representative and not all-inclusive.

To provide clinicians with a representative evidence base, whenever deemed appropriate or when published, the absolute risk difference and number needed to treat or harm are provided in the guideline (within tables), along with confidence intervals and data related to the relative treatment effects such as odds ratio, relative risk, hazard ratio, and incidence rate ratio.

1.2. Organization of the Writing Committee

The committee was composed of physicians and a nurse with broad expertise in the evaluation, care, and management of patients with heart failure (HF). The authors included general cardiologists, HF and transplant specialists, electrophysiologists, general internists, and physicians with methodological expertise. The committee included representatives from the ACCF, AHA, American Academy of Family Physicians, American College of Chest Physicians, Heart Rhythm Society, and International Society for Heart and Lung Transplantation.

1.3. Document Review and Approval

This document was reviewed by 2 official reviewers each nominated by both the ACCF and the AHA, as well as 1 to 2 reviewers each from the American Academy of Family Physicians, American College of Chest Physicians, Heart Rhythm Society, and International Society for Heart and Lung Transplantation, as well as 32 individual content reviewers (including members of the ACCF Adult Congenital and Pediatric Cardiology Council, ACCF Cardiovascular Team Council, ACCF Council on Cardiovascular Care for Older Adults, ACCF Electrophysiology Committee, ACCF Heart Failure and Transplant Council, ACCF Imaging Council, ACCF Prevention Committee, ACCF Surgeons' Scientific Council, and ACCF Task Force on Appropriate Use

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Criteria). All information on reviewers' RWI was distributed to the writing committee and is published in this document (Appendix 2).

This document was approved for publication by the governing bodies of the ACCF and AHA and endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation and Heart Rhythm Society.

Table 1. Applying Classification of Recommendation and Level of Evidence

SIZE OF TREATMENT EFFECT

ESTIMATE OF CERTAINTY (PRECISION) OF TREATMENT EFFECT	CLASS I *Benefit >>> Risk* Procedure/Treatment **SHOULD** be performed/ administered	CLASS IIa *Benefit >> Risk* *Additional studies with focused objectives needed* **IT IS REASONABLE** to perform procedure/administer treatment	CLASS IIb *Benefit ≥ Risk* *Additional studies with broad objectives needed; additional registry data would be helpful* Procedure/Treatment **MAY BE CONSIDERED**	CLASS III *No Benefit* or CLASS III *Harm* Procedure/Test / Treatment COR III: No benefit — Not Helpful / No Proven Benefit COR III: Harm — Excess Cost w/o Benefit or Harmful / Harmful to Patients
LEVEL A Multiple populations evaluated* Data derived from multiple randomized clinical trials or meta-analyses	■ Recommendation that procedure or treatment is useful/effective ■ Sufficient evidence from multiple randomized trials or meta-analyses	■ Recommendation in favor of treatment or procedure being useful/effective ■ Some conflicting evidence from multiple randomized trials or meta-analyses	■ Recommendation's usefulness/efficacy less well established ■ Greater conflicting evidence from multiple randomized trials or meta-analyses	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Sufficient evidence from multiple randomized trials or meta-analyses
LEVEL B Limited populations evaluated* Data derived from a single randomized trial or nonrandomized studies	■ Recommendation that procedure or treatment is useful/effective ■ Evidence from single randomized trial or nonrandomized studies	■ Recommendation in favor of treatment or procedure being useful/effective ■ Some conflicting evidence from single randomized trial or nonrandomized studies	■ Recommendation's usefulness/efficacy less well established ■ Greater conflicting evidence from single randomized trial or nonrandomized studies	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Evidence from single randomized trial or nonrandomized studies
LEVEL C Very limited populations evaluated* Only consensus opinion of experts, case studies, or standard of care	■ Recommendation that procedure or treatment is useful/effective ■ Only expert opinion, case studies, or standard of care	■ Recommendation in favor of treatment or procedure being useful/effective ■ Only diverging expert opinion, case studies, or standard of care	■ Recommendation's usefulness/efficacy less well established ■ Only diverging expert opinion, case studies, or standard of care	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Only expert opinion, case studies, or standard of care
Suggested phrases for writing recommendations	should is recommended is indicated is useful/effective/beneficial	is reasonable can be useful/effective/beneficial is probably recommended or indicated	may/might be considered may/might be reasonable usefulness/effectiveness is unknown/unclear/uncertain or not well established	COR III: No Benefit: is not recommended; is not indicated; should not be performed/ administered/ other; is not useful/ beneficial/ effective COR III: Harm: potentially harmful; causes harm; associated with excess morbidity/mortality; should not be performed/ administered/ other
Comparative effectiveness phrases†	treatment/strategy A is recommended/indicated in preference to treatment B treatment A should be chosen over treatment B	treatment/strategy A is probably recommended/indicated in preference to treatment B it is reasonable to choose treatment A over treatment B		

A recommendation with Level of Evidence B or C does not imply that the recommendation is weak. Many important clinical questions addressed in the guidelines do not lend themselves to clinical trials. Although randomized trials are unavailable, there may be a very clear clinical consensus that a particular test or therapy is useful or effective.

*Data available from clinical trials or registries about the usefulness/efficacy in different subpopulations, such as sex, age, history of diabetes, history of prior myocardial infarction, history of heart failure, and prior aspirin use.
†For comparative effectiveness recommendations (Class I and IIa; Level of Evidence A and B only), studies that support the use of comparator verbs should involve direct comparisons of the treatments or strategies being evaluated.

1.4. Scope of This Guideline With Reference to Other Relevant Guidelines or Statements

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This guideline covers multiple management issues for the adult patient with HF. Although of increasing importance, HF in children and congenital heart lesions in adults are not specifically addressed in this guideline. The reader is referred to publically available resources to address questions in these areas. However, this guideline does address HF with preserved ejection fraction (EF) in more detail and similarly revisits hospitalized HF. Additional areas of renewed interest are in stage D HF, palliative care, transition of care, and quality of care for HF. Certain management strategies appropriate for the patient at risk for HF or already affected by HF are also reviewed in numerous relevant clinical practice guidelines and scientific statements published by the ACCF/AHA Task Force on Practice Guidelines, AHA, ACCF Task Force on Appropriate Use Criteria, European Society of Cardiology, Heart Failure Society of America, and the National Heart, Lung, and Blood Institute. The writing committee saw no need to reiterate the recommendations contained in those guidelines and chose to harmonize recommendations when appropriate and eliminate discrepancies. This is especially the case for device-based therapeutics, where complete alignment between the HF guideline and the device-based therapy guideline was deemed imperative (4). Some recommendations from earlier guidelines have been updated as warranted by new evidence or a better understanding of earlier evidence, whereas others that were no longer accurate or relevant or which were overlapping were modified; recommendations from previous guidelines that were similar or redundant were eliminated or consolidated when possible.

The present document recommends a combination of lifestyle modifications and medications that constitute GDMT. GDMT is specifically referenced in the recommendations for the treatment of HF (Figure 1; Section 7.3.2). Both for GDMT and other recommended drug treatment regimens, the reader is advised to confirm dosages with product insert material and to evaluate carefully for contraindications and drug-drug interactions. Table 2 is a list of documents deemed pertinent to this effort and is intended for use as a resource; it obviates the need to repeat already extant guideline recommendations. Additional other HF guideline statements are highlighted as well for the purpose of comparison and completeness.

Table 2. Associated Guidelines and Statements

TnQTable3AACVPR indicates American Association of Cardiovascular and Pulmonary Rehabilitation; AATS, American Association for Thoracic Surgery; ACCF, American College of Cardiology Foundation; ACCP, American College of Chest Physicians; ACP, American College of Physicians; AHA, American Heart Association; ASA, American Stroke Association; ESC, European Society of Cardiology; HFSA, Heart Failure Society of America; HRS, Heart Rhythm Society; ISHLT, International Society for Heart and Lung Transplantation; NHLBI, National Heart, Lung, and Blood Institute; NICE, National Institute for Health and Clinical Excellence; PCNA, Preventive Cardiovascular Nurses Association; SCAI, Society for Cardiovascular Angiography and Interventions; STS, Society of Thoracic Surgeons; and WHF, World Heart Federation.

2. Definition of HF

HF is a complex clinical syndrome that results from any structural or functional impairment of ventricular filling or ejection of blood. The cardinal manifestations of HF are dyspnea and fatigue, which may limit exercise tolerance, and fluid retention, which may lead to pulmonary and/or splanchnic congestion and/or peripheral edema. Some patients have exercise intolerance but little evidence of fluid retention, whereas others complain

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primarily of edema, dyspnea, or fatigue. Because some patients present without signs or symptoms of volume overload, the term “heart failure” is preferred over “congestive heart failure.” There is no single diagnostic test for HF because it is largely a clinical diagnosis based on a careful history and physical examination.

The clinical syndrome of HF may result from disorders of the pericardium, myocardium, endocardium, heart valves, or great vessels or from certain metabolic abnormalities, but most patients with HF have symptoms due to impaired left ventricular (LV) myocardial function. It should be emphasized that HF is not synonymous with either cardiomyopathy or LV dysfunction; these latter terms describe possible structural or functional reasons for the development of HF. HF may be associated with a wide spectrum of LV functional abnormalities, which may range from patients with normal LV size and preserved EF to those with severe dilatation and/or markedly reduced EF. In most patients, abnormalities of systolic and diastolic dysfunction coexist, irrespective of EF. EF is considered important in classification of patients with HF because of differing patient demographics, comorbid conditions, prognosis, and response to therapies (35) and because most clinical trials selected patients based on EF. EF values are dependent on the imaging technique used, method of analysis, and operator. Because other techniques may indicate abnormalities in systolic function among patients with a preserved EF, it is preferable to use the terms preserved or reduced EF over preserved or reduced systolic function. For the remainder of this guideline, we will consistently refer to HF with preserved EF and HF with reduced EF as HF*p*EF and HF*r*EF, respectively (Table 3).

2.1. HF With Reduced EF (HFrEF)

In approximately half of patients with HF*r*EF, variable degrees of LV enlargement may accompany HF*r*EF (36, 37). The definition of HF*r*EF has varied, with guidelines of left ventricular ejection fraction (LVEF) ≤35%, <40%, and ≤40% (18, 19, 38). Randomized clinical trials (RCTs) in patients with HF have mainly enrolled patients with HF*r*EF with an EF ≤35% or ≤40%, and it is only in these patients that efficacious therapies have been demonstrated to date. For the present guideline, HF*r*EF is defined as the clinical diagnosis of HF and EF ≤40%. Those with LV systolic dysfunction commonly have elements of diastolic dysfunction as well (39). Although coronary artery disease (CAD) with antecedent myocardial infarction (MI) is a major cause of HF*r*EF, many other risk factors (Section 4.6) may lead to LV enlargement and HF*r*EF.

2.2. HF With Preserved EF (HFpEF)

In patients with clinical HF, studies estimate that the prevalence of HF*p*EF is approximately 50% (range 40% to 71%) (40). These estimates vary largely because of the differing EF cut-off criteria and challenges in diagnostic criteria for HF*p*EF. HF*p*EF has been variably classified as EF >40%, >45%, >50%, and ≥55%. Because some of these patients do not have entirely normal EF but also do not have major reduction in systolic function, the term *preserved EF* has been used. Patients with an EF in the range of 40% to 50% represent an intermediate group. These patients are often treated for underlying risk factors and comorbidities and with GDMT similar to that

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used in patients with HF*r*EF. Several criteria have been proposed to define the syndrome of HF*p*EF. These include (a) clinical signs or symptoms of HF; (b) evidence of preserved or normal LVEF; and (c) evidence of abnormal LV diastolic dysfunction that can be determined by Doppler echocardiography or cardiac catheterization (41). The diagnosis of HF*p*EF is more challenging than the diagnosis of HF*r*EF because it is largely one of excluding other potential noncardiac causes of symptoms suggestive of HF. Studies have suggested that the incidence of HF*p*EF is increasing and that a greater portion of patients hospitalized with HF have HF*p*EF (42). In the general population, patients with HF*p*EF are usually older women with a history of hypertension. Obesity, CAD, diabetes mellitus, atrial fibrillation (AF), and hyperlipidemia are also highly prevalent in HF*p*EF in population-based studies and registries (40, 43). Despite these associated cardiovascular risk factors, hypertension remains the most important cause of HF*p*EF, with a prevalence of 60% to 89% from large controlled trials, epidemiological studies, and HF registries (44). It has been recognized that a subset of patients with HF*p*EF previously had HF*r*EF (45). These patients with improvement or recovery in EF may be clinically distinct from those with persistently preserved or reduced EF. Further research is needed to better characterize these patients.

Table 3. Definitions of HF*r*EF and HF*p*EF
TnQTable4EF indicates ejection fraction; HF, heart failure; HF*p*EF, heart failure with preserved ejection fraction; and HF*r*EF, heart failure with reduced ejection fraction.

*See Online Data Supplement 1 (http://jaccjacc.cardiosource.com/DataSupp/ACCF/2013_HFGL_Evidence_Tables.pdf) for additional data on HF*p*EF.*

3. HF Classifications

Both the ACCF/AHA stages of HF (38) and the New York Heart Association (NYHA) functional classification (38, 46) provide useful and complementary information about the presence and severity of HF. The ACCF/AHA stages of HF emphasize the development and progression of disease and can be used to describe individuals and populations, whereas the NYHA classes focus on exercise capacity and the symptomatic status of the disease (Table 4).

The ACCF/AHA stages of HF recognize that both risk factors and abnormalities of cardiac structure are associated with HF. The stages are progressive and inviolate; once a patient moves to a higher stage, regression to an earlier stage of HF is not observed. Progression in HF stages is associated with reduced 5-year survival and increased plasma natriuretic peptide concentrations (47). Therapeutic interventions in each stage aimed at modifying risk factors (stage A), treating structural heart disease (stage B), and reducing morbidity and mortality (stages C and D) (covered in detail in Section 7) are reviewed in this document. The NYHA functional classification gauges the severity of symptoms in those with structural heart disease, primarily stages C and D. It is a subjective assessment by a clinician and can change frequently over short periods of time. Although

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reproducibility and validity may be problematic (48), the NYHA functional classification is an independent predictor of mortality (49). It is widely used in clinical practice and research and for determining the eligibility of patients for certain healthcare services.

Table 4. Comparison of ACCF/AHA Stages of HF and NYHA Functional Classifications
TnQTable5ACCF indicates American College of Cardiology Foundation; AHA, American Heart Association; HF, heart failure; and NYHA, New York Heart Association.

See Online Data Supplement 2 (http://jaccjacc.cardiosource.com/DataSupp/ACCF/2013_HFGL_Evidence_Tables.pdf) for additional data on ACCF/AHA stages of HF and NYHA functional classifications.

4. Epidemiology

The lifetime risk of developing HF is 20% for Americans ≥40 years of age (50). In the United States, HF incidence has largely remained stable over the past several decades, with >650,000 new HF cases diagnosed annually (51-53). HF incidence increases with age, rising from approximately 20 per 1,000 individuals 65 to 69 years of age to >80 per 1,000 individuals among those ≥85 years of age (52). Approximately 5.1 million persons in the United States have clinically manifest HF, and the prevalence continues to rise (51). In the Medicare-eligible population, HF prevalence increased from 90 to 121 per 1,000 beneficiaries from 1994 to 2003 (52). HF*r*EF and HF*p*EF each make up about half of the overall HF burden (54). One in 5 Americans will be >65 years of age by 2050 (55). Because HF prevalence is highest in this group, the number of Americans with HF is expected to significantly worsen in the future. Disparities in the epidemiology of HF have been identified. Blacks have the highest risk for HF (56). In the ARIC (Atherosclerosis Risk in Communities) study, incidence rate per 1,000 person-years was lowest among white women (52, 53) and highest among black men (57), with blacks having a greater 5-year mortality rate than whites (58). HF in non-Hispanic black males and females has a prevalence of 4.5% and 3.8%, respectively, versus 2.7% and 1.8% in non-Hispanic white males and females, respectively (51).

4.1. Mortality

Although survival has improved, the absolute mortality rates for HF remain approximately 50% within 5 years of diagnosis (53, 59). In the ARIC study, the 30-day, 1-year, and 5-year case fatality rates after hospitalization for HF were 10.4%, 22%, and 42.3%, respectively (58). In another population cohort study with 5-year mortality data, survival for stage A, B, C, and D HF was 97%, 96%, 75%, and 20%, respectively (47). Thirty-day postadmission mortality rates decreased from 12.6% to 10.8% from 1993 to 2005; however, this was due to lower in-hospital death rates. Postdischarge mortality actually increased from 4.3% to 6.4% during the same time frame (60). These observed temporal trends in HF survival are primarily restricted to patients with reduced EF and are not seen in those with preserved EF (40).

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See Online Data Supplement 3 (http://jaccjacc.cardiosource.com/DataSupp/ACCF/2013_HFGL_Evidence_Tables.pdf) for additional data on mortality.

4.2. Hospitalizations

HF is the primary diagnosis in >1 million hospitalizations annually (51). Patients hospitalized for HF are at high risk for all-cause rehospitalization, with a 1-month readmission rate of 25% (61). In 2010, physician office visits for HF cost $1.8 billion. The total cost of HF care in the United States exceeds $40 billion annually, with over half of these costs spent on hospitalizations (51).

4.3. Asymptomatic LV Dysfunction

The prevalence of asymptomatic LV systolic or diastolic dysfunction ranges from 6% to 21% and increases with age (62-64). In the Left Ventricular Dysfunction Prevention study, participants with untreated asymptomatic LV dysfunction had a 10% risk for developing HF symptoms and an 8% risk of death or HF hospitalization annually (65). In a community-based population, asymptomatic mild LV diastolic dysfunction was seen in 21% and moderate or severe diastolic dysfunction in 7%, and both were associated with an increased risk of symptomatic HF and mortality (64).

4.4. Health-Related Quality of Life and Functional Status

HF significantly decreases health-related quality of life (HRQOL), especially in the areas of physical functioning and vitality (66, 67). Lack of improvement in HRQOL after discharge from the hospital is a powerful predictor of rehospitalization and mortality (68, 69). ENREF_7 Women with HF have consistently been found to have poorer HRQOL than men (67, 70). Ethnic differences also have been found, with Mexican Hispanics reporting better HRQOL than other ethnic groups in the United States (71). Other determinants of poor HRQOL include depression, younger age, higher body mass index (BMI), greater symptom burden, lower systolic blood pressure, sleep apnea, low perceived control, and uncertainty about prognosis (70, 72-76). Memory problems may also contribute to poor HRQOL (76).

Pharmacological therapy is not a consistent determinant of HRQOL; therapies such as angiotensin-converting enzyme (ACE) inhibitors and angiotensin-receptor blockers (ARBs) improve HRQOL only modestly or delay the progressive worsening of HRQOL in HF (77). ENREF_15 At present, the only therapies shown to improve HRQOL are cardiac resynchronization therapy (CRT) (78) and certain disease management and educational approaches (79-82). Self-care and exercise may improve HRQOL, but the results of studies evaluating these interventions are mixed (83-86). Throughout this guideline we refer to meaningful survival as a state in which HRQOL is satisfactory to the patient.

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See Online Data Supplement 4 (http://jaccjacc.cardiosource.com/DataSupp/ACCF/2013_HFGL_Evidence_Tables.pdf) for additional data on HRQOL and functional capacity.

4.5. Economic Burden of HF

In 1 in 9 deaths in the United States, HF is mentioned on the death certificate. The number of deaths with any mention of HF was as high in 2006 as it was in 1995 (51). Approximately 7% of all cardiovascular deaths are due to HF.

As previously noted, in 2012, HF costs in the United States exceeded $40 billion (51). This total includes the cost of healthcare services, medications, and lost productivity. The mean cost of HF-related hospitalizations was $23,077 per patient and was higher when HF was a secondary rather than the primary diagnosis. Among patients with HF in 1 large population study, hospitalizations were common after HF diagnosis, with 83% of patients hospitalized at least once and 43% hospitalized at least 4 times. More than half of the hospitalizations were related to noncardiovascular causes (87-89).

4.6. Important Risk Factors for HF (Hypertension, Diabetes Mellitus, Metabolic Syndrome, and Atherosclerotic Disease)

Many conditions or comorbidities are associated with an increased propensity for structural heart disease. The expedient identification and treatment of these comorbid conditions may forestall the onset of HF (14, 27, 90). A list of the important documents that codify treatment for these concomitant conditions appears in Table 2.

Hypertension. Hypertension may be the single most important modifiable risk factor for HF in the United States. Hypertensive men and women have a substantially greater risk for developing HF than normotensive men and women (91). Elevated levels of diastolic and especially systolic blood pressure are major risk factors for the development of HF (91, 92). The incidence of HF is greater with higher levels of blood pressure, older age, and longer duration of hypertension. Long-term treatment of both systolic and diastolic hypertension reduces the risk of HF by approximately 50% (93-96). With nearly a quarter of the American population afflicted by hypertension and the lifetime risk of developing hypertension at >75% in the United States (97), strategies to control hypertension are a vital part of any public health effort to prevent HF.

Diabetes mellitus. Obesity and insulin resistance are important risk factors for the development of HF (98, 99). The presence of clinical diabetes markedly increases the likelihood of developing HF in patients without structural heart disease (100) and adversely affects the outcomes of patients with established HF (101, 102).

Metabolic syndrome. The metabolic syndrome includes any 3 of the following: abdominal adiposity, hypertriglyceridemia, low high-density lipoprotein, hypertension, and fasting hyperglycemia. The prevalence of metabolic syndrome in the United States exceeds 20% of persons ≥20 years of age and 40% of those >40 years

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of age (103). The appropriate treatment of hypertension, diabetes mellitus, and dyslipidemia (104) can significantly reduce the development of HF.

Atherosclerotic disease. Patients with known atherosclerotic disease (e.g., of the coronary, cerebral, or peripheral blood vessels) are likely to develop HF, and clinicians should seek to control vascular risk factors in such patients according to guidelines (13).

5. Cardiac Structural Abnormalities and Other Causes of HF

5.1. Dilated Cardiomyopathies

5.1.1. Definition and Classification of Dilated Cardiomyopathies

Dilated cardiomyopathy (DCM) refers to a large group of heterogeneous myocardial disorders that are characterized by ventricular dilation and depressed myocardial contractility in the absence of abnormal loading conditions such as hypertension or valvular disease. In clinical practice and multicenter HF trials, the etiology of HF has often been categorized into ischemic or nonischemic cardiomyopathy, with the term DCM used interchangeably with nonischemic cardiomyopathy. This approach fails to recognize that "nonischemic cardiomyopathy" may include cardiomyopathies due to volume or pressure overload, such as hypertension or valvular heart disease, which are not conventionally accepted as DCM (105). With the identification of genetic defects in several forms of cardiomyopathies, a new classification scheme based on genomics was proposed in 2006 (23). We recognize that classification of cardiomyopathies is challenging, mixing anatomic designations (i.e., hypertrophic and dilated) with functional designations (i.e., restrictive) and is unlikely to satisfy all users. The aim of the present guideline is to target appropriate diagnostic and treatment strategies for preventing the development and progression of HF in patients with cardiomyopathies; we do not wish to redefine new classification strategies for cardiomyopathies.

5.1.2. Epidemiology and Natural History of DCM

The age-adjusted prevalence of DCM in the United States averages 36 cases per 100,000 population, and DCM accounts for 10,000 deaths annually (106). In most multicenter RCTs and registries in HF, approximately 30% to 40% of enrolled patients have DCM (107-109). Compared with whites, African Americans have almost a 3-fold increased risk for developing DCM, irrespective of comorbidities or socioeconomic factors (108-110). Sex-related differences in the incidence and prognosis of DCM are conflicting and may be confounded by differing etiologies (108, 109, 111). The prognosis in patients with symptomatic HF and DCM is relatively poor, with 25% mortality at 1 year and 50% mortality at 5 years (112). Approximately 25% of patients with DCM with recent onset of HF symptoms will improve within a short time even in the absence of optimal GDMT (113), but patients with symptoms lasting >3 months who present with severe clinical decompensation generally have less

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chance of recovery (113). Patients with idiopathic DCM have a lower total mortality rate than patients with other types of DCM (114). However, GDMT is beneficial in all forms of DCM (78, 109, 115-117).

5.2. Familial Cardiomyopathies

Increasingly, it is recognized that many (20% to 35%) patients with an idiopathic DCM have a familial cardiomyopathy (defined as 2 closely related family members who meet the criteria for idiopathic DCM) (118, 119). Consideration of familial cardiomyopathies includes the increasingly important discovery of noncompaction cardiomyopathies. Advances in technology permitting high-throughput sequencing and genotyping at reduced costs have brought genetic screening to the clinical arena. For further information on this topic, the reader is referred to published guidelines, position statements, and expert consensus statements (118, 120-123) (Table 5).

Table 5. Screening of Family Members and Genetic Testing in Patients With Idiopathic or Familial DCM
TnQTable6DCM indicates dilated cardiomyopathy; and LV, left ventricular.

5.3. Endocrine and Metabolic Causes of Cardiomyopathy

5.3.1. Obesity

Obesity cardiomyopathy is defined as cardiomyopathy due entirely or predominantly to obesity (Section 7.3.1.5). Although the precise mechanisms causing obesity-related HF are not known, excessive adipose accumulation results in an increase in circulating blood volume. A subsequent, persistent increase in cardiac output, cardiac work, and systemic blood pressure (124) along with lipotoxicity-induced cardiac myocyte injury and myocardial lipid accumulation have been implicated as potential mechanisms (125, 126). A study with participants from the Framingham Heart Study reported that after adjustment for established risk factors, obesity was associated with significant future risk of development of HF (99). There are no large-scale studies of the safety or efficacy of weight loss with diet, exercise, or bariatric surgery in obese patients with HF.

5.3.2. Diabetic Cardiomyopathy

Diabetes mellitus is now well recognized as a risk factor for the development of HF independent of age, hypertension, obesity, hypercholesterolemia, or CAD. The association between mortality and hemoglobin A1c (HbA1c) in patients with diabetes mellitus and HF appears U-shaped, with the lowest risk of death in those patients with modest glucose control (7.1% <HbA1c ≤7.8%) and with increased risk with extremely high or low HbA1c levels (127). The optimal treatment strategy in patients with diabetes and HF is controversial; some studies have suggested potential harm with several glucose-lowering medications (127, 128). The safety and efficacy of diabetes therapies in HF, including metformin, sulfonylureas, insulin, and glucagon-like peptide analogues await further data from prospective clinical trials (129-131). Treatment with thiazolidinediones (e.g.,

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rosiglitazone) is associated with fluid retention in patients with HF (129, 132) and should be avoided in patients with NYHA class II through IV HF.

5.3.3. Thyroid Disease

Hyperthyroidism has been implicated in causing DCM but most commonly occurs with persistent sinus tachycardia or AF and may be related to tachycardia (133). Abnormalities in cardiac systolic and diastolic performance have been reported in hypothyroidism. However, the classic findings of myxedema do not usually indicate cardiomyopathy. The low cardiac output results from bradycardia, decreased ventricular filling, reduced cardiac contractility, and diminished myocardial work (133, 134).

5.3.4. Acromegaly and Growth Hormone Deficiency

Impaired cardiovascular function has been associated with reduced life expectancy in patients with growth hormone deficiency and excess. Experimental and clinical studies implicate growth hormone and insulin-like growth factor I in cardiac development (135). Cardiomyopathy associated with acromegaly is characterized by myocardial hypertrophy with interstitial fibrosis, lympho-mononuclear infiltration, myocyte necrosis, and biventricular concentric hypertrophy (135).

5.4. Toxic Cardiomyopathy

5.4.1. Alcoholic Cardiomyopathy

Chronic alcoholism is one of the most important causes of DCM (136). The clinical diagnosis is suspected when biventricular dysfunction and dilatation are persistently observed in a heavy drinker in the absence of other known causes for myocardial disease. Alcoholic cardiomyopathy most commonly occurs in men 30 to 55 years of age who have been heavy consumers of alcohol for >10 years (137). Women represent approximately 14% of the alcoholic cardiomyopathy cases but may be more vulnerable with less lifetime alcohol consumption (136, 138). The risk of asymptomatic alcoholic cardiomyopathy is increased in those consuming >90 g of alcohol per day (approximately 7 to 8 standard drinks per day) for >5 years (137). Interestingly, in the general population, mild to moderate alcohol consumption has been reported to be protective against development of HF (139, 140). These paradoxical findings suggest that duration of exposure and individual genetic susceptibility play an important role in pathogenesis. Recovery of LV function after cessation of drinking has been reported (141). Even if LV dysfunction persists, the symptoms and signs of HF improve after abstinence (141).

5.4.2. Cocaine Cardiomyopathy

Long-term abuse of cocaine may result in DCM even without CAD, vasculitis, or MI. Depressed LV function has been reported in 4% to 18% of asymptomatic cocaine abusers (142-144). The safety and efficacy of beta blockers for chronic HF due to cocaine use are unknown (145).

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5.4.3. Cardiotoxicity Related to Cancer Therapies

Several cytotoxic antineoplastic drugs, especially the anthracyclines, are cardiotoxic and can lead to long-term cardiac morbidity. Iron-chelating agents that prevent generation of oxygen free-radicals, such as dexrazoxane, are cardioprotective (146, 147), and reduce the occurrence and severity of anthracycline-induced cardiotoxicity and development of HF.

Other antineoplastic chemotherapies with cardiac toxicity are the monoclonal antibody trastuzumab (Herceptin), high-dose cyclophosphamide, taxoids, mitomycin-C, 5-fluorouracil, and the interferons (148). In contrast to anthracycline-induced cardiac toxicity, trastuzumab-related cardiac dysfunction does not appear to increase with cumulative dose, nor is it associated with ultrastructural changes in the myocardium. However, concomitant anthracycline therapy significantly increases the risk for cardiotoxicity during trastuzumab treatment. The cardiac dysfunction associated with trastuzumab is most often reversible on discontinuation of treatment and initiation of standard medical therapy for HF (149). The true incidence and reversibility of chemotherapy-related cardiotoxicity is not well documented, and meaningful interventions to prevent injury have not yet been elucidated.

5.4.4. Other Myocardial Toxins and Nutritional Causes of Cardiomyopathy

In addition to the classic toxins described above, a number of other toxic agents may lead to LV dysfunction and HF, including ephedra, cobalt, anabolic steroids, chloroquine, clozapine, amphetamine, methylphenidate, and catecholamines (150). Ephedra, which has been used for athletic performance enhancement and weight loss, was ultimately banned by the US Food and Drug Administration for its high rate of adverse cardiovascular outcomes, including LV systolic dysfunction, development of HF, and sudden cardiac death (SCD) (151).

Primary and secondary nutritional deficiencies may lead to cardiomyopathy. Chronic alcoholism, anorexia nervosa, AIDS, and pregnancy can account for other rare causes of thiamine deficiency–related cardiomyopathy in the western world (152). Deficiency in L-carnitine, a necessary cofactor for fatty acid oxidation, may be associated with a syndrome of progressive skeletal myopathy and cardiomyopathy (153).

5.5. Tachycardia-Induced Cardiomyopathy

Tachycardia-induced cardiomyopathy is a reversible cause of HF characterized by LV myocardial dysfunction caused by increased ventricular rate. The degree of dysfunction correlates with the duration and rate of the tachyarrhythmia. Virtually any supraventricular tachycardia with a rapid ventricular response may induce cardiomyopathy. Ventricular arrhythmias, including frequent premature ventricular complexes, may also induce cardiomyopathy. Maintenance of sinus rhythm or control of ventricular rate is critical to treating patients with tachycardia-induced cardiomyopathy (154). Reversibility of the cardiomyopathy with treatment of the arrhythmia is the rule, although this may not be complete in all cases. The underlying mechanisms for this are not well understood.

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Ventricular pacing at high rates may cause cardiomyopathy. Additionally, right ventricular pacing alone may exacerbate HF symptoms, increase hospitalization for HF, and increase mortality (155, 156). Use of CRT in patients with a conduction delay due to pacing may result in improved LV function and functional capacity.

5.6. Myocarditis and Cardiomyopathies Due to Inflammation

5.6.1. Myocarditis

Inflammation of the heart may cause HF in about 10% of cases of initially unexplained cardiomyopathy (105, 157). A variety of infectious organisms, as well as toxins and medications, most often postviral in origin, may cause myocarditis. In addition, myocarditis is also seen as part of other systemic diseases such as systemic lupus erythematosus and other myocardial muscle diseases such as HIV cardiomyopathy and possibly peripartum cardiomyopathy. Presentation may be acute, with a distinct onset, severe hemodynamic compromise, and severe LV dysfunction as seen in acute fulminant myocarditis, or it may be subacute, with an indistinct onset and better-tolerated LV dysfunction (158). Prognosis varies, with spontaneous complete resolution (paradoxically most often seen with acute fulminant myocarditis) (158) to the development of DCM despite immunosuppressive therapy (159). The role of immunosuppressive therapy is controversial (159). Targeting such therapy to specific individuals based on the presence or absence of viral genome in myocardial biopsy samples may improve response to immunosuppressive therapy (160).

Giant-cell myocarditis is a rare form of myocardial inflammation characterized by fulminant HF, often associated with refractory ventricular arrhythmias and a poor prognosis (161, 162). Histologic findings include diffuse myocardial necrosis with numerous multinucleated giant cells without granuloma formation. Consideration for advanced HF therapies, including immunosuppression, mechanical circulatory support (MCS), and transplantation is warranted.

5.6.2. Acquired Immunodeficiency Syndrome

The extent of immunodeficiency influences the incidence of HIV-associated DCM (163-165). In long-term echocardiographic follow-up (166), 8% of initially asymptomatic HIV-positive patients were diagnosed with DCM during the 5-year follow-up. Whether early treatment with ACE inhibitors and/or beta blockers will prevent or delay disease progression in these patients is unknown at this time.

5.6.3. Chagas' Disease

Although Chagas' disease is a relatively uncommon cause of DCM in North America, it remains an important cause of death in Central and South America (167). Symptomatic chronic Chagas' disease develops in an estimated 10% to 30% of infected persons, years or even decades after the *Trypanosoma cruzi* infection. Cardiac changes may include biventricular enlargement, thinning or thickening of ventricular walls, apical aneurysms,

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and mural thrombi. The conduction system is often affected, typically resulting in right bundle-branch block, left anterior fascicular block, or complete atrioventricular block.

5.7. Inflammation-Induced Cardiomyopathy: Noninfectious Causes

5.7.1. Hypersensitivity Myocarditis

Hypersensitivity to a variety of agents may result in allergic reactions that involve the myocardium, characterized by peripheral eosinophilia and a perivascular infiltration of the myocardium by eosinophils, lymphocytes, and histiocytes. A variety of drugs, most commonly the sulfonamides, penicillins, methyldopa, and other agents such as amphotericin B, streptomycin, phenytoin, isoniazid, tetanus toxoid, hydrochlorothiazide, dobutamine, and chlorthalidone have been reported to cause allergic hypersensitivity myocarditis (168). Most patients are not clinically ill but may die suddenly, presumably secondary to an arrhythmia.

5.7.2. Rheumatological/Connective Tissue Disorders

Along with a number of cardiac abnormalities (e.g., pericarditis, pericardial effusion, conduction system abnormalities, including complete atrioventricular heart block), DCM can be a rare manifestation of systemic lupus erythematosus and usually correlates with disease activity (169). Studies suggest that echocardiographic evidence of abnormal LV filling may reflect the presence of myocardial fibrosis and could be a marker of subclinical myocardial involvement in systemic lupus erythematosus patients (170).

Scleroderma is a rare cause of DCM. One echocardiographic study showed that despite normal LV dimensions or fractional shortening, subclinical systolic impairment was present in the majority of patients with scleroderma (171). Cardiac involvement in rheumatoid arthritis generally is in the form of myocarditis and/or pericarditis, and development of DCM is rare (172). Myocardial involvement in rheumatoid arthritis is thought to be secondary to microvasculitis and subsequent microcirculatory disturbances. Myocardial disease in rheumatoid arthritis can occur in the absence of clinical symptoms or abnormalities of the electrocardiogram (ECG) (173).

5.8. Peripartum Cardiomyopathy

Peripartum cardiomyopathy is a disease of unknown cause in which LV dysfunction occurs during the last trimester of pregnancy or the early puerperium. It is reported in 1:1,300 to 1:4,000 live births (174). Risk factors for peripartum cardiomyopathy include advanced maternal age, multiparity, African descent, and long-term tocolysis. Although its etiology remains unknown, most theories have focused on hemodynamic and immunologic causes (174). The prognosis of peripartum cardiomyopathy is related to the recovery of ventricular function. Significant improvement in myocardial function is seen in 30% to 50% of patients in the first 6 months after presentation (174). However, for those patients who do not recover to normal or near-normal function, the

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prognosis is similar to other forms of DCM (175). Cardiomegaly that persists for >4 to 6 months after diagnosis indicates a poor prognosis, with a 50% mortality rate at 6 years. Subsequent pregnancy in women with a history of peripartum cardiomyopathy may be associated with a further decrease in LV function and can result in clinical deterioration, including death. However, if ventricular function has normalized in women with a history of peripartum cardiomyopathy, the risk may be less (174). There is an increased risk of venous thromboembolism, and anticoagulation is recommended, especially if ventricular dysfunction is persistent.

5.9. Cardiomyopathy Caused By Iron Overload

Iron overload cardiomyopathy manifests itself as systolic or diastolic dysfunction secondary to increased deposition of iron in the heart and occurs with common genetic disorders such as primary hemochromatosis or with lifetime transfusion requirements as seen in beta-thalassemia major (176). Hereditary hemochromatosis, an autosomal recessive disorder, is the most common hereditary disease of Northern Europeans, with a prevalence of approximately 5 per 1,000. The actuarial survival rates of persons who are homozygous for the mutation of the hemochromatosis gene *C282Y* have been reported to be 95%, 93%, and 66%, at 5, 10, and 20 years, respectively (177). Similarly, in patients with thalassemia major, cardiac failure is one of the most frequent causes of death. Chelation therapy, including newer forms of oral chelators, such as deferoxamine, and phlebotomy, have dramatically improved the outcome of hemochromatosis, and the roles of gene therapy, hepcidin, and calcium channel blockers are being actively investigated (178).

5.10. Amyloidosis

Cardiac amyloidosis involves the deposition of insoluble proteins as fibrils in the heart, resulting in HF. Primary or AL amyloidosis (monoclonal kappa or lambda light chains), secondary amyloidosis (protein A), familial TTR amyloidosis (mutant transthyretin), dialysis-associated amyloidosis (beta-2-microglobulin), or senile TTR amyloidosis (wild-type transthyretin) can affect the heart, but cardiac involvement is primarily encountered in AL and TTR amyloidosis (179). The disease can be rapidly progressive, and, in patients with ventricular septum thickness >15 mm, LVEF <40%, and symptoms of HF, median survival may be <6 months (180). Cardiac biomarkers (e.g., B-type natriuretic peptide (BNP), cardiac troponin) have been reported to predict response and progression of disease and survival (181). Three percent to 4% of African Americans carry an amyloidogenic allele of the human serum protein transthyretin (TTR V122I), which appears to increase risk for cardiac amyloid deposition after 65 years of age (182).

5.11. Cardiac Sarcoidosis

Cardiac sarcoidosis is an underdiagnosed disease that may affect as many as 25% of patients with systemic sarcoidosis. Although most commonly recognized in patients with other manifestations of sarcoidosis, cardiac involvement may occur in isolation and go undetected. Cardiac sarcoidosis may present as

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asymptomatic LV dysfunction, HF, atrioventricular block, atrial or ventricular arrhythmia, and SCD (183). Although untested in clinical trials, early use of high-dose steroid therapy may halt or reverse cardiac damage (184). Cardiac magnetic resonance and cardiac positron emission tomographic scanning can identify cardiac involvement with patchy areas of myocardial inflammation and fibrosis. In the setting of ventricular tachyarrhythmia, patients may require placement of an implantable cardioverter-defibrillator (ICD) for primary prevention of SCD (185).

5.12. Stress (Takotsubo) Cardiomyopathy

Stress cardiomyopathy is characterized by acute reversible LV dysfunction in the absence of significant CAD, triggered by acute emotional or physical stress (23). This phenomenon is identified by a distinctive pattern of "apical ballooning," first described in Japan as takotsubo, and often affects postmenopausal women (186). A majority of patients have a clinical presentation similar to that of acute coronary syndrome (ACS) and may have transiently elevated cardiac enzymes.

6. Initial and Serial Evaluation of the HF Patient

6.1. Clinical Evaluation

6.1.1. History and Physical Examination: Recommendations

Class I

1. **A thorough history and physical examination should be obtained/performed in patients presenting with HF to identify cardiac and noncardiac disorders or behaviors that might cause or accelerate the development or progression of HF. (*Level of Evidence: C)***
2. **In patients with idiopathic DCM, a 3-generational family history should be obtained to aid in establishing the diagnosis of familial DCM. (*Level of Evidence: C)***
3. **Volume status and vital signs should be assessed at each patient encounter. This includes serial assessment of weight, as well as estimates of jugular venous pressure and the presence of peripheral edema or orthopnea (187-190). (*Level of Evidence: B)***

Despite advances in imaging technology and increasing availability of diagnostic laboratory testing, a careful history and physical examination remain the cornerstones in the assessment of patients with HF. The components of a focused history and physical examination for the patient with HF are listed in Table 6. The history provides clues to the etiology of the cardiomyopathy, including the diagnosis of familial cardiomyopathy (defined as ≥2 relatives with idiopathic DCM). Familial syndromes are now recognized to occur in 20% to 35% of patients with apparent idiopathic DCM (118); thus, a 3-generation family history should be obtained. The history also provides information about the severity of the disease and the patient's prognosis and identifies opportunities for therapeutic interventions. The physical examination provides information about the severity of illness and allows assessment of volume status and adequacy of perfusion. In advanced HF*r*EF, orthopnea and jugular venous pressure are useful findings to detect elevated LV filling pressures (187, 189, 190).

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Table 6. History and Physical Examination in HF
TnQTable7BMI indicates body mass index; DCM, dilated cardiomyopathy; GDMT, guideline-directed medical therapy; HF, heart failure; HF*r*EF, heart failure with reduced ejection fraction; ICD, implantable cardioverter-defibrillator; LV, left ventricular; and NYHA, New York Heart Association.

See Online Data Supplements 5, 6, and 7 (http://jaccjacc.cardiosource.com/DataSupp/ACCF/2013_HFGL_Evidence_Tables.pdf) for additional data on stress testing and clinical evaluation.

6.1.2. Risk Scoring: Recommendation
Class IIa

1. **Validated multivariable risk scores can be useful to estimate subsequent risk of mortality in ambulatory or hospitalized patients with HF (199-207).** ***(Level of Evidence: B)***

In the course of standard evaluation, clinicians should routinely assess the patient's potential for adverse outcome, because accurate risk stratification may help guide therapeutic decision making, including a more rapid transition to advanced HF therapies. A number of methods objectively assess risk, including biomarker testing (Section 6.3), as well as a variety of multivariable clinical risk scores (Table 7); these risk scores are for use in ambulatory (199, 203, 205, 206, 208) and hospitalized patients (200, 202, 204, 205, 209). Risk models specifically for patients with HF*p*EF have also been described (201).

One well-validated risk score, the Seattle Heart Failure Model, is available in an interactive application on the Internet (210) and provides robust information about risk of mortality in ambulatory patients with HF. For patients hospitalized with acutely decompensated HF, the model developed by ADHERE (Acute Decompensated Heart Failure National Registry) incorporates 3 routinely measured variables on hospital admission (i.e., systolic blood pressure, blood urea nitrogen, and serum creatinine) and stratifies subjects into categories with a 10-fold range of crude in-hospital mortality (from 2.1% to 21.9%) (200). Notably, clinical risk scores have not performed as well in estimating risk of hospital readmission (211). For this purpose, biomarkers such as natriuretic peptides hold considerable promise (212, 213) (Section 6.3).

Table 7. Selected M**ultivariable Risk Scores to Predict Outcome in HF**
TnQTable8ADHERE indicates Acute Decompensated Heart Failure National Registry; CHARM, Candesartan in Heart failure-Assessment of Reduction in Mortality and morbidity; CORONA, Controlled Rosuvastatin Multinational Trial in Heart Failure; EFFECT, Enhanced Feedback for Effective Cardiac Treatment; ESCAPE, Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness; HF, heart failure; HF*p*EF, heart failure with preserved ejection fraction; I-PRESERVE, Irbesartan in Heart Failure with Preserved Ejection Fraction Study; and OPTIMIZE, Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure.

See Online Data Supplement 8 (http://jaccjacc.cardiosource.com/DataSupp/ACCF/2013_HFGL_Evidence_Tables.pdf) for additional data on clinical evaluation risk scoring.

6.2. Diagnostic Tests: Recommendations

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Class I

1. **Initial laboratory evaluation of patients presenting with HF should include complete blood count, urinalysis, serum electrolytes (including calcium and magnesium), blood urea nitrogen, serum creatinine, glucose, fasting lipid profile, liver function tests, and thyroid-stimulating hormone.** ***(Level of Evidence: C)***
2. **Serial monitoring, when indicated, should include serum electrolytes and renal function.** ***(Level of Evidence: C)***
3. **A 12-lead ECG should be performed initially on all patients presenting with HF.** ***(Level of Evidence: C)***

Class IIa

1. **Screening for hemochromatosis or HIV is reasonable in selected patients who present with HF (216).** ***(Level of Evidence: C)***
2. **Diagnostic tests for rheumatologic diseases, amyloidosis, or pheochromocytoma are reasonable in patients presenting with HF in whom there is a clinical suspicion of these diseases.** ***(Level of Evidence: C)***

6.3. Biomarkers: Recommendations

A. Ambulatory/Outpatient

Class I

1. **In ambulatory patients with dyspnea, measurement of BNP or N-terminal pro-B-type natriuretic peptide (NT-proBNP) is useful to support clinical decision making regarding the diagnosis of HF, especially in the setting of clinical uncertainty (217-223).** ***(Level of Evidence: A)***
2. **Measurement of BNP or NT-proBNP is useful for establishing prognosis or disease severity in chronic HF (222, 224-229).** ***(Level of Evidence: A)***

Class IIa

1. **BNP- or NT-proBNP–guided HF therapy can be useful to achieve optimal dosing of GDMT in select clinically euvolemic patients followed in a well-structured HF disease management program (230-237).** ***(Level of Evidence: B)***

Class IIb

1. **The usefulness of serial measurement of BNP or NT-proBNP to reduce hospitalization or mortality in patients with HF is not well established (230-237).** ***(Level of Evidence: B)***
2. **Measurement of other clinically available tests such as biomarkers of myocardial injury or fibrosis may be considered for additive risk stratification in patients with chronic HF (238-244).** ***(Level of Evidence: B)***

B. Hospitalized/Acute

Class I

1. **Measurement of BNP or NT-proBNP is useful to support clinical judgment for the diagnosis of acutely decompensated HF, especially in the setting of uncertainty for the diagnosis (212, 245-250).** ***(Level of Evidence: A)***
2. **Measurement of BNP or NT-proBNP and/or cardiac troponin is useful for establishing prognosis or disease severity in acutely decompensated HF (248, 251-258).** ***(Level of Evidence: A)***

Class IIb

1. **The usefulness of BNP- or NT-proBNP–guided therapy for acutely decompensated HF is not well-established (259, 260).** ***(Level of Evidence: C)***

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2. **Measurement of other clinically available tests such as biomarkers of myocardial injury or fibrosis may be considered for additive risk stratification in patients with acutely decompensated HF (248, 253, 256, 257, 261-267).** ***(Level of Evidence: A)***

In addition to routine clinical laboratory tests**,** other biomarkers are gaining greater attention for their utility in HF management. These biomarkers may reflect various pathophysiological aspects of HF, including myocardial wall stress, hemodynamic abnormalities, inflammation, myocyte injury, neurohormonal upregulation, and myocardial remodeling, as well as extracellular matrix turnover. Thus, these biomarkers are potentially powerful adjuncts to current standards for the diagnosis, prognosis, and treatment of acute and chronic HF.

6.3.1. Natriuretic Peptides: BNP or NT-proBNP

BNP or its amino-terminal cleavage equivalent (NT-proBNP) is derived from a common 108-amino acid precursor peptide ($proBNP_{108}$) that is generated by cardiomyocytes in the context of numerous triggers, most notably myocardial stretch. Following several steps of processing, BNP and NT-proBNP are released from the cardiomyocyte, along with variable amounts of $proBNP_{108}$, the latter of which is detected by all assays that measure either "BNP" or "NT-proBNP."

Assays for BNP and NT-proBNP have been increasingly used to establish the presence and severity of HF. In general, BNP and NT-proBNP values are reasonably correlated, and either can be used in patient care settings as long as their respective absolute values and cut points are not used interchangeably. BNP and NT-proBNP are useful to support clinical judgment for the diagnosis or exclusion of HF, in the setting of chronic ambulatory HF (217-223) or acute decompensated HF (245-250); the value of natriuretic peptide testing is particularly significant when the etiology of dyspnea is unclear.

Although lower values of BNP or NT-proBNP exclude the presence of HF and higher values have reasonably high positive predictive value to diagnose HF, clinicians should be aware that elevated plasma levels for both natriuretic peptides have been associated with a wide variety of cardiac and noncardiac causes (Table 8) (268-271).

BNP and NT-proBNP levels improve with treatment of chronic HF (225, 272-274), with lowering of levels over time in general, correlating with improved clinical outcomes (248, 251, 254, 260). Thus, BNP or NT-proBNP "guided" therapy has been studied against standard care without natriuretic peptide measurement to determine whether guided therapy renders superior achievement of GDMT in patients with HF. However, RCTs have yielded inconsistent results.

The positive and negative natriuretic peptide–guided therapy trials differ primarily in their study populations, with successful trials enrolling younger patients and only those with HF*r*EF. In addition, a lower natriuretic peptide goal and/or a substantial reduction in natriuretic peptides during treatment are consistently present in the positive "guided" therapy trials (275). Although most trials examining the strategy of biomarker "guided" HF management were small and underpowered, 2 comprehensive meta-analyses concluded that BNP-guided therapy reduces all-cause mortality in patients with chronic HF compared with usual clinical care (231,

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232), especially in patients <75 years of age. This survival benefit may be attributed to increased achievement of GDMT. In some cases, BNP or NT-proBNP levels may not be easily modifiable. If the BNP or NT-proBNP value does not fall after aggressive HF care, risk for death or hospitalization for HF is significant. On the other hand, some patients with advanced HF have normal BNP or NT-proBNP levels or have falsely low BNP levels because of obesity and HF*p*EF. All of these patients should still receive appropriate GDMT.

Table 8. Selected Causes of Elevated Natriuretic Peptide Concentrations

TnQTable9LVH indicates left ventricular hypertrophy; and RV, right ventricular.

6.3.2. Biomarkers of Myocardial Injury: Cardiac Troponin T or I

Abnormal concentrations of circulating cardiac troponin are found in patients with HF, often without obvious myocardial ischemia and frequently in those without underlying CAD. This suggests ongoing myocyte injury or necrosis in these patients (238-241, 276). In chronic HF, elaboration of cardiac troponins is associated with impaired hemodynamics (238), progressive LV dysfunction (239), and increased mortality rates (238-241, 276). Similarly, in patients with acute decompensated HF, elevated cardiac troponin levels are associated with worse clinical outcomes and mortality (253, 257, 263); decrease in troponin levels over time with treatment is associated with a better prognosis than persistent elevation in patients with chronic (239) or acute HF (277). Given the tight association with ACS and troponin elevation as well as the link between MI and the development of acute HF (278), the measurement of troponin I or T should be routine in patients presenting with acutely decompensated HF syndromes.

6.3.3. Other Emerging Biomarkers

Besides natriuretic peptides or troponins, multiple other biomarkers, including those reflecting inflammation, oxidative stress, neurohormonal disarray, and myocardial and matrix remodeling, have been widely examined for their prognostic value in HF. Biomarkers of myocardial fibrosis, soluble ST2 and galectin-3 are not only predictive of hospitalization and death in patients with HF but also additive to natriuretic peptide levels in their prognostic value. Markers of renal injury may also offer additional prognostic value because renal function or injury may be involved in the pathogenesis, progression, decompensation, or complications in chronic or acute decompensated HF (242-244, 264, 265, 279). Strategies that combine multiple biomarkers may ultimately prove beneficial in guiding HF therapy in the future.

See Table 9 for a summary of recommendations from this section.

Table 9. Recommendations for Biomarkers in HF

TnQTable10COR indicates Class of Recommendation; GDMT, guideline-directed medical therapy; HF, heart failure; and LOE, Level of Evidence.

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6.4. Noninvasive Cardiac Imaging: Recommendations

See Table 10 for a summary of recommendations from this section.

Class I

1. **Patients with suspected or new-onset HF, or those presenting with acute decompensated HF, should undergo a chest x-ray to assess heart size and pulmonary congestion and to detect alternative cardiac, pulmonary, and other diseases that may cause or contribute to the patient's symptoms.** ***(Level of Evidence: C)***
2. **A 2-dimensional echocardiogram with Doppler should be performed during initial evaluation of patients presenting with HF to assess ventricular function, size, wall thickness, wall motion, and valve function.** ***(Level of Evidence: C)***
3. **Repeat measurement of EF and measurement of the severity of structural remodeling are useful to provide information in patients with HF who have had a significant change in clinical status; who have experienced or recovered from a clinical event; or who have received treatment, including GDMT, that might have had a significant effect on cardiac function; or who may be candidates for device therapy.** ***(Level of Evidence: C)***

Class IIa

1. **Noninvasive imaging to detect myocardial ischemia and viability is reasonable in patients presenting with de novo HF who have known CAD and no angina unless the patient is not eligible for revascularization of any kind.** ***(Level of Evidence: C)***
2. **Viability assessment is reasonable in select situations when planning revascularization in HF patients with CAD (281-285).** ***(Level of Evidence: B)***
3. **Radionuclide ventriculography or magnetic resonance imaging can be useful to assess LVEF and volume when echocardiography is inadequate.** ***(Level of Evidence: C)***
4. **Magnetic resonance imaging is reasonable when assessing myocardial infiltrative processes or scar burden (286-288).** ***(Level of Evidence: B)***

Class III: No Benefit

1. **Routine repeat measurement of LV function assessment in the absence of clinical status change or treatment interventions should not be performed (289, 290).** ***(Level of Evidence: B)***

The chest x-ray is important for the evaluation of patients presenting with signs and symptoms of HF because it assesses cardiomegaly and pulmonary congestion and may reveal alternative causes, cardiopulmonary or otherwise, of the patient's symptoms. Apart from congestion, however, other findings on chest x-ray are associated with HF only in the context of clinical presentation. Cardiomegaly may be absent in HF. A chest x-ray may also show other cardiac chamber enlargement, increased pulmonary venous pressure, interstitial or alveolar edema, valvular or pericardial calcification, or coexisting thoracic diseases. Considering its low sensitivity and specificity, the chest x-ray should not be the sole determinant of the specific cause of HF. Moreover, a supine chest x-ray has limited value in acute decompensated HF.

Although a complete history and physical examination are important first steps, the most useful diagnostic test in the evaluation of patients with or at risk for HF (e.g., postacute MI) is a comprehensive 2-dimensional echocardiogram; coupled with Doppler flow studies, the transthoracic echocardiogram can identify abnormalities of myocardium, heart valves, and pericardium. Echocardiography can reveal subclinical HF and

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predict risk of subsequent events (291-295). Use of echocardiograms in patients with suspected HF improves disease identification and provision of appropriate medical care (296).

Echocardiographic evaluation should address whether LVEF is reduced, LV structure is abnormal, and other structural abnormalities are present that could account for the clinical presentation. This information should be quantified, including numerical estimates of EF measurement, ventricular dimensions, wall thickness, calculations of ventricular volumes, and evaluation of chamber geometry and regional wall motion. Documentation of LVEF is an HF quality-of-care performance measure (297). Right ventricular size and function as well as atrial size and dimensions should also be measured. All valves should be evaluated for anatomic and flow abnormalities. Secondary changes, particularly the severity of mitral and tricuspid valve insufficiency, should be determined. Noninvasive hemodynamic data constitute important additional information. Mitral valve inflow pattern, pulmonary venous inflow pattern, and mitral annular velocity provide data about LV filling and left atrial pressure. The tricuspid valve regurgitant gradient, coupled with measurement of inferior vena cava diameter and its response during respiration, provides estimates of systolic pulmonary artery pressure and central venous pressure. Many of these abnormalities are prognostically important and can be present without manifest HF.

Serial echocardiographic evaluations are useful because evidence of cardiac reverse remodeling can provide important information in patients who have had a change in clinical status or have experienced or recovered from an event or treatment that affects cardiac function. However, the routine repeat assessment of ventricular function in the absence of changing clinical status or a change in treatment intervention is not indicated.

The preference for echocardiography as an imaging modality is due to its widespread availability and lack of ionizing radiation; however, other imaging modalities may be of use. Magnetic resonance imaging assesses LV volume and EF measurements at least as accurately as echocardiography. However, additional information about myocardial perfusion, viability, and fibrosis from magnetic resonance imaging can help identify HF etiology and assess prognosis (298). Magnetic resonance imaging provides high anatomical resolution of all aspects of the heart and surrounding structure, leading to its recommended use in known or suspected congenital heart diseases (5). Cardiac computed tomography can also provide accurate assessment of cardiac structure and function, including the coronary arteries (299). An advantage of cardiac computed tomography over echocardiography may be its ability to characterize the myocardium, but studies have yet to demonstrate the importance of this factor. Reports of cardiac computed tomography in patients with suspected HF are limited. Furthermore, both cardiac computed tomography and magnetic resonance imaging lose accuracy with high heart rates. Radionucleotide ventriculography may also be used for evaluation of cardiac function when other tests are unavailable or inadequate. However, as a planar technique, radionuclide ventriculography cannot directly assess valvular structure, function, or ventricular wall thickness; it may be more useful for assessing LV volumes in patients with significant baseline wall motion abnormalities or

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distorted geometry. Ventriculography is highly reproducible (300). Single photon emission computed tomography or positron emission tomography scans are not primarily used to determine LV systolic global and regional function unless these parameters are quantified from the resultant images during myocardial perfusion and/or viability assessment (301, 302). Candidates for coronary revascularization who present with a high suspicion for obstructive CAD should undergo coronary angiography. Stress nuclear imaging or echocardiography may be an acceptable option for assessing ischemia in patients presenting with HF who have known CAD and no angina unless they are ineligible for revascularization (303). Although the results of the STICH (Surgical Treatment for Ischemic Heart Failure) trial have cast doubt on the role of myocardial viability assessment to determine the mode of therapy (304), the data are nevertheless predictive of a positive outcome. When these data are taken into consideration with multiple previous studies demonstrating the usefulness of this approach (281-285), it becomes reasonable to recommend viability assessment when treating patients with HF*r*EF who have known CAD (14).

Table 10. Recommendations for Noninvasive Cardiac Imaging

TnQTable11CAD indicates coronary artery disease; COR, Class of Recommendation; EF, ejection fraction; HF, heart failure; LOE, Level of Evidence; LV, left ventricular; LVEF, left ventricular ejection fraction; and MRI, magnetic resonance imaging.

See Online Data Supplement 9 (http://jaccjacc.cardiosource.com/DataSupp/ACCF/2013_HFGL_Evidence_Tables.pdf) for additional data on imaging–echocardiography.

6.5. Invasive Evaluation: Recommendations

See Table 11 for a summary of recommendations from this section.

Class I

1. **Invasive hemodynamic monitoring with a pulmonary artery catheter should be performed to guide therapy in patients who have respiratory distress or clinical evidence of impaired perfusion in whom the adequacy or excess of intracardiac filling pressures cannot be determined from clinical assessment. (*Level of Evidence: C*)**

Class IIa

1. **Invasive hemodynamic monitoring can be useful for carefully selected patients with acute HF who have persistent symptoms despite empiric adjustment of standard therapies and**
   - **a. whose fluid status, perfusion, or systemic or pulmonary vascular resistance is uncertain;**
   - **b. whose systolic pressure remains low, or is associated with symptoms, despite initial therapy;**
   - **c. whose renal function is worsening with therapy;**
   - **d. who require parenteral vasoactive agents; or**
   - **e. who may need consideration for MCS or transplantation. (*Level of Evidence: C*)**
2. **When ischemia may be contributing to HF, coronary arteriography is reasonable for patients eligible for revascularization. *(Level of Evidence: C)***
3. **Endomyocardial biopsy can be useful in patients presenting with HF when a specific diagnosis is suspected that would influence therapy. *(Level of Evidence: C)***

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Class III: No Benefit

1. **Routine use of invasive hemodynamic monitoring is not recommended in normotensive patients with acute decompensated HF and congestion with symptomatic response to diuretics and vasodilators (305).** ***(Level of Evidence: B)***

Class III: Harm

1. **Endomyocardial biopsy should not be performed in the routine evaluation of patients with HF.** ***(Level of Evidence: C)***

6.5.1. Right-Heart Catheterization

There has been no established role for routine or periodic invasive hemodynamic measurements in the management of HF. Most drugs used for the treatment of HF are prescribed on the basis of their ability to improve symptoms or survival rather than their effect on hemodynamic variables. The initial and target doses of these drugs are generally selected on the basis of controlled trial experience rather than changes produced in cardiac output or pulmonary capillary wedge pressure. Hemodynamic monitoring is indicated in patients with clinically indeterminate volume status and those refractory to initial therapy, particularly if intracardiac filling pressures and cardiac output are unclear. Patients with clinically significant hypotension (systolic blood pressure typically <90 mm Hg or symptomatic low systolic blood pressure) and/or worsening renal function during initial therapy might also benefit from invasive hemodynamic measurements (305, 306). Patients being considered for cardiac transplantation or placement of an MCS device are also candidates for complete right-heart catheterization, including an assessment of pulmonary vascular resistance, a necessary part of the initial transplantation evaluation. Invasive hemodynamic monitoring should be performed in patients with (1) presumed cardiogenic shock requiring escalating pressor therapy and consideration of MCS; (2) severe clinical decompensation in which therapy is limited by uncertain contributions of elevated filling pressures, hypoperfusion, and vascular tone; (3) apparent dependence on intravenous inotropic infusions after initial clinical improvement; or (4) persistent severe symptoms despite adjustment of recommended therapies. On the other hand, routine use of invasive hemodynamic monitoring is not recommended in normotensive patients with acute decompensated HF who have a symptomatic response to diuretics and vasodilators. This reinforces the concept that right-heart catheterization is best reserved for those situations where a specific clinical or therapeutic question needs to be addressed.

6.5.2. Left-Heart Catheterization

Left-heart catheterization or coronary angiography is indicated for patients with HF and angina and may be useful for those patients without angina but with LV dysfunction. Invasive coronary angiography should be used in accordance with the ACCF/AHA coronary artery bypass graft (CABG) and percutaneous coronary intervention Guidelines (10, 12) (Table 2) and should only be performed in patients who are potentially eligible for revascularization (307-309). In patients with known CAD and angina or with significant ischemia diagnosed by ECG or noninvasive testing and impaired ventricular function, coronary angiography is indicated. Among

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those without a prior diagnosis, CAD should be considered as a potential etiology of impaired LV function and should be excluded wherever possible. Coronary angiography may be considered in these circumstances to detect and localize large-vessel coronary obstructions. In patients in whom CAD has been excluded as the cause of LV dysfunction, coronary angiography is generally not indicated unless a change in clinical status suggests interim development of ischemic disease.

6.5.3. Endomyocardial Biopsy

Endomyocardial biopsy can be useful when seeking a specific diagnosis that would influence therapy, and biopsy should thus be considered in patients with rapidly progressive clinical HF or worsening ventricular dysfunction that persists despite appropriate medical therapy. Endomyocardial biopsy should also be considered in patients suspected of having acute cardiac rejection status after heart transplantation or having myocardial infiltrative processes. A specific example is to determine chemotherapy for primary cardiac amyloidosis. Additional other indications for endomyocardial biopsy include in patients with rapidly progressive and unexplained cardiomyopathy, those in whom active myocarditis, especially giant cell myocarditis, is being considered (310). Routine endomyocardial biopsy is not recommended in all cases of HF, given limited diagnostic yield and the risk of procedure-related complications.

Table 11. Recommendations for Invasive Evaluation
TnQTable12COR indicates Class of Recommendation; HF, heart failure; and LOE, Level of Evidence.

See Online Data Supplement 10 (http://jaccjacc.cardiosource.com/DataSupp/ACCF/2013_HFGL_Evidence_Tables.pdf) for additional data on biopsy.

7. Treatment of Stages A to D

7.1. Stage A: Recommendations

Class I

1. **Hypertension and lipid disorders should be controlled in accordance with contemporary guidelines to lower the risk of HF (27, 94, 311-314).** ***(Level of Evidence: A)***
2. **Other conditions that may lead to or contribute to HF, such as obesity, diabetes mellitus, tobacco use, and known cardiotoxic agents, should be controlled or avoided.** ***(Level of Evidence: C)***

7.1.1. Recognition and Treatment of Elevated Blood Pressure

The lifetime risk for development of hypertension is considerable and represents a major public health issue (97). Elevated blood pressure is a major risk factor for the development of both HF*p*EF and HF*r*EF (91, 92), a risk that extends across all age ranges. Long-term treatment of both systolic and diastolic hypertension has been shown to reduce the risk of incident HF by approximately 50% (94, 311-314). Treatment of hypertension is particularly beneficial in older patients (311). One trial of a diuretic-based program demonstrated a number

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needed to treat of 52 to prevent 1 HF event in 2 years (311). In another study, elderly patients with a history or ECG evidence of prior MI had a >80% risk reduction for incident HF with aggressive blood pressure control (94). Given the robust outcomes with blood pressure reduction, clinicians should lower both systolic and diastolic blood pressure in accordance with published guidelines (27).

Choice of antihypertensive therapy should also follow guidelines (27), with specific options tailored to concomitant medical problems, such as diabetes mellitus or CAD. Diuretic-based antihypertensive therapy has repeatedly been shown to prevent HF in a wide range of patients; ACE inhibitors, ARBs, and beta blockers are also effective. Data are less clear for calcium antagonists and alpha blockers in reducing the risk for incident HF.

7.1.2. Treatment of Dyslipidemia and Vascular Risk

Patients with known atherosclerotic disease are likely to develop HF. Clinicians should seek to control vascular risk factors in such patients according to guidelines (28). Aggressive treatment of hyperlipidemia with statins reduces the likelihood of HF in at-risk patients (315, 316). Long-term treatment with ACE inhibitors in similar patients may also decrease the risk of HF (314, 317).

7.1.3. Obesity and Diabetes Mellitus

Obesity and overweight have been repeatedly linked to an increased risk for HF (99, 318, 319). Presumably, the link between obesity and risk for HF is explained by the clustering of risk factors for heart disease in those with elevated BMI, (i.e., the metabolic syndrome). Similarly, insulin resistance, with or without diabetes mellitus, is also an important risk factor for the development of HF (92, 320-323). Diabetes mellitus is an especially important risk factor for women and may, in fact, triple the risk for developing HF (91, 324). Dysglycemia appears to be directly linked to risk, with HbA1c concentrations powerfully predicting incident HF. Those with HbA1c >10.5% had a nearly 4-fold increase in the risk for HF compared with those with a value of <6.5% (322). Current consensus advocates that clinicians should make every effort to control hyperglycemia, although such control has not yet been shown to reduce the subsequent risk of HF. Additionally, standard therapies for diabetes mellitus, such as use of ACE inhibitors or ARBs, can prevent the development of other risk factors for HF, such as renal dysfunction (325, 326), and may themselves directly lower the likelihood of HF (327-329). Although risk models for the development of incident HF in patients with diabetes mellitus have been developed (323), their prospective use to reduce risk has not been validated. Despite the lack of supportive, prospective, randomized data, consensus exists that risk factor recognition and modification are vital for the prevention of HF among at-risk patients (e.g., obese patients or patients with diabetes mellitus).

7.1.4. Recognition and Control of Other Conditions That May Lead to HF

A substantial genetic risk exists in some patients for the development of HF. As noted in Section 6.1, obtaining a 3-generation family history of HF is recommended. Adequate therapy of AF is advisable, given a clear association between uncontrolled heart rate and development of HF. Many therapeutic agents can exert

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important cardiotoxic effects, with consequent risk for HF, and clinicians should be aware of such risk. For example, cardiotoxic chemotherapy regimens and trastuzumab (particularly anthracycline based) may increase the risk for HF in certain patients (330-332); it may be reasonable to evaluate those who are receiving (or who have received) such agents for LV dysfunction. The use of advanced echocardiographic techniques or biomarkers to identify increased HF risk in those receiving chemotherapy may be useful (333) but remain unvalidated as yet.

Tobacco use is strongly associated with risk for incident HF (92, 320, 334), and patients should be strongly advised about the hazards of smoking, with attendant efforts at quitting. Cocaine and amphetamines are anecdotally but strongly associated with HF, and their avoidance is mandatory. Although it is recognized that alcohol consumption is associated with subsequent development of HF (92, 139, 140), there is some uncertainty about the amount of alcohol ingested and the likelihood of developing HF, and there may be sex differences as well. Nevertheless, the heavy use of alcohol has repeatedly been associated with heightened risk for development of HF. Therefore, patients should be counseled about their alcohol intake.

Although several epidemiological studies have revealed an independent link between risk for incident HF and biomarkers such as natriuretic peptides (335, 336), highly sensitive troponin (337), and measures of renal function such as creatinine, phosphorus, urinary albumin, or albumin-creatinine ratio (320, 323, 334, 336, 338-340), it remains unclear whether the risk for HF reflected by any of these biomarkers is modifiable. Although routine screening with BNP before echocardiography may be a cost-effective strategy to identify high-risk patients (341), routine measurement of biomarkers in stage A patients is not yet justified.

See Online Data Supplement 11 (http://jaccjacc.cardiosource.com/DataSupp/ACCF/2013_HFGL_Evidence_Tables.pdf) for additional data on stage A HF.

7.2. Stage B: Recommendations

See Table 12 for a summary of recommendations from this section.

Class I

1. **In all patients with a recent or remote history of MI or ACS and reduced EF, ACE inhibitors should be used to prevent symptomatic HF and reduce mortality (342-344). In patients intolerant of ACE inhibitors, ARBs are appropriate unless contraindicated (314, 345).** ***(Level of Evidence: A)***
2. **In all patients with a recent or remote history of MI or ACS and reduced EF, evidence-based beta blockers should be used to reduce mortality (346-348).** ***(Level of Evidence: B)***
3. **In all patients with a recent or remote history of MI or ACS, statins should be used to prevent symptomatic HF and cardiovascular events (104, 349-354).** ***(Level of Evidence: A)***
4. **In patients with structural cardiac abnormalities, including LV hypertrophy, in the absence of a history of MI or ACS, blood pressure should be controlled in accordance with clinical practice guidelines for hypertension to prevent symptomatic HF (27, 94, 311-313).** ***(Level of Evidence: A)***
5. **ACE inhibitors should be used in all patients with a reduced EF to prevent symptomatic HF, even if they do not have a history of MI (65, 344).** ***(Level of Evidence: A)***
6. **Beta blockers should be used in all patients with a reduced EF to prevent symptomatic HF, even if they do not have a history of MI.** ***(Level of Evidence: C)***

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Class IIa

1. **To prevent sudden death, placement of an ICD is reasonable in patients with asymptomatic ischemic cardiomyopathy who are at least 40 days post-MI, have an LVEF of 30% or less, are on appropriate medical therapy, and have reasonable expectation of survival with a good functional status for more than 1 year (355).** ***(Level of Evidence: B)***

Class III: Harm

1. **Nondihydropyridine calcium channel blockers with negative inotropic effects may be harmful in asymptomatic patients with low LVEF and no symptoms of HF after MI.** ***(Level of Evidence: C)***

Patients with reduced LVEF may not have HF symptoms and are most often identified during an evaluation for another disorder (e.g., abnormal heart sounds, abnormal ECG, abnormal chest x-ray, hypertension or hypotension, an arrhythmia, acute MI, or pulmonary or systemic thromboembolic event). However, the cost-effectiveness of routine periodic population screening for asymptomatic reduced LVEF is not recommended at this time. Echocardiographic evaluation should be performed in selected patients who are at high risk of reduced LVEF (e.g., those with a strong family history of cardiomyopathy, long-standing hypertension, previous MI, or those receiving cardiotoxic therapies). In addition, it should be acknowledged that many adults may have asymptomatic valvular abnormalities or congenital heart lesions that if unrecognized could lead to the development of clinical HF. Although these asymptomatic patients are in stage B as well, the management of valvular and congenital heart disease is beyond the scope of this guideline.

7.2.1. Management Strategies for Stage B

In general, all recommendations for patients with stage A HF also apply to those with stage B HF, particularly with respect to control of blood pressure in the patient with LV hypertrophy (27, 94, 311, 312) and the optimization of lipids with statins (349, 356). CAD is a major risk factor for the development of HF and a key target for prevention of HF. The 5-year risk of developing HF after acute MI is 7% and 12% for men and women, respectively; for men and women between the ages of 40 and 69 and those >70 years of age, the risk is 22% and 25%, respectively (51). Current evidence supports the use of ACE inhibitors and (to a lower level of evidence) beta-blocker therapy to impede maladaptive LV remodeling in patients with stage B HF and low LVEF to improve mortality and morbidity (344). At 3-year follow-up, those patients treated with ACE inhibitors demonstrated combined endpoints of reduced hospitalization or death, a benefit that extended up to a 12-year follow-up (65). ARBs are reasonable alternatives to ACE inhibitors. In 1 study, losartan reduced adverse outcomes in a population with hypertension (357), and in another study of patients post-MI with low LVEF, valsartan was equivalent to captopril (345). Data with beta blockers are less convincing in a population with known CAD, although in 1 trial (346) carvedilol therapy in patients with stage B and low LVEF was associated with a 31% relative risk reduction in adverse long-term outcomes. In patients with previously established

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structural heart disease, the administration of agents known to have negative inotropic properties such as nondihydropyridine calcium channel blockers and certain antiarrhythmics should be avoided.

Elevations in both systolic and diastolic blood pressure are major risk factors for developing LV hypertrophy, another form of stage B (91, 92). Although the magnitude of benefit varies with the trial selection criteria, target blood pressure reduction, and HF criteria, effective hypertension treatment invariably reduces HF events. Consequently, long-term treatment of both systolic and diastolic hypertension reduces the risk of moving from stage A or B to stage C HF (93, 94, 311, 329). Several large controlled studies have uniformly demonstrated that optimal blood pressure control decreases the risk of new HF by approximately 50% (96). It is imperative that strategies to control hypertension be part of any effort to prevent HF.

Clinicians should lower both systolic and diastolic blood pressure in accordance with published guidelines (27). Target levels of blood pressure lowering depend on major cardiovascular risk factors, (e.g., CAD, diabetes mellitus, or renal disease) (358). Thus, when an antihypertensive regimen is devised, optimal control of blood pressure should remain the primary goal, with the choice of drugs determined by the concomitant medical problems.

Diuretic-based antihypertensive therapy has been shown to prevent HF in a wide range of target populations (359, 360). In refractory hypertensive patients, spironolactone (25 mg) should be considered as an additional agent (27). Eplerenone, in synergy with enalapril, has also demonstrated reduction in LV mass (361).

ACE inhibitors and beta blockers are also effective in the prevention of HF (27). Nevertheless, neither ACE inhibitors nor beta blockers as single therapies are superior to other antihypertensive drug classes, including calcium channel blockers, in the reduction of all cardiovascular outcomes. However, in patients with type 2 diabetes mellitus, ACE inhibitors and ARBs significantly reduced the incidence of HF in patients (327-329). In contrast, calcium channel blockers and alpha blockers were less effective in preventing the HF syndrome, particularly in HF*r*EF (359).

The Framingham studies have shown a 60% increased risk of death in patients with asymptomatic low LVEF compared with those with normal LVEF; almost half of these patients remained free of HF before their death (62-65). MADIT-II (Multicenter Automatic Defibrillator Implantation Trial II) (362) demonstrated a 31% relative risk reduction in all-cause mortality in patients with post-MI with LVEF ≤30% receiving a prophylactic ICD compared with standard of care (355). These findings provided justification for broad adoption of ICDs for primary prevention of SCD in the post-MI setting with reduced LVEF, even in the absence of HF symptoms, that is, patients in stage B HF.

Several other ACCF/AHA guidelines addressing the appropriate management of patients with stage B—those with cardiac structural abnormalities but no symptoms of HF—are listed in Table 13.

Table 12. Recommendations for Treatment of Stage B HF

TnQTable13ACE indicates angiotensin-converting enzyme; ARB, angiotensin-receptor blocker; COR, Class of Recommendation; EF, ejection fraction; GDMT, guideline-directed medical therapy; HF, heart failure; ICD, implantable

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cardioverter-defibrillator; LOE, Level of Evidence; LVEF, left ventricular ejection fraction; MI, myocardial infarction; and N/A, not available.

Table 13. Other ACCF/AHA Guidelines Addressing Patients With Stage B HF

TnQTable14ACCF indicates American College of Cardiology Foundation; AHA, American Heart Association; CABG, coronary artery bypass graft; GDMT, guideline-directed medical therapy; HF, heart failure; MI, myocardial infarction; PCI, percutaneous coronary intervention; SIHD, stable ischemic heart disease; STEMI, ST-elevation myocardial infarction; UA/NSTEMI, unstable angina/non–ST-elevation myocardial infarction; and VHD, valvular heart disease.

See Online Data Supplement 12 (http://jaccjacc.cardiosource.com/DataSupp/ACCF/2013_HFGL_Evidence_Tables.pdf) for additional data on stage B HF.

7.3. Stage C

See Online Data Supplement 13 (http://jaccjacc.cardiosource.com/DataSupp/ACCF/2013_HFGL_Evidence_Tables.pdf) for additional data on stage C HF.

7.3.1. Nonpharmacological Interventions

7.3.1.1. Education: Recommendation

Class I

1. **Patients with HF should receive specific education to facilitate HF self-care (363-368). *(Level of Evidence: B)***

The self-care regimen for patients with HF is complex and multifaceted (363). Patients need to understand how to monitor their symptoms and weight fluctuations, restrict their sodium intake, take their medications as prescribed, and stay physically active. Education regarding these recommendations is necessary, albeit not always sufficient, to significantly improve outcomes. After discharge, many patients with HF need disease management programs, which are reviewed in Section 11.

A systematic review of 35 educational intervention studies for patients with HF demonstrated that education improved knowledge, self-monitoring, medication adherence, time to hospitalization, and days in the hospital (363). Patients who receive in-hospital education have higher knowledge scores at discharge and 1 year later when compared with those who did not receive in-hospital education (364). Data have called into question the survival benefit of discharge education (369, 370). However, prior data have suggested that discharge education may result in fewer days of hospitalization, lower costs, and lower mortality rates within a 6-month follow-up (365). Patients educated in all 6 categories of the HF core measures from The Joint Commission were significantly less likely to be readmitted for any cause, including HF (366). Even a single home-based educational intervention for patients and families has been shown to decrease emergency visits and unplanned hospitalizations in adults with HF (367).

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See Online Data Supplement 14 (http://jaccjacc.cardiosource.com/DataSupp/ACCF/2013_HFGL_Evidence_Tables.pdf) for additional data on patient nonadherence.

7.3.1.2. Social Support

Social support is thought to buffer stress and promote treatment adherence and a healthy lifestyle (371). Most studies examining the relationship between social support and hospitalization in adults with HF have found that a lack of social support is associated with higher hospitalization rates (372, 373)_ENREF_3 and mortality risk (374, 375). _ENREF_5

7.3.1.3. Sodium Restriction: Recommendation

Class IIa

1. **Sodium restriction is reasonable for patients with symptomatic HF to reduce congestive symptoms. (*Level of Evidence: C*)**

Dietary sodium restriction is commonly recommended to patients with HF and is endorsed by many guidelines (18, 376, 377). The data on which this recommendation is drawn upon, however, are modest, and variances in protocols, fluid intake, measurement of sodium intake and compliance, and other clinical and therapeutic characteristics among these studies make it challenging to compare data and draw definitive conclusions. Observational data suggest an association between dietary sodium intake with fluid retention and risk for hospitalization (378, 379). Other studies, however, have signaled a worsening neurohormonal profile with sodium restriction in HF (380-390). Sodium homeostasis is altered in patients with HF as opposed to healthy individuals, which may partially explain these trends. In most of these studies, patients were not receiving GDMT; no study to date has evaluated the effects of sodium restriction on neurohormonal activation and outcomes in optimally treated patients with HF. With the exception of 1 observational study that evaluated patients with HF*p*EF (383), all other studies have focused on patients with HF*r*EF. These data are mostly from white patients; when the differences in cardiovascular and renal pathophysiology among races are considered, the effects of sodium restriction in nonwhite patients with HF cannot be ascertained from these studies. To make this more complicated, the 3 RCTs that assessed outcomes with sodium restriction have all shown that lower sodium intake is associated with worse outcomes in patients with HF*r*EF (384-386).

These limitations make it difficult to give precise recommendations about daily sodium intake and whether it should vary with respect to the type of HF (e.g., HF*r*EF versus HF*p*EF), disease severity (e.g., NYHA class), HF-related comorbidities (e.g., renal dysfunction), or other characteristics (e.g., age or race). Because of the association between sodium intake and hypertension, LV hypertrophy, and cardiovascular disease, the AHA recommendation for restriction of sodium to 1,500 mg/d appears to be appropriate for most patients with stage A and B HF (387-392). However, for patients with stage C and D HF, currently there are insufficient data to

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endorse any specific level of sodium intake. Because sodium intake is typically high (>4 g/d) in the general population, clinicians should consider some degree (e.g., <3 g) of sodium restriction in patients with stage C and D HF for symptom improvement.

7.3.1.4. Treatment of Sleep Disorders: Recommendation

Class IIa

1. **Continuous positive airway pressure (CPAP) can be beneficial to increase LVEF and improve functional status in patients with HF and sleep apnea (393-396)** _ENREF_2**.** ***(Level of Evidence: B)***

Sleep disorders are common in patients with HF. A study of adults with chronic HF treated with evidence-based therapies found that 61% had either central or obstructive sleep apnea (397). Despite having less sleep time and sleep efficiency compared with those without HF, patients with HF, including those with documented sleep disorders, rarely report excessive daytime sleepiness (398). Thus, a high degree of suspicion for sleep disorders should be maintained for these patients. The decision to refer a patient to a sleep study should be based on clinical judgment.

The primary treatment for obstructive sleep apnea is nocturnal CPAP. In a major trial, CPAP for obstructive sleep apnea was effective in decreasing the apnea–hypopnea index, improving nocturnal oxygenation, increasing LVEF, lowering norepinephrine levels, and increasing the distance walked in 6 minutes; these benefits were sustained for up to 2 years (394). Smaller studies suggest that CPAP can improve cardiac function, sympathetic activity, and HRQOL in patients with HF and obstructive sleep apnea (395, 396).

See Online Data Supplement 15 (http://jaccjacc.cardiosource.com/DataSupp/ACCF/2013_HFGL_Evidence_Tables.pdf) for additional data on the treatment of sleep disorders.

7.3.1.5. Weight Loss

Obesity is defined as a BMI ≥30 kg/m^2. Patients with HF who have a BMI between 30 and 35 kg/m^2 have lower mortality and hospitalization rates than those with a BMI in the normal range (99). Weight loss may reflect cachexia caused by the higher total energy expenditure associated with HF compared with that of healthy sedentary subjects (399). _ENREF_2 The diagnosis of cardiac cachexia independently predicts a worse prognosis (191). _ENREF_3 At the other end of the continuum, morbidly obese patients may have worse outcomes compared with patients within the normal weight range and those who are obese. A U-shaped distribution curve has been suggested in which mortality is greatest in cachectic patients; lower in normal, overweight, and mildly obese patients; and higher again in more severely obese patients (400).

Although there are anecdotal reports about symptomatic improvement after weight reduction in obese patients with HF (401, 402), large-scale clinical trials on the role of weight loss in patients with HF with obesity

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have not been performed. Because of reports of development of cardiomyopathy, sibutramine is contraindicated in HF (403).

7.3.1.6. Activity, Exercise Prescription, and Cardiac Rehabilitation: Recommendations

Class I

1. **Exercise training (or regular physical activity) is recommended as safe and effective for patients with HF who are able to participate to improve functional status (404-407).** ***(Level of Evidence: A)***

Class IIa

1. **Cardiac rehabilitation can be useful in clinically stable patients with HF to improve functional capacity, exercise duration, HRQOL, and mortality (404, 406-411).** ***(Level of Evidence: B)***

Exercise training in patients with HF is safe and has numerous benefits. Meta-analyses show that cardiac rehabilitation reduces mortality; improves functional capacity, exercise duration, and HRQOL; and reduces hospitalizations (409). Other benefits include improved endothelial function, blunted catecholamine spillover, increased peripheral oxygen extraction, and reduced hospital admission (405, 407, 410, 411).

Many RCTs of exercise training in HF have been conducted, but the statistical power of most was low (408). A major trial of exercise and HF randomly assigned 2,331 patients (mean EF, 25%; ischemic etiology, 52%) to either exercise training for 3 months versus usual care (406). In unadjusted analyses, there was no significant difference at the end of the study in either total mortality or hospitalizations. When adjusted for coronary heart disease risk factors, there was an 11% reduction in all-cause mortality, cardiovascular disease mortality, or hospitalizations ($p<0.03$) in the exercise training group (406). A meta-analysis demonstrated improved peak oxygen consumption and decreased all-cause mortality with exercise (409).

See Online Data Supplement 16 (http://jaccjacc.cardiosource.com/DataSupp/ACCF/2013_HFGL_Evidence_Tables.pdf) for additional data on cardiac exercise.

7.3.2. Pharmacological Treatment for Stage C HF*r*EF: Recommendations

Class I

1. **Measures listed as Class I recommendations for patients in stages A and B are recommended where appropriate for patients in stage C. (*Levels of Evidence: A, B, and C as appropriate*)**
2. **GDMT as depicted in Figure 1 should be the mainstay of pharmacological therapy for HF*r*EF (108, 343, 345, 346, 412-426).** ***(Level of Evidence: A)***

Figure 1. Stage C HF*r*EF: evidence-based, guideline-directed medical therapy.

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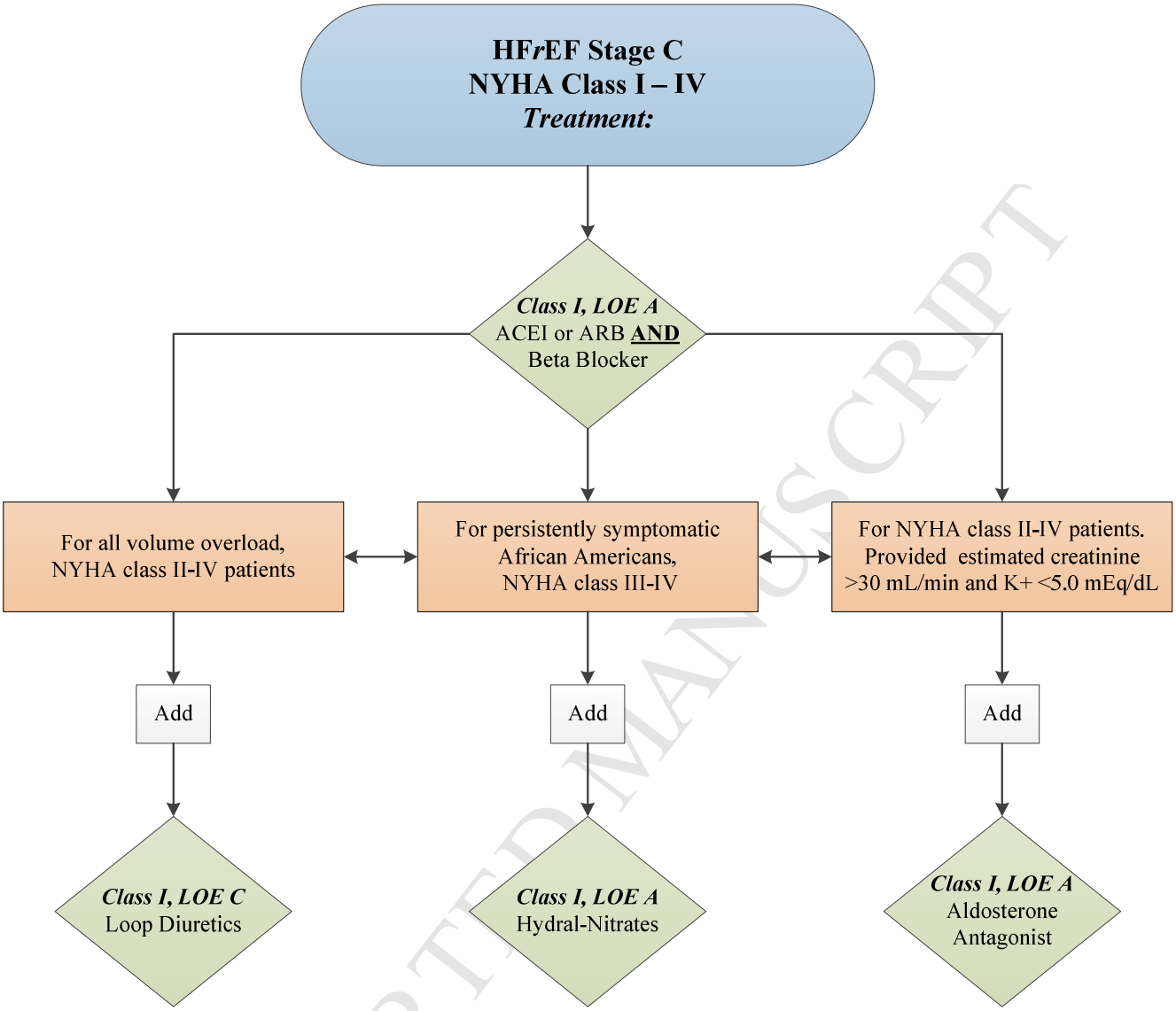

ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; HF*r*EF, heart failure with reduced ejection fraction; Hydral-Nitrates, hydralazine and isosorbide dinitrate; LOE, Level of Evidence; and NYHA, New York Heart Association.

7.3.2.1. Diuretics: Recommendation

Class I

1. **Diuretics are recommended in patients with HF*r*EF who have evidence of fluid retention, unless contraindicated, to improve symptoms. (*Level of Evidence: C*)**

Diuretics inhibit the reabsorption of sodium or chloride at specific sites in the renal tubules. Bumetanide, furosemide, and torsemide act at the loop of Henle (thus, the term loop diuretics), whereas thiazides, metolazone, and potassium-sparing agents (e.g., spironolactone) act in the distal portion of the tubule (427, 428). Loop diuretics have emerged as the preferred diuretic agents for use in most patients with HF. Thiazide diuretics

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may be considered in hypertensive patients with HF and mild fluid retention because they confer more persistent antihypertensive effects.

Controlled trials have demonstrated the ability of diuretic drugs to increase urinary sodium excretion and decrease physical signs of fluid retention in patients with HF (429, 430). In intermediate-term studies, diuretics have been shown to improve symptoms and exercise tolerance in patients with HF (431-433); however, diuretic effects on morbidity and mortality are not known. Diuretics are the only drugs used for the treatment of HF that can adequately control the fluid retention of HF. Appropriate use of diuretics is a key element in the success of other drugs used for the treatment of HF. The use of inappropriately low doses of diuretics will result in fluid retention. Conversely, the use of inappropriately high doses of diuretics will lead to volume contraction, which can increase the risk of hypotension and renal insufficiency.

7.3.2.1.1. Diuretics: Selection of Patients

Diuretics should be prescribed to all patients who have evidence of, and to most patients with a prior history of, fluid retention. Diuretics should generally be combined with an ACE inhibitor, beta blocker, and aldosterone antagonist. Few patients with HF will be able to maintain target weight without the use of diuretics.

7.3.2.1.2. Diuretics: Initiation and Maintenance

The most commonly used loop diuretic for the treatment of HF is furosemide, but some patients respond more favorably to other agents in this category (e.g., bumetanide, torsemide) because of their increased oral bioavailability (434, 435). Table 14 lists oral diuretics recommended for use in the treatment of chronic HF. In outpatients with HF, diuretic therapy is commonly initiated with low doses, and the dose is increased until urine output increases and weight decreases, generally by 0.5 to 1.0 kg daily. Further increases in the dose or frequency (i.e., twice-daily dosing) of diuretic administration may be required to maintain an active diuresis and sustain weight loss. The ultimate goal of diuretic treatment is to eliminate clinical evidence of fluid retention. Diuretics are generally combined with moderate dietary sodium restriction. Once fluid retention has resolved, treatment with the diuretic should be maintained in some patients to prevent the recurrence of volume overload. Patients are commonly prescribed a fixed dose of diuretic, but the dose of these drugs frequently may need adjustment. In many cases, this adjustment can be accomplished by having patients record their weight each day and adjusting the diuretic dosage if weight increases or decreases beyond a specified range. Patients may become unresponsive to high doses of diuretic drugs if they consume large amounts of dietary sodium, are taking agents that can block the effects of diuretics (e.g., nonsteroidal anti-inflammatory drugs [NSAIDs], including cyclo-oxygenase-2 inhibitors) (436-438) or have a significant impairment of renal function or perfusion (434). Diuretic resistance can generally be overcome by the intravenous administration of diuretics (including the use of continuous infusions) (439) or combination of different diuretic classes (e.g., metolazone with a loop diuretic) (440-443).

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7.3.2.1.3. Diuretics: Risks of Treatment

The principal adverse effects of diuretics include electrolyte and fluid depletion, as well as hypotension and azotemia. Diuretics can cause the depletion of potassium and magnesium, which can predispose patients to serious cardiac arrhythmias (444). The risk of electrolyte depletion is markedly enhanced when 2 diuretics are used in combination.

Table 14. Oral Diuretics Recommended for Use in the Treatment of Chronic HF
TnQTable15*Eplerenone, although also a diuretic, is primarily used in chronic HF.
†Higher doses may occasionally be used with close monitoring.
HF indicates heart failure; IV, intravenous; and N/A, not applicable.

See Online Data Supplement 17 (http://jaccjacc.cardiosource.com/DataSupp/ACCF/2013_HFGL_Evidence_Tables.pdf) for additional data on diuretics.

7.3.2.2. ACE Inhibitors: Recommendation

Class I

1. **ACE inhibitors are recommended in patients with HF*r*EF and current or prior symptoms, unless contraindicated, to reduce morbidity and mortality (343, 412-414). (*Level of Evidence: A*)**

7.3.2.2.1. ACE Inhibitors: Selection of Patients

ACE inhibitors can reduce the risk of death and reduce hospitalization in HF*r*EF. The benefits of ACE inhibition were seen in patients with mild, moderate, or severe symptoms of HF and in patients with or without CAD. ACE inhibitors should be prescribed to all patients with HF*r*EF. Unless there is a contraindication, ACE inhibitors are used together with a beta blocker. Patients should not be given an ACE inhibitor if they have experienced life-threatening adverse reactions (i.e., angioedema) during previous medication exposure or if they are pregnant or plan to become pregnant. Clinicians should prescribe an ACE inhibitor with caution if the patient has very low systemic blood pressures (systolic blood pressure <80 mm Hg), markedly increased serum levels of creatinine (>3 mg/dL), bilateral renal artery stenosis, or elevated levels of serum potassium (>5.0 mEq/L).

7.3.2.2.2. ACE Inhibitors: Initiation and Maintenance

The available data suggest that there are no differences among available ACE inhibitors in their effects on symptoms or survival (414). Treatment with an ACE inhibitor should be initiated at low doses (Table 15), followed by gradual dose increments if lower doses have been well tolerated. Renal function and serum potassium should be assessed within 1 to 2 weeks of initiation of therapy and periodically thereafter, especially in patients with preexisting hypotension, hyponatremia, diabetes mellitus, azotemia, or in those taking potassium supplements. In controlled clinical trials that were designed to evaluate survival, the dose of the ACE inhibitor

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was not determined by a patient's therapeutic response but was increased until the predetermined target dose was reached (343, 413, 414). Clinicians should attempt to use doses that have been shown to reduce the risk of cardiovascular events in clinical trials. If these target doses of an ACE inhibitor cannot be used or are poorly tolerated, intermediate doses should be used with the expectation that there are likely to be only small differences in efficacy between low and high doses. Abrupt withdrawal of treatment with an ACE inhibitor can lead to clinical deterioration and should be avoided.

7.3.2.2.3. ACE Inhibitors: Risks of Treatment

The majority of the adverse reactions of ACE inhibitors can be attributed to the 2 principal pharmacological actions of these drugs: those related to angiotensin suppression and those related to kinin potentiation. Other types of adverse effects may also occur (e.g., rash and taste disturbances). Up to 20% of patients will experience an ACE inhibitor–induced cough. With the use of ACE inhibitors, particular care should be given to the patient's volume status, renal function, and concomitant medications (Sections 7.3.2.1 and 7.3.2.9). However, most HF patients (85% to 90%) can tolerate these drugs.

See Online Data Supplement 18 (http://jaccjacc.cardiosource.com/DataSupp/ACCF/2013_HFGL_Evidence_Tables.pdf) for additional data on ACE inhibitors.

Table 15. Drugs Commonly Used for Stage C HF*r*EF
TnQTable16ACE indicates angiotensin-converting enzyme; ARB, angiotensin-receptor blocker; CR, controlled release; CR/XL, controlled release/extended release; HF*r*EF, heart failure with reduced ejection fraction; and N/A, not applicable.

7.3.2.3. ARBs: Recommendations

Class I

1. **ARBs are recommended in patients with HF*r*EF with current or prior symptoms who are ACE inhibitor intolerant, unless contraindicated, to reduce morbidity and mortality (108, 345, 415, 450). (*Level of Evidence: A*)**

Class IIa

1. **ARBs are reasonable to reduce morbidity and mortality as alternatives to ACE inhibitors as first-line therapy for patients with HF*r*EF, especially for patients already taking ARBs for other indications, unless contraindicated (451-456). (*Level of Evidence: A*)**

Class llb

1. **Addition of an ARB may be considered in persistently symptomatic patients with HF*r*EF who are already being treated with an ACE inhibitor and a beta blocker in whom an aldosterone antagonist is not indicated or tolerated (420, 457). (*Level of Evidence: A*)**

Class III: Harm

1. **Routine *combined* use of an ACE inhibitor, ARB, and aldosterone antagonist is potentially harmful for patients with HF*r*EF. (*Level of Evidence: C*)**

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ARBs were developed with the rationale that a) angiotensin II production continues in the presence of ACE inhibition, driven through alternative enzyme pathways and b) interference with the renin-angiotensin system without inhibition of kininase would produce all of the benefits of ACE inhibitors while minimizing the risk of adverse reactions to them. However, it is now known that some of the benefits of ACE inhibitors may be related to the accumulation of kinins rather than to the suppression of angiotensin II formation, whereas some of the adverse effects of ACE inhibitors in HF are related to the suppression of angiotensin II formation.

In several placebo-controlled studies, long-term therapy with ARBs produced hemodynamic, neurohormonal, and clinical effects consistent with those expected after interference with the renin-angiotensin system. Reduced hospitalization and mortality have been demonstrated. ACE inhibitors remain the first choice for inhibition of the renin-angiotensin system in systolic HF, but ARBs can now be considered a reasonable alternative.

7.3.2.3.1. ARBs: Selection of Patients

ARBs are used in patients with HF*r*EF who are ACE inhibitor intolerant; an ACE-inhibition intolerance primarily related to cough is the most common indication. In addition, an ARB may be used as an alternative to an ACE inhibitor in patients who are already taking an ARB for another reason, such as hypertension, and who subsequently develop HF. Angioedema occurs in <1% of patients who take an ACE inhibitor, but it occurs more frequently in blacks. Because its occurrence may be life-threatening, clinical suspicion of this reaction justifies the subsequent avoidance of all ACE inhibitors for the lifetime of the patient. ACE inhibitors should not be initiated in any patient with a history of angioedema. Although ARBs may be considered as alternative therapy for patients who have developed angioedema while taking an ACE inhibitor, there are some patients who have also developed angioedema with ARBs, and caution is advised when substituting an ARB in a patient who has had angioedema associated with use of an ACE inhibitor (458-461).

7.3.2.3.2. ARBs: Initiation and Maintenance

When used, ARBs should be initiated with the starting doses shown in Table 15. Many of the considerations with initiation of an ARB are similar to those with initiation of an ACE inhibitor, as discussed previously. Blood pressure (including postural blood pressure changes), renal function, and potassium should be reassessed within 1 to 2 weeks after initiation and followed closely after changes in dose. Patients with systolic blood pressure <80 mm Hg, low serum sodium, diabetes mellitus, and impaired renal function merit close surveillance during therapy with inhibitors of the renin angiotensin-aldosterone system. Titration is generally achieved by doubling doses. For stable patients, it is reasonable to add therapy with beta-blocking agents before full target doses of either ACE inhibitors or ARBs are reached.

7.3.2.3.3. ARBs: Risks of Treatment

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The risks of ARBs are attributed to suppression of angiotensin stimulation. These risks of hypotension, renal dysfunction, and hyperkalemia are greater when combined with another inhibitor of this neurohormonal axis, such as ACE inhibitors or aldosterone antagonists.

See Online Data Supplement 19 (http://jaccjacc.cardiosource.com/DataSupp/ACCF/2013_HFGL_Evidence_Tables.pdf) for additional data on ARBs.

7.3.2.4. Beta Blockers: Recommendation

Class I

1. **Use of 1 of the 3 beta blockers proven to reduce mortality (i.e., bisoprolol, carvedilol, and sustained-release metoprolol succinate) is recommended for all patients with current or prior symptoms of HF*r*EF, unless contraindicated, to reduce morbidity and mortality (346, 416-419, 448). (*Level of Evidence: A*)**

Long-term treatment with beta blockers can lessen the symptoms of HF, improve the patient's clinical status, and enhance the patient's overall sense of well-being (462-469). In addition, like ACE inhibitors, beta blockers can reduce the risk of death and the combined risk of death or hospitalization (117, 447, 448, 470, 471). These benefits of beta blockers were seen in patients with or without CAD and in patients with or without diabetes mellitus, as well as in women and blacks. The favorable effects of beta blockers were also observed in patients already taking ACE inhibitors.

Three beta blockers have been shown to be effective in reducing the risk of death in patients with chronic HF*r*EF: bisoprolol and sustained-release metoprolol (succinate), which selectively block beta-1–receptors; and carvedilol, which blocks alpha-1–, beta-1–, and beta-2–receptors. Positive findings with these 3 agents, however, should not be considered a beta-blocker class effect. Bucindolol lacked uniform effectiveness across different populations, and short-acting metoprolol tartrate was less effective in HF clinical trials. Beta-1 selective blocker nebivolol demonstrated a modest reduction in the primary endpoint of all-cause mortality or cardiovascular hospitalization but did not affect mortality alone in an elderly population that included patients with HF*p*EF (472).

7.3.2.4.1. Beta Blockers: Selection of Patients

Beta blockers should be prescribed to all patients with stable HF*r*EF unless they have a contraindication to their use or are intolerant of these drugs. Because of its favorable effects on survival and disease progression, a clinical trial–proven beta blocker should be initiated as soon as HF*r*EF is diagnosed. Even when symptoms are mild or improve with other therapies, beta-blocker therapy is important and should not be delayed until symptoms return or disease progression is documented. Therefore, even if patients have little disability and

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experience seemingly minimal symptomatic benefit, they should still be treated with a beta blocker to reduce the risks of disease progression, clinical deterioration, and sudden death (117, 448, 469-471).

Patients need not take high doses of ACE inhibitors before initiation of beta-blocker therapy. In patients taking a low dose of an ACE inhibitor, the addition of a beta blocker produces a greater improvement in symptoms and reduction in the risk of death than does an increase in the dose of the ACE inhibitor, even to the target doses used in clinical trials (445, 473). In patients with a current or recent history of fluid retention, beta blockers should not be prescribed without diuretics, because diuretics are needed to maintain sodium and fluid balance and prevent the exacerbation of fluid retention that can accompany the initiation of beta-blocker therapy (474, 475). Beta blockers may be considered in patients who have reactive airway disease or asymptomatic bradycardia but should be used cautiously in patients with persistent symptoms of either condition.

7.3.2.4.2. Beta Blockers: Initiation and Maintenance

Treatment with a beta blocker should be initiated at very low doses (Table 15), followed by gradual increments in dose if lower doses have been well tolerated. Patients should be monitored closely for changes in vital signs and symptoms during this uptitration period. Planned increments in the dose of a beta blocker should be delayed until any adverse effects observed with lower doses have disappeared. When such a cautious approach was used, most patients (approximately 85%) enrolled in clinical trials who received beta blockers were able to tolerate short- and long-term treatment with these drugs and achieve the maximum planned trial dose (117, 447, 448, 470). Data show that beta blockers can be safely started before discharge even in patients hospitalized for HF, provided they do not require intravenous inotropic therapy for HF (476). Clinicians should make every effort to achieve the target doses of the beta blockers shown to be effective in major clinical trials. Even if symptoms do not improve, long-term treatment should be maintained to reduce the risk of major clinical events. Abrupt withdrawal of treatment with a beta blocker can lead to clinical deterioration and should be avoided (477).

7.3.2.4.3. Beta Blockers: Risks of Treatment

Initiation of treatment with a beta blocker may produce 4 types of adverse reactions that require attention and management: fluid retention and worsening HF; fatigue; bradycardia or heart block; and hypotension. The occurrence of fluid retention or worsening HF is not generally a reason for the permanent withdrawal of treatment. Such patients generally respond favorably to intensification of conventional therapy, and once treated, they remain excellent candidates for long-term treatment with a beta blocker. The slowing of heart rate and cardiac conduction produced by beta blockers is generally asymptomatic and thus requires no treatment; however, if the bradycardia is accompanied by dizziness or lightheadedness or if second- or third-degree heart block occurs, clinicians should decrease the dose of the beta blocker. Clinicians may minimize the risk of hypotension by administering the beta blocker and ACE inhibitor at different times during the day. Hypotensive symptoms may also resolve after a decrease in the dose of diuretics in patients who are volume depleted. If

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hypotension is accompanied by other clinical evidence of hypoperfusion, beta-blocker therapy should be decreased or discontinued pending further patient evaluation. The symptom of fatigue is multifactorial and is perhaps the hardest symptom to address with confidence. Although fatigue may be related to beta blockers, other causes of fatigue should be considered, including sleep apnea, overdiuresis, or depression.

See Online Data Supplement 20 (http://jaccjacc.cardiosource.com/DataSupp/ACCF/2013_HFGL_Evidence_Tables.pdf) for additional data on beta blockers.

7.3.2.5. Aldosterone Receptor Antagonists: Recommendations

Class I

1. **Aldosterone receptor antagonists [or mineralocorticoid receptor antagonists] are recommended in patients with NYHA class II-IV and who have LVEF of 35% or less, unless contraindicated, to reduce morbidity and mortality. Patients with NYHA class II should have a history of prior cardiovascular hospitalization or elevated plasma natriuretic peptide levels to be considered for aldosterone receptor antagonists. Creatinine should be 2.5 mg/dL or less in men or 2.0 mg/dL or less in women (or estimated glomerular filtration rate >30 mL/min/1.73 m^2), and potassium should be less than 5.0 mEq/L. Careful monitoring of potassium, renal function, and diuretic dosing should be performed at initiation and closely followed thereafter to minimize risk of hyperkalemia and renal insufficiency (425, 426, 478).** ***(Level of Evidence: A)***
2. **Aldosterone receptor antagonists are recommended to reduce morbidity and mortality following an acute MI in patients who have LVEF of 40% or less who develop symptoms of HF or who have a history of diabetes mellitus, unless contraindicated (446).** ***(Level of Evidence: B)***

Class III: Harm

1. **Inappropriate use of aldosterone receptor antagonists is potentially harmful because of life-threatening hyperkalemia or renal insufficiency when serum creatinine is more than 2.5 mg/dL in men or more than 2.0 mg/dL in women (or estimated glomerular filtration rate <30 mL/min/1.73 m^2), and/or potassium more than 5.0 mEq/L (479, 480).** ***(Level of Evidence: B)***

The landmark RALES trial (Randomized Aldactone Evaluation Study) (425) showed a 30% reduction in all-cause mortality as well as a reduced risk of SCD and HF hospitalizations with the use of spironolactone in patients with chronic HF*r*EF and LVEF <35%. Eplerenone has been shown to reduce all-cause deaths, cardiovascular deaths, or HF hospitalizations in a wider range of patients with HF*r*EF (426, 446).

7.3.2.5.1. Aldosterone Receptor Antagonists: Selection of Patients

Clinicians should strongly consider the addition of the aldosterone receptor antagonists spironolactone or eplerenone for all patients with HF*r*EF who are already on ACE inhibitors (or ARBs) and beta blockers. Although the entry criteria for the trials of aldosterone receptor antagonists excluded patients with a creatinine >2.5 mg/dL, the majority of patients had much lower creatinine (95% of patients had creatinine ≤1.7 mg/dL) (425, 426, 446). In contrast, one third of patients in EMPHASIS-HF (Eplerenone in Mild Patients

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Hospitalization and Survival Study in Heart Failure) had an estimated glomerular filtration rate of <60 mL/min/1.73m^2 (426). Note also that the entry criteria for the EMPHASIS-HF trial were age of at least ≥55 years, NYHA class II symptoms, and an EF of no more than 30% (or, if >30% to 35%, a QRS duration of >130 ms on ECG). To minimize the risk of life-threatening hyperkalemia in euvolemic patients with HF*r*EF, patients should have initial serum creatinine <2.5 mg/dL (or an estimated glomerular filtration rate >30 mL/min/1.73 m^2) without recent worsening and serum potassium <5.0 mEq/L without a history of severe hyperkalemia. Careful patient selection and risk assessment with availability of close monitoring is essential in initiating the use of aldosterone receptor antagonists.

7.3.2.5.2. Aldosterone Receptor Antagonists: Initiation and Maintenance

Spironolactone should be initiated at a dose of 12.5 to 25 mg daily, while eplerenone should be initiated at a dose of 25 mg/d, increasing to 50 mg daily. For those with concerns of hyperkalemia or marginal renal function (estimated glomerular filtration rate 30 to 49 mL/min/1.73 m^2), an initial regimen of every-other-day dosing is advised (Table 16). After initiation of aldosterone receptor antagonists, potassium supplementation should be discontinued (or reduced and carefully monitored in those with a history of hypokalemia; Table 17), and patients should be counseled to avoid foods high in potassium and NSAIDs. Potassium levels and renal function should be rechecked within 2 to 3 days and again at 7 days after initiation of an aldosterone receptor antagonist. Subsequent monitoring should be dictated by the general clinical stability of renal function and fluid status but should occur at least monthly for the first 3 months and every 3 months thereafter. The addition or an increase in dosage of ACE inhibitors or ARBs should trigger a new cycle of monitoring.

There are limited data to support or refute that spironolactone and eplerenone are interchangeable. The perceived difference between eplerenone and spironolactone is the selectivity of aldosterone receptor antagonism and not the effectiveness of blocking mineralocorticoid activity. In RALES, there was increased incidence (10%) of gynecomastia or breast pain with use of spironolactone (a nonselective antagonist). The incidence of these adverse events was <1% in EPHESUS (Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study**)** and EMPHASIS-HF without any difference in adverse events between the eplerenone and placebo (426, 446).

Table 16. Drug Dosing for Aldosterone Receptor Antagonists

TnQTable17*After dose initiation for K^+, increase ≤6.0 mEq/L or worsening renal function, hold until K^+ <5.0 mEq/L. Consider restarting reduced dose after confirming resolution of hyperkalemia/renal insufficiency for at least 72 h.
eGFR indicates estimated glomerular filtration rate; and, K^+, potassium.
Adapted from Butler et al. (481).

Table 17. Strategies to Minimize the Risk of Hyperkalemia in Patients Treated With Aldosterone Antagonists

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TnQTable18*Although the entry criteria for the trials of aldosterone antagonists included creatinine <2.5 mg/dL, the majority of patients had much lower creatinine; in 1 trial (425), 95% of patients had creatinine ≤1.7 mg/dL.
ACE indicates angiotensin-converting enzyme.

7.3.2.5.3. Aldosterone Receptor Antagonists: Risks of Treatment

The major risk associated with use of aldosterone receptor antagonists is hyperkalemia due to inhibition of potassium excretion, ranging from 2% to 5% in large clinical trials (425, 426, 446), to 24% to 36% in population-based registries (479, 480). Routine triple combination of an ACE inhibitor, ARB, and aldosterone receptor antagonist should be avoided.

The development of potassium levels >5.5 mEq/L (approximately 12% in EMPHASIS-HF (426)) should generally trigger discontinuation or dose reduction of the aldosterone receptor antagonist unless other causes are identified. The development of worsening renal function should lead to careful evaluation of the entire medical regimen and consideration for stopping the aldosterone receptor antagonist. Patients should be instructed specifically to stop the aldosterone receptor antagonist during an episode of diarrhea or dehydration or while loop diuretic therapy is interrupted.

7.3.2.6. Hydralazine and Isosorbide Dinitrate: Recommendations

Class I

1. **The combination of hydralazine and isosorbide dinitrate is recommended to reduce morbidity and mortality for patients self-described as African Americans with NYHA class III–IV HF*r*EF receiving optimal therapy with ACE inhibitors and beta blockers, unless contraindicated (423, 424). (*Level of Evidence: A*)**

Class IIa

1. **A combination of hydralazine and isosorbide dinitrate can be useful to reduce morbidity or mortality in patients with current or prior symptomatic HF*r*EF who cannot be given an ACE inhibitor or ARB because of drug intolerance, hypotension, or renal insufficiency, unless contraindicated (449). (*Level of Evidence: B*)**

In a large-scale trial that compared the vasodilator combination with placebo, the use of hydralazine and isosorbide dinitrate reduced mortality but not hospitalizations in patients with HF treated with digoxin and diuretics but not an ACE inhibitor or beta blocker (449). However, in 2 other trials that compared the vasodilator combination with an ACE inhibitor, the ACE inhibitor produced more favorable effects on survival (412, 482). A post hoc retrospective analysis of these vasodilator trials demonstrated particular efficacy of isosorbide dinitrate and hydralazine in the African American cohort (423). In a subsequent trial, which was limited to patients self-described as African American, the addition of a fixed-dose combination of hydralazine and isosorbide dinitrate to standard therapy with an ACE inhibitor or ARB, a beta blocker, and an aldosterone antagonist offered significant benefit (424).

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7.3.2.6.1. Hydralazine and Isosorbide Dinitrate: Selection of Patients

The combination of hydralazine and isosorbide dinitrate is recommended for African Americans with HF*r*EF who remain symptomatic despite concomitant use of ACE inhibitors, beta blockers, and aldosterone antagonists. Whether this benefit is evident in non–African Americans with HF*r*EF remains to be investigated. The combination of hydralazine and isosorbide dinitrate should not be used for the treatment of HF*r*EF in patients who have no prior use of standard neurohumoral antagonist therapy and should not be substituted for ACE inhibitor or ARB therapy in patients who are tolerating therapy without difficulty. Despite the lack of data with the vasodilator combination in patients who are intolerant of ACE inhibitors or ARBs, the combined use of hydralazine and isosorbide dinitrate may be considered as a therapeutic option in such patients.

7.3.2.6.2. Hydralazine and Isosorbide Dinitrate: Initiation and Maintenance

If the fixed-dose combination is available, the initial dose should be 1 tablet containing 37.5 mg of hydralazine hydrochloride and 20 mg of isosorbide dinitrate 3 times daily. The dose can be increased to 2 tablets 3 times daily for a total daily dose of 225 mg of hydralazine hydrochloride and 120 mg of isosorbide dinitrate. When the 2 drugs are used separately, both pills should be administered at least 3 times daily. Initial low doses of the drugs given separately may be progressively increased to a goal similar to that achieved in the fixed-dose combination trial (424).

7.3.2.6.3. Hydralazine and Isosorbide Dinitrate: Risks of Treatment

Adherence to this combination has generally been poor because of the large number of tablets required, frequency of administration, and the high incidence of adverse reactions (412, 449). Frequent adverse effects include headache, dizziness, and gastrointestinal complaints. Nevertheless, the benefit of these drugs can be substantial and warrant a slower titration of the drugs to enhance tolerance of the therapy.

See Table 18 for a summary of the treatment benefit of GDMT in HF*r*EF.

Table 18. Medical Therapy for Stage C HF*r*EF: Magnitude of Benefit Demonstrated in RCTs
TnQTable19ACE indicates angiotensin-converting enzyme; ARB, angiotensin-receptor blocker; GDMT, guideline-directed medical therapy; HF, heart failure; HF*r*EF, heart failure with reduced ejection fraction; NNT, number needed to treat; RCTs, randomized controlled trials; and RR, relative risk.
Adapted with permission from Fonarow et al (483).

7.3.2.7. Digoxin: Recommendation

Class IIa

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1. **Digoxin can be beneficial in patients with HF*r*EF, unless contraindicated, to decrease hospitalizations for HF (484-491). (*Level of Evidence: B*)**

Several placebo-controlled trials have shown that treatment with digoxin for 1 to 3 months can improve symptoms, HRQOL, and exercise tolerance in patients with mild to moderate HF (485-491). These benefits have been seen regardless of the underlying rhythm (normal sinus rhythm or AF), cause of HF (ischemic or nonischemic cardiomyopathy), or concomitant therapy (with or without ACE inhibitors). In a long-term trial that primarily enrolled patients with NYHA class II or III HF, treatment with digoxin for 2 to 5 years had no effect on mortality but modestly reduced the combined risk of death and hospitalization (484).

7.3.2.7.1. Digoxin: Selection of Patients

Clinicians may consider adding digoxin in patients with persistent symptoms of HF*r*EF during GDMT. Digoxin may also be added to the initial regimen in patients with severe symptoms who have not yet responded symptomatically during GDMT.

Alternatively, treatment with digoxin may be delayed until the patient's response to GDMT has been defined and may be used only in patients who remain symptomatic despite therapy with the neurohormonal antagonists. If a patient is taking digoxin but not an ACE inhibitor or a beta blocker, treatment with digoxin should not be withdrawn, but appropriate therapy with the neurohormonal antagonists should be instituted. Digoxin is prescribed occasionally in patients with HF and AF, but beta blockers are usually more effective when added to digoxin in controlling the ventricular response, particularly during exercise (492-495).

Patients should not be given digoxin if they have significant sinus or atrioventricular block unless the block has been addressed with a permanent pacemaker. The drug should be used cautiously in patients taking other drugs that can depress sinus or atrioventricular nodal function or affect digoxin levels (e.g., amiodarone or a beta blocker), even though such patients usually tolerate digoxin without difficulty.

7.3.2.7.2. Digoxin: Initiation and Maintenance

Therapy with digoxin is commonly initiated and maintained at a dose of 0.125 to 0.25 mg daily. Low doses (0.125 mg daily or every other day) should be used initially if the patient is >70 years of age, has impaired renal function, or has a low lean body mass (496). Higher doses (e.g., digoxin 0.375 to 0.50 mg daily) are rarely used or needed in the management of patients with HF. There is no reason to use loading doses of digoxin to initiate therapy in patients with HF.

Doses of digoxin that achieve a plasma concentration of drug in the range of 0.5 to 0.9 ng/mL are suggested, given the limited evidence currently available. There has been no prospective, randomized evaluation of the relative efficacy or safety of different plasma concentrations of digoxin. Retrospective analysis of 2

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studies of digoxin withdrawal found that prevention of worsening HF by digoxin at lower concentrations in plasma (0.5 to 0.9 ng/mL) was as great as that achieved at higher concentrations (497, 498).

7.3.2.7.3. Digoxin: Risks of Treatment

When administered with attention to dose and factors that alter its metabolism, digoxin is well tolerated by most patients with HF (499). The principal adverse reactions occur primarily when digoxin is administered in large doses, especially in the elderly, but large doses are not necessary for clinical benefits (500-502). The major adverse effects include cardiac arrhythmias (e.g., ectopic and re-entrant cardiac rhythms and heart block), gastrointestinal symptoms (e.g., anorexia, nausea, and vomiting), and neurological complaints (e.g., visual disturbances, disorientation, and confusion). Overt digoxin toxicity is commonly associated with serum digoxin levels >2 ng/mL.

However, toxicity may also occur with lower digoxin levels, especially if hypokalemia, hypomagnesemia, or hypothyroidism coexists (503, 504). The concomitant use of clarithromycin, dronedarone, erythromycin, amiodarone, itraconazole, cyclosporine, propafenone, verapamil, or quinidine can increase serum digoxin concentrations and may increase the likelihood of digoxin toxicity (505-507). The dose of digoxin should be reduced if treatment with these drugs is initiated. In addition, a low lean body mass and impaired renal function can also elevate serum digoxin levels, which may explain the increased risk of digoxin toxicity in elderly patients.

7.3.2.8. Other Drug Treatment

7.3.2.8.1. Anticoagulation: Recommendations

Class I

1. **Patients with chronic HF with permanent/persistent/paroxysmal AF and an additional risk factor for cardioembolic stroke (history of hypertension, diabetes mellitus, previous stroke or transient ischemic attack, or ≥75 years of age) should receive chronic anticoagulant therapy* (508-514).** ***(Level of Evidence: A)***
2. **The selection of an anticoagulant agent (warfarin, dabigatran, apixaban, or rivaroxaban) for permanent/persistent/paroxysmal AF should be individualized on the basis of risk factors, cost, tolerability, patient preference, potential for drug interactions, and other clinical characteristics, including time in the international normalized ratio therapeutic range if the patient has been taking warfarin. (*Level of Evidence: C*)**

Class IIa

1. **Chronic anticoagulation is reasonable for patients with chronic HF who have permanent/persistent/paroxysmal AF but are without an additional risk factor for cardioembolic stroke* (509-511, 515-517).** ***(Level of Evidence: B)***

Class III: No Benefit

1. **Anticoagulation is not recommended in patients with chronic HF*r*EF without AF, a prior thromboembolic event, or a cardioembolic source (518-520).** ***(Level of Evidence: B)***

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**In the absence of contraindications to anticoagulation.*

Patients with chronic HF*r*EF are at an increased risk of thromboembolic events due to stasis of blood in dilated hypokinetic cardiac chambers and in peripheral blood vessels (521, 522) and perhaps due to increased activity of procoagulant factors (523). However, in large-scale studies, the risk of thromboembolism in clinically stable patients has been low (1% to 3% per year), even in those with a very depressed EF and echocardiographic evidence of intracardiac thrombi (524-528). These rates are sufficiently low to limit the detectable benefit of anticoagulation in these patients.

In several retrospective analyses, the risk of thromboembolic events was not lower in patients with HF taking warfarin than in patients not treated with antithrombotic drugs (524, 526, 527). The use of warfarin was associated with a reduction in major cardiovascular events and death in patients with HF in some studies but not in others (518, 529, 530). An RCT that compared the outcome of patients with HF*r*EF assigned to aspirin, warfarin, or clopidogrel was completed (519), but no therapy appeared to be superior. Another trial compared aspirin with warfarin in patients with reduced LVEF, sinus rhythm, and no cardioembolic source and demonstrated no difference in either the primary outcome of death, stroke, or intracerebral hemorrhage (520). There was also no difference in the combined outcome of death, ischemic stroke, intracerebral hemorrhage, MI, or HF hospitalization. There was a significant increase in major bleeding with warfarin. Given that there is no overall benefit of warfarin and an increased risk of bleeding, there is no compelling evidence to use warfarin or aspirin in patients with HF*r*EF in the absence of a specific indication.

The efficacy of long-term warfarin for the prevention of stroke in patients with AF is well established. However, the ACCF/AHA guidelines for chronic AF (6) recommend use of the $CHADS_2$ [Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, previous Stroke/transient ischemic attack (doubled risk weight)] score to assess patient risk for adverse outcomes before initiating anticoagulation therapy. More recently, a revised score, CHADS2-VASc, has been suggested as more applicable to a wider range of patients (531), but this revised score has not yet been fully studied in patients with HF. Regardless of whether patients receive rhythm or rate control, anticoagulation is recommended for patients with HF and AF for stroke prevention in the presence of at least 1 additional risk factor. For patients with HF and AF in the absence of another cardioembolic risk factor, anticoagulation is reasonable.

Trials of newer oral anticoagulants have compared efficacy and safety with warfarin therapy rather than placebo. Several new oral anticoagulants are now available, including the factor Xa inhibitors apixaban and rivaroxaban and the direct thrombin inhibitor dabigatran (508, 512-514). These drugs have few food and drug interactions compared with warfarin and no need for routine coagulation monitoring or dose adjustment. The fixed dosing together with fewer interactions may simplify patient management, particularly with the polypharmacy commonly seen in HF. These drugs have a potential for an improved benefit–risk profile compared with warfarin, which may increase their use in practice, especially in those at increased bleeding risk. However, important adverse effects have been noted with these new anticoagulants, including gastrointestinal

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distress, which may limit compliance. At present, there is no commercially available agent to reverse the effect of these newer drugs. Trials comparing new anticoagulants with warfarin have enrolled >10,000 patients with HF. As more detailed evaluations of the comparative benefits and risks of these newer agents in patients with HF are still pending, the writing committee considered their use in patients with HF and nonvalvular AF as an alternative to warfarin to be reasonable.

The benefit afforded by low-dose aspirin in patients with systolic HF but no previous MI or known CAD (or specifically in patients proven free of CAD) remains unknown. A Cochrane review failed to find sufficient evidence to support its use (532). Retrospective and observational studies again had conflicting results and used very different criteria to identify patients as nonischemic, with some demonstrating protection from aspirin overall (532) or only in patients with more severe depression of systolic function (518), whereas others found no benefit from aspirin (530). The high incidence of diabetes mellitus and hypertension in most HF studies, combined with a failure to use objective methods to exclude CAD in enrolled patients, may leave this question unanswered. Currently, data are insufficient to recommend aspirin for empiric primary prevention in HF patients known to be free of atherosclerotic disease and without additional risk factors.

See Online Data Supplement 21 (http://jaccjacc.cardiosource.com/DataSupp/ACCF/2013_HFGL_Evidence_Tables.pdf) for additional data on anticoagulants.

7.3.2.8.2. Statins: Recommendation

Class III: No Benefit

1. **Statins are not beneficial as adjunctive therapy when prescribed solely for the diagnosis of HF in the absence of other indications for their use (533-538).** ***(Level of Evidence: A)***

Statin therapy has been broadly implicated in prevention of adverse cardiovascular events, including new-onset HF. Originally designed to lower cholesterol in patients with cardiovascular disease, statins are increasingly recognized for their favorable effects on inflammation, oxidative stress, and vascular performance. Several observational and post hoc analyses from large clinical trials have implied that statin therapy may provide clinical benefit to patients with HF (533-536). However, 2 large RCTs have demonstrated that rosuvastatin has neutral effects on long-term outcomes in patients with chronic HF*r*EF when added to standard GDMT (537, 538). At present, statin therapy should not be prescribed primarily for the treatment of HF to improve clinical outcomes.

See Online Data Supplement 22 (http://jaccjacc.cardiosource.com/DataSupp/ACCF/2013_HFGL_Evidence_Tables.pdf) for additional data on statin therapy.

7.3.2.8.3. Omega-3 Fatty Acids: Recommendation

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Class IIa

1. **Omega-3 polyunsaturated fatty acid (PUFA) supplementation is reasonable to use as adjunctive therapy in patients with NYHA class II-IV symptoms and HF*r*EF or HF*p*EF, unless contraindicated, to reduce mortality and cardiovascular hospitalizations (539, 540). (*Level of Evidence B*)**

Supplementation with omega-3 PUFA has been evaluated as an adjunctive therapy for cardiovascular disease and HF (541). Trials in primary and secondary prevention of coronary heart disease showed that omega-3 PUFA supplementation results in a 10% to 20% risk reduction in fatal and nonfatal cardiovascular events. The GISSI (Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico) Prevenzione trial demonstrated a 21% reduction in death among post-MI patients taking 1 g of omega-3 PUFA (850 to 882 mg of eicosapentaenoic acid [EPA] and docosahexaenoic acid [DHA] as ethyl esters in the ratio of 1:1.2) (542). Post hoc subgroup analysis revealed that this reduction in mortality and SCD was concentrated in the approximately 2,000 patients with reduced LVEF (539). The GISSI-HF investigators randomized 6,975 patients in NYHA class II–IV chronic HF to 1 g daily of omega-3 PUFA (850 to 882 mg EPA/DHA) or matching placebo. Death from any cause was reduced from 29% with placebo to 27% in those treated with omega-3 PUFA (540). The outcome of death or admission to hospital for a cardiovascular event was also significantly reduced. In reported studies, this therapy has been safe and very well tolerated (540-543). Further investigations are needed to better define optimal dosing and formulation of omega-3 PUFA supplements. The use of omega-3 PUFA supplementation is reasonable as adjunctive therapy in patients with chronic HF.

See Online Data Supplement 23 (http://jaccjacc.cardiosource.com/DataSupp/ACCF/2013_HFGL_Evidence_Tables.pdf) for additional data on omega-3 fatty acids.

7.3.2.9. Drugs of Unproven Value or That May Worsen HF: Recommendations

Class III: No Benefit

1. **Nutritional supplements as treatment for HF are not recommended in patients with current or prior symptoms of HF*r*EF (544, 545). (*Level of Evidence: B*)**
2. **Hormonal therapies other than to correct deficiencies are not recommended for patients with current or prior symptoms of HF*r*EF. (*Level of Evidence: C*)**

Class III: Harm

1. **Drugs known to adversely affect the clinical status of patients with current or prior symptoms of HF*r*EF are potentially harmful and should be avoided or withdrawn whenever possible (e.g., most antiarrhythmic drugs, most calcium channel blocking drugs (except amlodipine), NSAIDs, or thiazolidinediones) (546-557). *(Level of Evidence: B)***
2. **Long-term use of infused positive inotropic drugs is potentially harmful for patients with HF*r*EF, except as palliation for patients with end-stage disease who cannot be stabilized with standard medical treatment (see recommendations for stage D). (*Level of Evidence: C*)**

7.3.2.9.1. Nutritional Supplements and Hormonal Therapies

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Patients with HF, particularly those treated with diuretics, may become deficient in vitamins and micronutrients. Several nutritional supplements (e.g., coenzyme Q10, carnitine, taurine, and antioxidants) and hormonal therapies (e.g., growth hormone or thyroid hormone) have been proposed for the treatment of HF (558-563). Testosterone has also been evaluated for its beneficial effect in HF with modest albeit preliminary effects (564). Aside from replenishment of documented deficiencies, published data have failed to demonstrate benefit for routine vitamin, nutritional, or hormonal supplementation (565). In most data or other literature regarding nutraceuticals, there are issues, including outcomes analyses, adverse effects, and drug-nutraceutical interactions, that remain unresolved.

No clinical trials have demonstrated improved survival rates with use of nutritional or hormonal therapy, with the exception of omega-3 fatty acid supplementation as previously noted. Some studies have suggested a possible effect for coenzyme Q10 in reduced hospitalization rates, dyspnea, and edema in patients with HF, but these benefits have not been seen uniformly (566-569). Because of possible adverse effects and drug interactions of nutritional supplements and their widespread use, clinicians caring for patients with HF should routinely inquire about their use. Until more data are available, nutritional supplements or hormonal therapies are not recommended for the treatment of HF.

7.3.2.9.2. Antiarrhythmic Agents

With atrial and ventricular arrhythmias contributing to the morbidity and mortality of HF, various classes of antiarrhythmic agents have been repeatedly studied in large RCTs. Instead of conferring survival benefit, however, nearly all antiarrhythmic agents increase mortality in the HF population (548-550). Most antiarrhythmics have some negative inotropic effect and some, particularly the class I and class III antiarrhythmic drugs, have proarrhythmic effects. Hence, class I sodium channel antagonists and the class III potassium channel blockers d-sotalol and dronedarone should be avoided in patients with HF. Amiodarone and dofetilide are the only antiarrhythmic agents to have neutral effects on mortality in clinical trials of patients with HF and thus are the preferred drugs for treating arrhythmias in this patient group (570-573).

See Online Data Supplement 24 (http://jaccjacc.cardiosource.com/DataSupp/ACCF/2013_HFGL_Evidence_Tables.pdf) for additional data on antiarrhythmic agents.

7.3.2.9.3. Calcium Channel Blockers: Recommendation

Class III: No Benefit

1. **Calcium channel blocking drugs are not recommended as routine treatment for patients with HF*r*EF (551, 574, 575). (*Level of Evidence: A*)**

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By reducing peripheral vasoconstriction and LV afterload, calcium channel blockers were thought to have a potential role in the management of chronic HF. However, first-generation dihydropyridine and nondihydropyridine calcium channel blockers also have myocardial depressant activity. Several clinical trials have demonstrated either no clinical benefit or even worse outcomes in patients with HF treated with these drugs (546, 547, 551-553). Despite their greater selectivity for calcium channels in vascular smooth muscle cells, second-generation calcium channel blockers, dihydropyridine derivatives such as amlodipine and felodipine, have failed to demonstrate any functional or survival benefit in patients with HF (575-579). Amlodipine, however, may be considered in the management of hypertension or ischemic heart disease in patients with HF because it is generally well tolerated and had neutral effects on morbidity and mortality in large RCTs. In general, calcium channel blockers should be avoided in patients with HF*r*EF.

See Online Data Supplement 25 (http://jaccjacc.cardiosource.com/DataSupp/ACCF/2013_HFGL_Evidence_Tables.pdf) for additional data on calcium channel blockers.

7.3.2.9.4. Nonsteroidal Anti-Inflammatory Drugs

NSAIDs inhibit the synthesis of renal prostaglandins, which mediate vasodilation in the kidneys and directly inhibit sodium resorption in the thick ascending loop of Henle and collecting tubule. Hence, NSAIDs can cause sodium and water retention and blunt the effects of diuretics. Several observational cohort studies have revealed increased morbidity and mortality in patients with HF using either nonselective or selective NSAIDs (554-556, 580-582).

See Online Data Supplement 26 (http://jaccjacc.cardiosource.com/DataSupp/ACCF/2013_HFGL_Evidence_Tables.pdf) for additional data on NSAIDs.

7.3.2.9.5. Thiazolidinediones

Thiazolidinediones increase insulin sensitivity by activating nuclear peroxisome proliferator-activated receptor gamma. Expressed in virtually all tissues, peroxisome proliferator-activated receptor gamma also regulates sodium reabsorption in the collecting ducts of the kidney. In clinical trials, thiazolidinediones have been associated with increased incidence of HF events, even in those without any prior history of clinical HF (557, 583-588).

See Table 19 for a summary of recommendations from this section and Table 20 for strategies for achieving optimal GDMT; see Online Data Supplement 27 (http://jaccjacc.cardiosource.com/DataSupp/ACCF/2013_HFGL_Evidence_Tables.pdf) for additional data on thiazolidinediones.

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Table 19. Recommendations for Pharmacological Therapy for Management of Stage C HF*r*EF
TnQTable20*In the absence of contraindications to anticoagulation.
ACE indicates angiotensin-converting enzyme; AF, atrial fibrillation; ARB, angiotensin-receptor blocker; COR, Class of Recommendation; DM, diabetes mellitus; GDMT, guideline-directed medical therapy; HF, heart failure; HF*p*EF, heart failure with preserved ejection fraction; HF*r*EF, heart failure with reduced ejection fraction; LOE, Level of Evidence; LVEF, left ventricular ejection fraction; MI, myocardial infarction; N/A, not available; NYHA, New York Heart Association; and PUFA, polyunsaturated fatty acids.

Table 20. Strategies for Achieving Optimal GDMT
TnQTable21ACE indicates angiotensin-converting enzyme; ARB, angiotensin-receptor blocker; CRT, cardiac resynchronization therapy; GDMT, guideline-directed medical therapy; and HRQOL, health-related quality of life.

7.3.3. Pharmacological Treatment for Stage C HF*p*EF: Recommendations

See Table 21 for a summary of recommendations from this section.

Class I

1. **Systolic and diastolic blood pressure should be controlled in patients with HF*p*EF in accordance with published clinical practice guidelines to prevent morbidity (27, 91). *(Level of Evidence: B)***
2. **Diuretics should be used for relief of symptoms due to volume overload in patients with HF*p*EF. *(Level of Evidence: C)***

Class IIa

1. **Coronary revascularization is reasonable in patients with CAD in whom symptoms (angina) or demonstrable myocardial ischemia is judged to be having an adverse effect on symptomatic HF*p*EF despite GDMT. (*Level of Evidence: C*)**
2. **Management of AF according to published clinical practice guidelines in patients with HF*p*EF is reasonable to improve symptomatic HF (Section 9.1). (*Level of Evidence: C*)**
3. **The use of beta-blocking agents, ACE inhibitors, and ARBs in patients with hypertension is reasonable to control blood pressure in patients with HF*p*EF. (*Level of Evidence: C*)**

Class IIb

1. **The use of ARBs might be considered to decrease hospitalizations for patients with HF*p*EF (589). (*Level of Evidence: B*)**

Class III: No Benefit

1. **Routine use of nutritional supplements is not recommended for patients with HF*p*EF. (*Level of Evidence: C*)**

Trials using comparable and efficacious agents for HF*r*EF have generally been disappointing (590). Thus, most of the recommended therapies for HF*p*EF are directed at symptoms, especially comorbidities, and risk factors that may worsen cardiovascular disease.

Blood pressure control concordant with existing hypertension guidelines remains the most important recommendation in patients with HF*p*EF. Evidence from an RCT has shown that improved blood pressure control reduces hospitalization for HF (591), decreases cardiovascular events, and reduces HF mortality in patients without prevalent HF (311). In hypertensive patients with HF*p*EF, aggressive treatment (often with

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several drugs with complementary mechanisms of action) is recommended. ACE inhibitors and/or ARBs are often considered as first-line agents. Specific blood pressure targets in HF*p*EF have not been firmly established; thus, the recommended targets are those used for general hypertensive populations.

CAD is common in patients with HF*p*EF (592); however, there are no studies to determine the impact of revascularization on symptoms or outcomes specifically in patients with HF*p*EF. In general, contemporary revascularization guidelines (10, 12) should be used in the care of patients with HF*p*EF and concomitant CAD. Specific to this population, it might be reasonable to consider revascularization in patients for whom ischemia appears to contribute to HF symptoms, although this determination can be difficult.

Theoretical mechanisms for the worsening of HF symptoms by AF among patients with HF*p*EF include shortened diastolic filling time with tachycardia and the loss of atrial contribution to LV diastolic filling. Conversely, chronotropic incompetence is also a concern. Slowing the heart rate is useful in tachycardia but not in normal resting heart rate; a slow heart rate prolongs diastasis and worsens chronotropic incompetence. Currently, there are no specific trials of rate versus rhythm control in HF*p*EF.

Table 21. Recommendations for Treatment of HF*p*EF
TnQTable22ACE indicates angiotensin-converting enzyme; AF, atrial fibrillation; ARBs, angiotensin-receptor blockers; CAD, coronary artery disease; COR, Class of Recommendation; GDMT, guideline-directed medical therapy; HF, heart failure; HF*p*EF, heart failure with preserved ejection fraction; and LOE, Level of Evidence.

7.3.4. Device Therapy for Stage C HF*r*EF: Recommendations

See Table 22 for a summary of recommendations from this section.

Class I

1. **ICD therapy is recommended for primary prevention of SCD to reduce total mortality in selected patients with nonischemic DCM or ischemic heart disease at least 40 days post-MI with LVEF of 35% or less and NYHA class II or III symptoms on chronic GDMT, who have reasonable expectation of meaningful survival for more than 1 year (355, 593). *(Level of Evidence: A)**
2. **CRT is indicated for patients who have LVEF of 35% or less, sinus rhythm, left bundle-branch block (LBBB) with a QRS duration of 150 ms or greater, and NYHA class II, III, or ambulatory IV symptoms on GDMT. *(Level of Evidence: A for NYHA class III/IV* (38, 78, 116, 594); *Level of Evidence: B for NYHA class II* (595, 596))**
3. **ICD therapy is recommended for primary prevention of SCD to reduce total mortality in selected patients at least 40 days post-MI with LVEF of 30% or less, and NYHA class I symptoms while receiving GDMT, who have reasonable expectation of meaningful survival for more than 1 year (362, 597, 598). *(Level of Evidence: B)**

Class IIa

1. **CRT can be useful for patients who have LVEF of 35% or less, sinus rhythm, a non-LBBB pattern with a QRS duration of 150 ms or greater, and NYHA class III/ambulatory class IV symptoms on GDMT (78, 116, 594, 596). *(Level of Evidence: A)***
2. **CRT can be useful for patients who have LVEF of 35% or less, sinus rhythm, LBBB with a QRS duration of 120 to 149 ms, and NYHA class II, III, or ambulatory IV symptoms on GDMT (78, 116, 594-596, 599). *(Level of Evidence: B)***

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3. **CRT can be useful in patients with AF and LVEF of 35% or less on GDMT if a) the patient requires ventricular pacing or otherwise meets CRT criteria and b) atrioventricular nodal ablation or pharmacological rate control will allow near 100% ventricular pacing with CRT (600-605).** ***(Level of Evidence: B)***
4. **CRT can be useful for patients on GDMT who have LVEF of 35% or less, and are undergoing placement of a new or replacement device with anticipated requirement for significant (>40%) ventricular pacing (155, 602, 606, 607).** ***(Level of Evidence: C)***

Class IIb

1. **The usefulness of implantation of an ICD is of uncertain benefit to prolong meaningful survival in patients with a high risk of nonsudden death as predicted by frequent hospitalizations, advanced frailty, or comorbidities such as systemic malignancy or severe renal dysfunction (608-611).** ***(Level of Evidence: B)****
2. **CRT may be considered for patients who have LVEF of 35% or less, sinus rhythm, a non-LBBB pattern with QRS duration of 120 to 149 ms, and NYHA class III/ambulatory class IV on GDMT (596, 612).** ***(Level of Evidence: B)***
3. **CRT may be considered for patients who have LVEF of 35% or less, sinus rhythm, a non-LBBB pattern with a QRS duration of 150 ms or greater, and NYHA class II symptoms on GDMT (595, 596).** ***(Level of Evidence: B)***
4. **CRT may be considered for patients who have LVEF of 30% or less, ischemic etiology of HF, sinus rhythm, LBBB with a QRS duration of 150 ms or greater, and NYHA class I symptoms on GDMT (595, 596).** ***(Level of Evidence: C)***

Class III: No Benefit

1. **CRT is not recommended for patients with NYHA class I or II symptoms and non-LBBB pattern with QRS duration less than 150 ms (595, 596, 612).** ***(Level of Evidence: B)***
2. **CRT is not indicated for patients whose comorbidities and/or frailty limit survival with good functional capacity to less than 1 year (38).** ***(Level of Evidence: C)***

See Figure 2. Indications for CRT Therapy Algorithm.

**Counseling should be specific to each individual patient and should include documentation of a discussion about the potential for sudden death and nonsudden death from HF or noncardiac conditions. Information should be provided about the efficacy, safety, and potential complications of an ICD and the potential for defibrillation to be inactivated if desired in the future, notably when a patient is approaching end of life. This will facilitate shared decision making between patients, families, and the medical care team about ICDs (30).*

7.3.4.1. Implantable Cardioverter-Defibrillator

Patients with reduced LVEF are at increased risk for ventricular tachyarrhythmias leading to SCD. Sudden death in HF*r*EF has been substantially decreased by neurohormonal antagonists that alter disease progression and also protect against arrhythmias. Nonetheless, patients with systolic dysfunction remain at increased risk for SCD due to ventricular tachyarrhythmias. Patients who have had sustained ventricular tachycardia, ventricular fibrillation, unexplained syncope, or cardiac arrest are at highest risk for recurrence. Indications for ICD therapy as secondary prevention of SCD in these patients is also discussed in the ACCF/AHA/HRS device-based therapy guideline (613).

The use of ICDs for primary prevention of SCD in patients with HF*r*EF without prior history of arrhythmias or syncope has been evaluated in multiple RCTs. ICD therapy for primary prevention was

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demonstrated to reduce all-cause mortality. For patients with LVEF ≤30% after remote MI, use of ICD therapy led to a 31% decrease in mortality over 20 months, for an absolute decrease of 5.6% (362). For patients with mild to moderate symptoms of HF with LVEF ≤35% due either to ischemic or nonischemic etiology, there was a 23% decrease in mortality over a 5-year period, for an absolute decrease of 7.2% (593). For both these trials, the survival benefit appeared after the first year. Other smaller trials were consistent with this degree of benefit, except for patients within the first 40 days after acute MI, in whom SCD was decreased but there was an increase in other events such that there was no net benefit for survival (598, 614). Both SCD and total mortality are highest in patients with HF*r*EF with class IV symptoms, in whom ICDs are not expected to prolong meaningful survival and are not indicated except in those for whom heart transplantation or MCS is anticipated.

The use of ICDs for primary prevention in patients with HF*r*EF should be considered only in the setting of optimal GDMT and with a minimum of 3 to 6 months of appropriate medical therapy. A repeat assessment of ventricular function is appropriate to assess any recovery of ventricular function on GDMT that would be above the threshold where an ICD is indicated. This therapy will often improve ventricular function to a range for which the risk of sudden death is too low to warrant placement of an ICD. In addition, the trials of ICDs for primary prevention of SCD studied patients who were already on GDMT.

ICDs are highly effective in preventing death from ventricular arrhythmias, but frequent shocks can decrease HRQOL and lead to posttraumatic stress syndrome (615). Therapy with antiarrhythmic drugs and catheter ablation for ventricular tachycardia can decrease the number of ICD shocks given and can sometimes improve ventricular function in cases of very frequent ventricular tachyarrhythmias. Refined device programming can optimize pacing therapies to avert the need for shocks, minimize inappropriate shocks, and avoid aggravation of HF by frequent ventricular pacing. Although there have been occasional recalls of device generators, these are exceedingly rare in comparison to complications related to intracardiac device leads, such as fracture and infection.

ICDs are indicated only in patients with a reasonable expectation of survival with good functional status beyond a year, but the range of uncertainty remains wide. The complex decision about the relative risks and benefits of ICDs for primary prevention of SCD must be individualized for each patient. Unlike other therapies that can prolong life with HF, the ICD does not modify the disease except in conjunction with CRT. Patients with multiple comorbidities have a higher rate of implant complications and higher competing risks of death from noncardiac causes (616). Older patients, who are at a higher risk of nonsudden death, are often underrepresented in the pivotal trials where the average patient is <65 years of age (617). The major trials for secondary prevention of SCD showed no benefit in patients >75 years of age (618), and a meta-analysis of primary prevention of SCD also suggested lesser effectiveness of ICDs (619). Populations of patients with multiple HF hospitalizations, particularly in the setting of chronic kidney disease, have a median survival rate of <2 years, during which the benefit of the ICD may not be realized (608). There is widespread recognition of the

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need for further research to identify patients most and least likely to benefit from ICDs for primary prevention of SCD in HF. Similar considerations apply to the decision to replace the device generator.

Consideration of ICD implantation is highly appropriate for shared decision making (30). The risks and benefits carry different relative values depending on patient goals and preferences. Discussion should include the potential for SCD and nonsudden death from HF or noncardiac conditions. Information should be provided in a format that patients can understand about the estimated efficacy, safety, and potential complications of an ICD and the ease with which defibrillation can be inactivated if no longer desired (620). As the prevalence of implantable devices increases, it is essential that clearly defined processes be in place to support patients and families when decisions about deactivation arise (621).

7.3.4.2. Cardiac Resynchronization Therapy

In approximately one third of patients, HF progression is accompanied by substantial prolongation of the QRS interval, which is associated with worse outcome (622). Multisite ventricular pacing (termed CRT or biventricular pacing) can improve ventricular contractile function, diminish secondary mitral regurgitation, reverse ventricular remodeling, and sustain improvement in LVEF. Increased blood pressure with CRT can allow increased titration of neurohormonal antagonist medications that may further contribute to improvement. Benefits were proven initially in trials of patients with NYHA class III or ambulatory class IV HF symptoms and QRS duration of $\geq$120 to 130 ms. These results have included a decrease of approximately 30% in rehospitalization and reductions in all-cause mortality in the range of 24% to 36%. Improvement in survival is evident as early as the first 3 months of therapy. Functional improvements have been demonstrated on average as a 1 to 2 mL/kg/min increase in peak oxygen consumption, 50- to 70-meter increase in 6-minute walk distance, and a reduction of 10 points or more in the 0- to 105-point scale of the Minnesota Living With Heart Failure Questionnaire, all considered clinically significant. These results include patients with a wide range of QRS duration and, in most cases, sinus rhythm (78, 116, 594, 623).

Although it is still not possible to predict with confidence which patients will improve with CRT, further experiences have provided some clarification. Benefit appears confined largely to patients with a QRS duration of at least 150 ms and LBBB pattern (624-628). The weight of the evidence has been accumulated from patients with sinus rhythm, with meta-analyses indicating substantially less clinical benefit in patients with permanent AF (604, 605). Because effective CRT requires a high rate of ventricular pacing (629), the benefit for patients with AF is most evident in patients who have undergone atrioventricular nodal ablation, which ensures obligate ventricular pacing (601-603).

In general, most data derive from patients with class III symptoms. Patients labeled as having class IV symptoms account for a small minority of patients enrolled. Furthermore, these patients, characterized as “ambulatory” NYHA class IV, are not refractory due to fluid retention, frequently hospitalized for HF, or dependent on continuous intravenous inotropic therapy. CRT should not be considered as “rescue” therapy for

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stage D HF. In addition, patients with significant noncardiac limitations are unlikely to derive major benefit from CRT.

Since publication of the 2009 HF guideline (38), new evidence supports extension of CRT to patients with milder symptoms. LV remodeling was consistently reversed or halted, with benefit also in reduction of HF hospitalizations (595, 596, 599). In this population with low 1-year mortality, reduction of HF hospitalization dominated the composite primary endpoints, but a mortality benefit was subsequently observed in a 2-year extended follow-up study (630) and in a meta-analysis of 5 trials of CRT in mild HF that included 4,213 patients with class II symptoms (631). Overall benefits in class II HF were noted only in patients with QRS $\geq$150 ms and LBBB, with an adverse impact with shorter QRS duration or non-LBBB.

The entry criterion for LVEF in CRT trials has ranged from $\leq$30% to $\leq$40%. The trials with class III-IV symptoms included patients with LVEF $\leq$35% (78, 116, 594). The 2 individual trials showing improvement in mortality with class II HF included patients with LVEF $\leq$30% (632, 633). Trials demonstrating significant improvement in LV size and EF have included patients with LVEF $\leq$35% (115) and LVEF $\leq$40% (599), which also showed reduction in the secondary endpoint of time to hospitalization and a reduction in the composite of clinical HF events comparable to that of all of the CRT trials (624). The congruence of evidence from the totality of CRT trials with regard to remodeling and HF events supports a common threshold of 35% for benefit from CRT in patients with class II, III, and IV HF symptoms. For patients with class II HF, all but 1 of the trials tested CRT in combination with an ICD, whereas there is evidence for benefit with both CRT-defibrillator and CRT alone in patients with class III-IV symptoms (78, 116).

Although the weight of evidence is substantial for patients with class II symptoms, these CRT trials have included only 372 patients with class I symptoms, most with concomitant ICD for the postinfarction indication (595, 599). Considering the risk–benefit ratio for class I, more concern is raised by the early adverse events, which in 1 trial occurred in 13% of patients with CRT-ICD compared with 6.7% in patients with ICD only (596). On the basis of limited data from MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial-Cardiac Resynchronization Therapy), CRT-ICD may be considered for patients with class I symptoms >40 days after MI, LVEF $\leq$30%, sinus rhythm, LBBB, and QRS $\geq$150 ms (595).

These indications for CRT all include expectation for ongoing GDMT and diuretic therapy as needed for fluid retention. In addition, regular monitoring is required after device implantation because adjustment of HF therapies and reprogramming of device intervals may be required. The trials establishing the benefit of these interventions were conducted in centers offering expertise in both implantation and follow-up. Recommendations for CRT are made with the expectation that they will be performed in centers with expertise and outcome comparable to that of the trials that provide the bases of evidence. The benefit–risk ratio for this intervention would be anticipated to be diminished for patients who do not have access to these specialized care settings or who are nonadherent.

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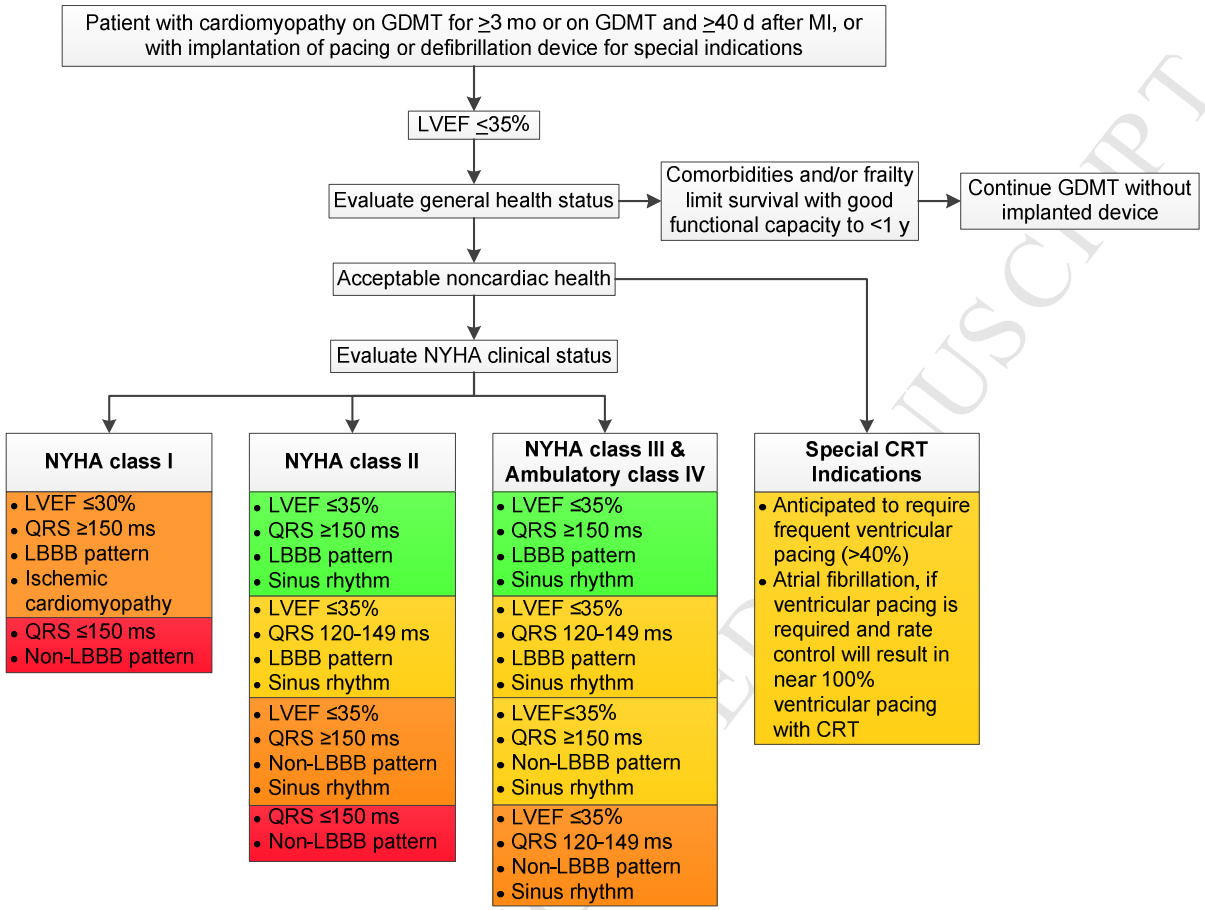
Figure 2. Indications for CRT Therapy Algorithm.



Colors correspond to the class of recommendations in the ACCF/AHA Table 1.

Benefit for NYHA class I and II patients has only been shown in CRT-D trials, and while patients may not experience immediate symptomatic benefit, late remodeling may be avoided along with long-term HF consequences. There are no trials that support CRT-pacing (without ICD) in NYHA class I and II patients. Thus, it is anticipated these patients would receive CRT-D unless clinical reasons or personal wishes make CRT-pacing more appropriate. In patients who are NYHA class III and ambulatory class IV, CRT-D may be chosen but clinical reasons and personal wishes may make CRT-pacing appropriate to improve symptoms and quality of life when an ICD is not expected to produce meaningful benefit in survival.

CRT indicates cardiac resynchronization therapy; CRT-D, cardiac resynchronization therapy-defibrillator; GDMT, guideline-directed medical therapy; HF, heart failure; ICD, implantable cardioverter-defibrillator; LBBB, left bundle-branch block; LV, left ventricular; LVEF, left ventricular ejection fraction; MI, myocardial infarction; and NYHA, New York Heart Association.

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Table 22. Recommendations for Device Therapy for Management of Stage C HF

TnQTable23*Counseling should be specific to each individual patient and should include documentation of a discussion about the potential for sudden death and nonsudden death from HF or noncardiac conditions. Information should be provided about the efficacy, safety, and potential complications of an ICD and the potential for defibrillation to be inactivated if desired in the future, notably when a patient is approaching end of life. This will facilitate shared decision making between patients, families, and the medical care team about ICDs (30).

AF indicates atrial fibrillation; AV, atrioventricular; COR, Class of Recommendation; CRT, cardiac resynchronization therapy; GDMT, guideline-directed medical therapy; HF, heart failure; HF*r*EF, heart failure with reduced ejection fraction; ICD, implantable cardioverter-defibrillator; LBBB, left bundle-branch block; LOE, Level of Evidence; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NYHA, New York Heart Association; and SCD, sudden cardiac death.

See Online Data Supplements 28 and 29 (http://jaccjacc.cardiosource.com/DataSupp/ACCF/2013_HFGL_Evidence_Tables.pdf) for additional data on device therapy and CRT.

7.4. Stage D

7.4.1. Definition of Advanced HF

A subset of patients with chronic HF will continue to progress and develop persistently severe symptoms despite maximum GDMT. Various terminologies have been used to describe this group of patients who are classified with ACCF/AHA stage D HF, including "advanced HF," "end-stage HF," and "refractory HF." In the 2009 ACCF/AHA HF guideline, stage D was defined as "patients with truly refractory HF who might be eligible for specialized, advanced treatment strategies, such as MCS, procedures to facilitate fluid removal, continuous inotropic infusions, or cardiac transplantation or other innovative or experimental surgical procedures, or for end-of-life care, such as hospice" (38). The European Society of Cardiology has developed a definition of advanced HF with objective criteria that can be useful (32) (Table 23). There are clinical clues that may assist clinicians in identifying patients who are progressing toward advanced HF (Table 24). The Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) has developed 7 profiles that further stratify patients with advanced HF (Table 25) (635).

7.4.2. Important Considerations in Determining If the Patient Is Refractory

Patients considered to have stage D HF should be thoroughly evaluated to ascertain that the diagnosis is correct and that there are no remediable etiologies or alternative explanations for advanced symptoms. For example, it is important to determine that HF and not a concomitant pulmonary disorder is the basis of dyspnea. Similarly, in those with presumed cardiac cachexia, other causes of weight loss should be ruled out. Likewise, other reversible factors such as thyroid disorders should be treated. Severely symptomatic patients presenting with a new diagnosis of HF can often improve substantially if they are initially stabilized. Patients should also be evaluated for nonadherence to medications (636-639), sodium restriction (640), and/or daily weight monitoring (641). Finally, a careful review of prior medical management should be conducted to verify that all evidence-based therapies likely to improve clinical status have been considered.

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Table 23. ESC Definition of Advanced HF

TnQTable24BNP indicates B-type natriuretic peptide; CRT, cardiac resynchronization therapy; ESC, European Society of Cardiology; GDMT, guideline-directed medical therapy; HF, heart failure; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; PA, pulmonary artery; PWCP, pulmonary capillary wedge pressure; and RAP, right atrial pressure.
Adapted from Metra et al (32).

Table 24. Clinical Events and Findings Useful for Identifying Patients With Advanced HF

TnQTable25ACE indicates angiotensin-converting enzyme; BUN, blood urea nitrogen; ED, emergency department; HF, heart failure; and ICD, implantable cardioverter-defibrillator.
Adapted from Russell et al (642).

Table 25. INTERMACS Profiles

TnQTable26*Modifier options: Profiles 3-6 can be modified with the designation FF (frequent flyer) for patients with recurrent decompensations leading to frequent (generally at least 2 in last 3 mo or 3 in last 6 mo) emergency department visits or hospitalizations for intravenous diuretics, ultrafiltration, or brief inotropic therapy. Profile 3 can be modified in this fashion if the patient is usually at home. If a Profile 7 patient meets the definition of FF, the patient should be moved to Profile 6 or worse. Other modifier options include A (arrhythmia), which should be used in the presence of recurrent ventricular tachyarrhythmias contributing to the overall clinical course (e.g., frequent ICD shocks or requirement of external defibrillation, usually more than twice weekly); or TCS (temporary circulatory support) for hospitalized patients profiles 1-3 (635).
ICD indicates implantable cardioverter-defibrillator; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; and NYHA, New York Heart Association.
Adapted from Stevenson et al (643).

See Online Data Supplements 30 and 31 (http://jaccjacc.cardiosource.com/DataSupp/ACCF/2013_HFGL_Evidence_Tables.pdf) for additional data on therapies—important considerations and sildenafil.

7.4.3. Water Restriction: Recommendation

Class IIa

1. **Fluid restriction (1.5 to 2 L/d) is reasonable in stage D, especially in patients with hyponatremia, to reduce congestive symptoms. *(Level of Evidence: C)***

Recommendations for fluid restriction in HF are largely driven by clinical experience. Sodium and fluid balance recommendations are best implemented in the context of weight and symptom monitoring programs. Routine strict fluid restriction in all patients with HF regardless of symptoms or other considerations does not appear to result in significant benefit (644). Limiting fluid intake to around 2 L/d is usually adequate for most hospitalized patients who are not diuretic resistant or significantly hyponatremic. In 1 study, patients on a similar sodium and diuretic regimen showed higher readmission rates with higher fluid intake, suggesting that fluid intake affects HF outcomes (385). Strict fluid restriction may best be used in patients who are either refractory to diuretics or have hyponatremia. Fluid restriction, especially in conjunction with sodium restriction, enhances volume management with diuretics. Fluid restriction is important to manage hyponatremia, which is relatively common with advanced HF and portends a poor prognosis (645, 646). Fluid restriction may improve serum sodium concentration; however, it is difficult to achieve and maintain. In hot or low-humidity climates, excessive fluid

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restriction predisposes patients with advanced HF to the risk of heat stroke. Hyponatremia in HF is primarily due to an inability to excrete free water. Norepinephrine and angiotensin II activation result in decreased sodium delivery to the distal tubule, whereas arginine vasopressin increases water absorption from the distal tubule. In addition, angiotensin II also promotes thirst. Thus, sodium and fluid restriction in advanced patients with HF is important.

7.4.4. Inotropic Support: Recommendations

Class I

1. **Until definitive therapy (e.g., coronary revascularization, MCS, heart transplantation) or resolution of the acute precipitating problem, patients with cardiogenic shock should receive temporary intravenous inotropic support to maintain systemic perfusion and preserve end-organ performance.** ***(Level of Evidence: C)***

Class IIa

1. **Continuous intravenous inotropic support is reasonable as "bridge therapy" in patients with stage D refractory to GDMT and device therapy who are eligible for and awaiting MCS or cardiac transplantation (647, 648).** ***(Level of Evidence: B)***

Class IIb

1. **Short-term, continuous intravenous inotropic support may be reasonable in those hospitalized patients presenting with documented severe systolic dysfunction who present with low blood pressure and significantly depressed cardiac output to maintain systemic perfusion and preserve end-organ performance (592, 649, 650).** ***(Level of Evidence: B)***
2. **Long-term, continuous intravenous inotropic support may be considered as palliative therapy for symptom control in select patients with stage D despite optimal GDMT and device therapy who are not eligible for either MCS or cardiac transplantation (651-653).** ***(Level of Evidence: B)***

Class III: Harm

1. **Long-term use of either continuous or intermittent, intravenous parenteral positive inotropic agents, in the absence of specific indications or for reasons other than palliative care, is potentially harmful in the patient with HF (416, 654-659).** ***(Level of Evidence: B)***
2. **Use of parenteral inotropic agents in hospitalized patients without documented severe systolic dysfunction, low blood pressure, or impaired perfusion, and evidence of significantly depressed cardiac output, with or without congestion, is potentially harmful (592, 649, 650).** ***(Level of Evidence: B)***

Despite improving hemodynamic compromise, positive inotropic agents have not demonstrated improved outcomes in patients with HF in either the hospital or outpatient setting (416, 654-658). Regardless of their mechanism of action (e.g., inhibition of phosphodiesterase, stimulation of adrenergic or dopaminergic receptors, calcium sensitization), chronic oral inotrope treatment increased mortality, mostly related to arrhythmic events. Parenteral inotropes, however, remain as an option to help the subset of patients with HF who are refractory to other therapies and are suffering consequences from end-organ hypoperfusion. Inotropes should be considered only in such patients with systolic dysfunction who have low cardiac index and evidence of systemic

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hypoperfusion and/or congestion (Table 26). To minimize adverse effects, lower doses are preferred. Similarly, the ongoing need for inotropic support and the possibility of discontinuation should be regularly assessed.

See Online Data Supplements 32 and 33 (http://jaccjacc.cardiosource.com/DataSupp/ACCF/2013_HFGL_Evidence_Tables.pdf) for additional data on inotropes.

Table 26. Intravenous Inotropic Agents Used in Management of HF

TnQTable27t ½ Indicates elimination half-life; BP, blood pressure; CI, contraindication; CO, cardiac output; F, fever; H, hepatic; HA, headache; HF, heart failure; HR, heart rate; LFT, liver function test; MAO-I, monoamine oxidase inhibitor; N, nausea; N/A, not applicable; N/R, not recommended; P, plasma; PDE, phosphodiesterase; PVR, pulmonary vascular resistance; R, renal; SVR, systemic vascular resistance; and T, tachyarrhythmias.

7.4.5. Mechanical Circulatory Support: Recommendations

Class IIa

1. **MCS is beneficial in carefully selected* patients with stage D HF*r*EF in whom definitive management (e.g., cardiac transplantation) or cardiac recovery is anticipated or planned (660-667). *(Level of Evidence: B)***
2. **Nondurable MCS, including the use of percutaneous and extracorporeal ventricular assist devices (VADs), is reasonable as a "bridge to recovery" or "bridge to decision" for carefully selected* patients with HF*r*EF with acute, profound hemodynamic compromise (668-671). *(Level of Evidence: B)***
3. **Durable MCS is reasonable to prolong survival for carefully selected* patients with stage D HF*r*EF (672-675). *(Level of Evidence: B)***

*Although optimal patient selection for MCS remains an active area of investigation, general indications for referral for MCS therapy include patients with LVEF <25% and NYHA class III-IV functional status despite GDMT, including, when indicated, CRT, with either high predicted 1- to 2-y mortality (e.g., as suggested by markedly reduced peak oxygen consumption, clinical prognostic scores) or dependence on continuous parenteral inotropic support. Patient selection requires a multidisciplinary team of experienced advanced HF and transplantation cardiologists, cardiothoracic surgeons, nurses, and, ideally, social workers and palliative care clinicians.

MCS has emerged as a viable therapeutic option for patients with advanced stage D HF*r*EF refractory to optimal GDMT and cardiac device intervention. Since its initial use 50 years ago for postcardiotomy shock (676), the implantable VAD continues to evolve.

Designed to assist the native heart, VADs are differentiated by the implant location (intracorporeal versus extracorporeal), approach (percutaneous versus surgical), flow characteristic (pulsatile versus continuous), pump mechanism (volume displacement, axial, centrifugal), and the ventricle(s) supported (left, right, biventricular). VADs are effective in both the short-term (hours to days) management of acute decompensated, hemodynamically unstable HF*r*EF that is refractory to inotropic support, and the long-term (months to years) management of stage D chronic HF*r*EF. Nondurable, or temporary, MCS provides an opportunity for decisions about the appropriateness of transition to definitive management such as cardiac surgery or durable, that is, permanent, MCS or, in the case of improvement and recovery, suitability for device removal. Nondurable MCS thereby may be helpful as either a bridge to decision or a bridge to recovery.

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More common scenarios for MCS, however, are long-term strategies, including 1) bridge to transplantation, 2) bridge to candidacy, and 3) destination therapy. Bridge to transport and destination therapy have the strongest evidence base with respect to survival, functional capacity, and HRQOL benefits.

Data from INTERMACS provides valuable information on risk factors and outcomes for patients undergoing MCS. The greatest risk factors for death among patients undergoing BTT include acuity and severity of clinical condition and evidence of right ventricular failure (677). MCS may also be used as a bridge to candidacy. Retrospective studies have shown reduction in pulmonary pressures with MCS therapy in patients with HF considered to have "fixed" pulmonary hypertension (661-663). Thus, patients who may be transplant-ineligible due to irreversible severe pulmonary hypertension may become eligible with MCS support over time. Other bridge-to-candidacy indications may include obesity and tobacco use in patients who are otherwise candidates for cardiac transplantation. There is ongoing interest in understanding how MCS facilitates LV reverse remodeling. Current scientific and translational research in the area aims to identify clinical, cellular, molecular, and genomic markers of cardiac recovery in the patient with VAD (678, 679).

See Online Data Supplements 34 and 35 (http://jaccjacc.cardiosource.com/DataSupp/ACCF/2013_HFGL_Evidence_Tables.pdf) for additional data on MCS and left VADs.

7.4.6. Cardiac Transplantation: Recommendation

Class I

1. **Evaluation for cardiac transplantation is indicated for carefully selected patients with stage D HF despite GDMT, device, and surgical management (680).** ***(Level of Evidence: C)***

Cardiac transplantation is considered the gold standard for the treatment of refractory end-stage HF. Since the first successful cardiac transplantation in 1967, advances in immunosuppressive therapy have vastly improved the long-term survival of transplant recipients with a 1-, 3-, and 5-year posttransplant survival rate of 87.8%, 78.5%, and 71.7% in adults, respectively (681). Similarly, cardiac transplantation has been shown to improve functional status and HRQOL (682-688). The greatest survival benefit is seen in those patients who are at highest risk of death from advanced HF (689). Cardiopulmonary exercise testing helps refine candidate selection (690-696). Data suggest acceptable posttransplant outcomes in patients with reversible pulmonary hypertension (697), hypertrophic cardiomyopathy (698), peripartum cardiomyopathy (699), restrictive cardiomyopathy (700, 701), and muscular dystrophy (702). Selected patients with stage D HF and poor prognosis should be referred to a cardiac transplantation center for evaluation and transplant consideration. Determination of HF prognosis is addressed in Sections 6.1.2 and 7.4.2. The listing criteria and evaluation and management of patients undergoing cardiac transplantation are described in detail by the International Society for Heart and Lung Transplantation (680).

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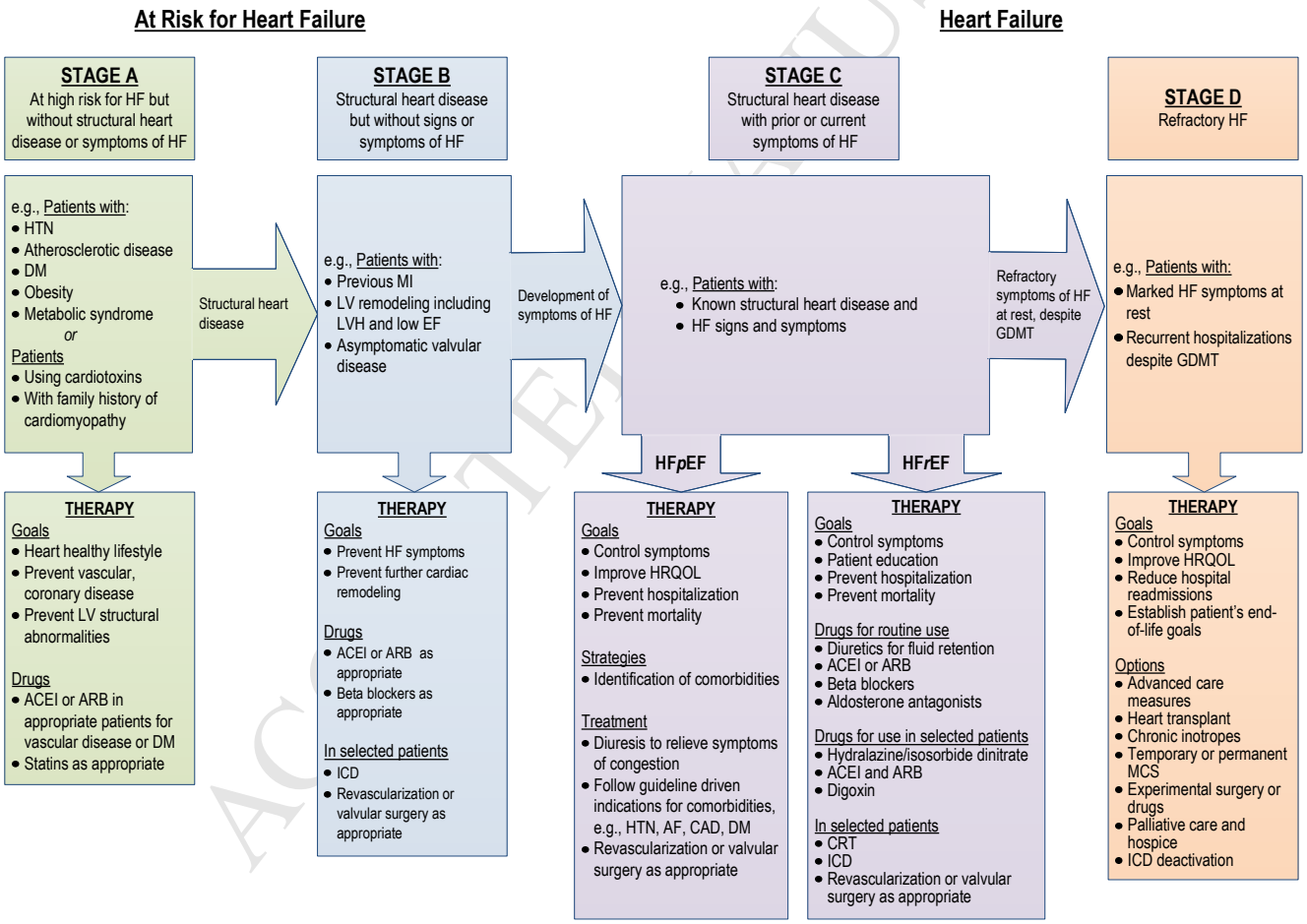
See Table 27 for a summary of recommendations from this section, Figure 3 for the stages of HF development; and online Data Supplement 36 (http://jaccjacc.cardiosource.com/DataSupp/ACCF/2013_HFGL_Evidence_Tables.pdf) for additional data on transplantation.

Table 27. Recommendations for Inotropic Support, MCS, and Cardiac Transplantation

TnQTable28*Although optimal patient selection for MCS remains an active area of investigation, general indications for referral for MCS therapy include patients with LVEF <25% and NYHA class III-IV functional status despite GDMT, including, when indicated, CRT, with either high predicted 1- to 2-y mortality (as suggested by markedly reduced peak oxygen consumption, clinical prognostic scores, etc.) or dependence on continuous parenteral inotropic support. Patient selection requires a multidisciplinary team of experienced advanced HF and transplantation cardiologists, cardiothoracic surgeons, nurses, and, ideally, social workers and palliative care clinicians.

BTT indicates bridge to transplant; COR, Class of Recommendation; CRT, cardiac resynchronization therapy; EF, ejection fraction; GDMT, guideline-directed medical therapy; HF, heart failure; HF*r*EF, heart failure with reduced ejection fraction; LOE, Level of Evidence; MCS, mechanical circulatory support; and NYHA, New York Heart Association.

Figure 3. Stages in the development of HF and recommended therapy by stage.



ACEI indicates angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin-receptor blocker; CAD, coronary artery disease; CRT, cardiac resynchronization therapy; DM, diabetes mellitus; EF, ejection fraction; GDMT, guideline-directed medical therapy; HF, heart failure; HF*p*EF, heart failure with preserved ejection fraction; HF*r*EF, heart failure with reduced ejection fraction; HRQOL, health-related quality of life; HTN, hypertension; ICD, implantable cardioverter-defibrillator; LV, left ventricular; LVH, left ventricular hypertrophy; MCS, mechanical circulatory support; and MI, myocardial infarction.

Adapted from Hunt et al (38).

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8. The Hospitalized Patient

8.1. Classification of Acute Decompensated HF

Hospitalization for HF is a growing and major public health issue (703). Presently, HF is the leading cause of hospitalization among patients >65 years of age (51); the largest percentage of expenditures related to HF are directly attributable to hospital costs. Moreover, in addition to costs, hospitalization for acutely decompensated HF represents a sentinel prognostic event in the course of many patients with HF, with a high risk for recurrent hospitalization (e.g., 50% at 6 months) and a 1-year mortality rate of approximately 30% (211, 704). The AHA has published a scientific statement about this condition (705).

There is no widely accepted nomenclature for HF syndromes requiring hospitalization. Patients are described as having "acute HF," "acute HF syndromes," or "acute(ly) decompensated HF"; while the third has gained greatest acceptance, it too has limitations, for it does not make the important distinction between those with a de novo presentation of HF from those with worsening of previously chronic stable HF.

Data from HF registries have clarified the profile of patients with HF requiring hospitalization (107, 704, 706, 707). Characteristically, such patients are elderly or near elderly, equally male or female, and typically have a history of hypertension, as well as other medical comorbidities, including chronic kidney disease, hyponatremia, hematologic abnormalities, and chronic obstructive pulmonary disease (107, 706, 708-713). A relatively equal percentage of patients with acutely decompensated HF have impaired versus preserved LV systolic function (707, 714, 715); clinically, patients with preserved systolic function are older, more likely to be female, to have significant hypertension, and to have less CAD. The overall morbidity and mortality for both groups is high.

Hospitalized patients with HF can be classified into important subgroups. These include patients with acute coronary ischemia, accelerated hypertension and acutely decompensated HF, shock, and acutely worsening right HF. Patients who develop HF decompensation after surgical procedures also bear mention. Each of these various categories of HF has specific etiologic factors leading to decompensation, presentation, management, and outcomes.

Noninvasive modalities can be used to classify the patient with hospitalized HF. The history and physical examination allows estimation of a patient's hemodynamic status, that is, the degree of congestion ("dry" versus "wet"), as well as the adequacy of their peripheral perfusion ("warm" versus "cold") (716) (Figure 4). Chest radiography is variably sensitive for the presence of interstitial or alveolar edema, even in the presence of elevated filling pressures. Thus, a normal chest radiograph does not exclude acutely decompensated HF (717). The utility of natriuretic peptides in patients with acutely decompensated HF has been described in detail in Section 6.3.1. Both BNP and NT-proBNP are useful for the identification or exclusion of acutely decompensated HF in dyspneic patients (247, 249, 250, 718, 719), particularly in the context of uncertain diagnosis (720-722). Other options for diagnostic evaluation of patients with suspected acutely decompensated

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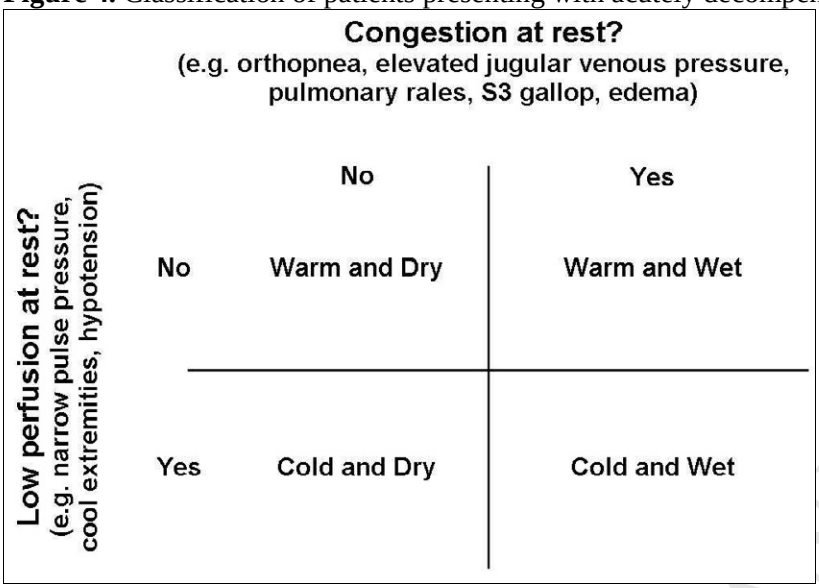
HF, such as acoustic cardiography (723), bioimpedance vector monitoring (724), or noninvasive cardiac output monitoring (725) are not yet validated.

Figure 4. Classification of patients presenting with acutely decompensated HF.



Adapted with permission from Nohria et al (716).

8.2. Precipitating Causes of Decompensated HF: Recommendations

Class I

1. **ACS precipitating acute HF decompensation should be promptly identified by ECG and serum biomarkers, including cardiac troponin testing, and treated optimally as appropriate to the overall condition and prognosis of the patient. *(Level of Evidence: C)***
2. **Common precipitating factors for acute HF should be considered during initial evaluation, as recognition of these conditions is critical to guide appropriate therapy. (*Level of Evidence: C)***

ACS is an important cause of worsening or new-onset HF (726). Although acute ST-segment elevation myocardial infarction can be readily apparent on an ECG, other ACS cases may be more challenging to diagnose. Complicating the clinical scenario is that many patients with acute HF, with or without CAD, have serum troponin levels that are elevated (727).

However, many other patients may have low levels of detectable troponins not meeting criteria for an acute ischemic event (278, 728). Registry data have suggested that the use of coronary angiography is low for patients hospitalized with decompensated HF, and opportunities to diagnose important CAD may be missed (729). For the patient with newly discovered HF, clinicians should always consider the possibility that CAD is an underlying cause of HF (726).

Besides ACS, several other precipitating causes of acute HF decompensation must be carefully assessed to inform appropriate treatment, optimize outcomes, and prevent future acute events in patients with HF (730). See list below.

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Common Factors That Precipitate Acute Decompensated HF

- Nonadherence with medication regimen, sodium and/or fluid restriction
- Acute myocardial ischemia
- Uncorrected high blood pressure
- AF and other arrhythmias
- Recent addition of negative inotropic drugs (e.g., verapamil, nifedipine, diltiazem, beta blockers)
- Pulmonary embolus
- Initiation of drugs that increase salt retention (e.g., steroids, thiazolidinediones, NSAIDs)
- Excessive alcohol or illicit drug use
- Endocrine abnormalities (e.g., diabetes mellitus, hyperthyroidism, hypothyroidism)
- Concurrent infections (e.g., pneumonia, viral illnesses)
- Additional acute cardiovascular disorders (e.g., valve disease endocarditis, myopericarditis, aortic dissection)

Hypertension is an important contributor to acute HF, particularly among blacks, women, and those with HF*p*EF (731). In the ADHERE registry, almost 50% of patients admitted with HF had blood pressure >140/90 mm Hg (107). Abrupt discontinuation of antihypertensive therapy may precipitate worsening HF. The prevalence of AF in patients with acute HF is >30% (731). Infection increases metabolic demands in general. Pulmonary infections, which are common in patients with HF, may add hypoxia to the increased metabolic demands and is associated with worse outcomes (730). The sepsis syndrome is associated with reversible myocardial depression that is likely mediated by cytokine release (732). Patients with HF are hypercoagulable, and the possibility of pulmonary embolus as an etiology of acute decompensation should be considered. Deterioration of renal function can be both a consequence and contributor to decompensated HF. Restoration of normal thyroid function in those with hypothyroidism or hyperthyroidism may reverse abnormal cardiovascular function (733). In patients treated with amiodarone, thyroid disturbances should be suspected.

Excessive sodium and fluid intake may precipitate acute HF (379, 384). Medication nonadherence for financial or other reasons is a major cause of hospital admission (734). Several drugs may precipitate acute HF (e.g., calcium channel blockers, antiarrhythmic agents, glucocorticoids, NSAIDs and cyclooxygenase-2 inhibitors, thiazolidinediones, and over-the-counter agents like pseudoephedrine). Finally, excessive alcohol intake and use of illicit drugs, such as cocaine and methamphetamine, also need to be investigated as potential causes of HF decompensation.

See Online Data Supplement 37 (http://jaccjacc.cardiosource.com/DataSupp/ACCF/2013_HFGL_Evidence_Tables.pdf) for additional data on comorbidities in the hospitalized patient.

8.3. Maintenance of GDMT During Hospitalization: Recommendations

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Class I

1. **In patients with HF*r*EF experiencing a symptomatic exacerbation of HF requiring hospitalization during chronic maintenance treatment with GDMT, it is recommended that GDMT be continued in the absence of hemodynamic instability or contraindications (195, 735, 736). *(Level of Evidence: B)***
2. **Initiation of beta-blocker therapy is recommended after optimization of volume status and successful discontinuation of intravenous diuretics, vasodilators, and inotropic agents. Beta-blocker therapy should be initiated at a low dose and only in stable patients. Caution should be used when initiating beta blockers in patients who have required inotropes during their hospital course (195, 735, 736). *(Level of Evidence: B)***

The patient's maintenance HF medications should be carefully reviewed on admission, and it should be decided whether adjustments should be made as a result of the hospitalization. In the majority of patients with HF*r*EF who are admitted to the hospital, oral HF therapy should be continued, or even uptitrated, during hospitalization. It has been demonstrated that continuation of ACE inhibitors or ARBs and beta blockers for most patients is well tolerated and results in better outcomes (195, 735, 736). Withholding of, or reduction in, beta-blocker therapy should be considered only in patients hospitalized after recent initiation or increase in beta-blocker therapy or with marked volume overload or marginal/low cardiac output. Patients admitted with significant worsening of renal function should be considered for a reduction in, or temporary discontinuation of ACE inhibitors, ARBs, and/or aldosterone antagonists until renal function improves. Although it is important to ensure that evidence-based medications are instituted before hospital discharge, it is equally critical to reassess medications on admission and adjust their administration in light of the worsening HF.

8.4. Diuretics in Hospitalized Patients: Recommendations

Class I

1. **Patients with HF admitted with evidence of significant fluid overload should be promptly treated with intravenous loop diuretics to reduce morbidity (737, 738). *(Level of Evidence: B)***
2. **If patients are already receiving loop diuretic therapy, the initial intravenous dose should equal or exceed their chronic oral daily dose and should be given as either intermittent boluses or continuous infusion. Urine output and signs and symptoms of congestion should be serially assessed, and the diuretic dose should be adjusted accordingly to relieve symptoms, reduce volume excess, and avoid hypotension (739). *(Level of Evidence: B)***
3. **The effect of HF treatment should be monitored with careful measurement of fluid intake and output, vital signs, body weight that is determined at the same time each day, and clinical signs and symptoms of systemic perfusion and congestion. Daily serum electrolytes, urea nitrogen, and creatinine concentrations should be measured during the use of intravenous diuretics or active titration of HF medications. *(Level of Evidence: C)***

Class IIa

1. **When diuresis is inadequate to relieve symptoms, it is reasonable to intensify the diuretic regimen using either:**
   a. **higher doses of intravenous loop diuretics (38, 739). *(Level of Evidence: B)*;**
   b. **addition of a second (e.g., thiazide) diuretic (740-743). *(Level of Evidence: B)*.**

Class IIb

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1. **Low-dose dopamine infusion may be considered in addition to loop diuretic therapy to improve diuresis and better preserve renal function and renal blood flow (744, 745). (*Level of Evidence: B)***

Patients with significant fluid overload should be initially treated with loop diuretics given intravenously during hospitalization. Therapy should begin in the emergency department without delay, as early therapy has been associated with better outcomes (737, 738). Patients should be carefully monitored, including serial evaluation of volume status and systemic perfusion. Monitoring of daily weight, supine and standing vital signs, and fluid input and output is necessary for daily management. Assessment of daily electrolytes and renal function should be performed while intravenous diuretics are administered or HF medications are actively titrated. Intravenous loop diuretics have the potential to reduce glomerular filtration rate, further worsen neurohumoral activation, and produce electrolyte disturbances. Thus, although the use of diuretics may relieve symptoms, their impact on mortality has not been well studied. Diuretics should be administered at doses sufficient to achieve optimal volume status and relieve congestion without inducing an excessively rapid reduction in intravascular volume, which could result in hypotension, renal dysfunction, or both. Because loop diuretics have a relatively short half-life, sodium reabsorption in the tubules will occur once the tubular concentration of the diuretics declines. Therefore, limiting sodium intake and dosing the diuretic continuously or multiple times per day will enhance diuretic effectiveness (434, 737, 746-748).

Some patients may present with moderate to severe renal dysfunction such that the diuretic response may be blunted, necessitating higher initial diuretic doses. In many cases, reduction of fluid overload may improve congestion and improve renal function, particularly if significant venous congestion is reduced (749). Clinical experience suggests it is difficult to determine whether congestion has been adequately treated in many patients, and registry data have confirmed that patients are frequently discharged after a net weight loss of only a few pounds. Although patients may rapidly improve symptomatically, they may remain congested or hemodynamically compromised. Routine use of serial natriuretic peptide measurement or Swan-Ganz catheter has not been conclusively shown to improve outcomes among these patients. Nevertheless, careful evaluation of all physical findings, laboratory parameters, weight change, and net fluid change should be considered before discharge.

When a patient does not respond to initial intravenous diuretics, several options may be considered. Efforts should be made to make certain that congestion persists and that another hemodynamic profile or alternate disease process is not evident. If there is doubt about the fluid status, consideration should be given for assessment of filling pressures and cardiac output using right-heart catheterization. If volume overload is confirmed, the dose of the loop diuretic should be increased to ensure that adequate drug levels reach the kidney. Adding a second diuretic, typically a thiazide, can improve diuretic responsiveness (435, 442, 443). Theoretically, continuous diuretic infusion may enhance diuresis because continuous diuretic delivery to the nephron avoids rebound sodium and fluid reabsorption (440, 441, 750, 751). However, the DOSE (Diuretic Optimization Strategies Evaluation) trial did not find any significant difference between continuous infusion

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versus intermittent bolus strategies for symptoms, diuresis, or outcomes (739). It is reasonable to try an alternate approach of using either bolus or continuous infusion therapy different from the initial strategy among patients who are resistant to diuresis. Finally, some data suggest that low-dose dopamine infusion in addition to loop diuretics may improve diuresis and better preserve renal function, although ongoing trials will provide further data on this effect (744).

See Online Data Supplement 17 (http://jaccjacc.cardiosource.com/DataSupp/ACCF/2013_HFGL_Evidence_Tables.pdf) for additional data on diuretics.

8.5. Renal Replacement Therapy—Ultrafiltration: Recommendations

Class IIb

1. **Ultrafiltration may be considered for patients with obvious volume overload to alleviate congestive symptoms and fluid weight (752).** ***(Level of Evidence: B)***
2. **Ultrafiltration may be considered for patients with refractory congestion not responding to medical therapy.** ***(Level of Evidence: C)***

If all diuretic strategies are unsuccessful, ultrafiltration may be considered. Ultrafiltration moves water and small- to medium-weight solutes across a semipermeable membrane to reduce volume overload. Because the electrolyte concentration is similar to plasma, relatively more sodium can be removed than by diuretics (753-755). Initial studies supporting use of ultrafiltration in HF were small but provided safety and efficacy data in acute HF (755-757). Use of ultrafiltration in HF has been shown to reduce neurohormone levels and increase diuretic responsiveness. In a larger trial of 200 unselected patients with acute HF, ultrafiltration did reduce weight compared with bolus or continuous diuretics at 48 hours, had similar effects on the dyspnea score compared with diuretics, and improved readmission rate at 90 days (752). A randomized acute HF trial in patients with cardiorenal syndrome and persistent congestion has failed to demonstrate a significant advantage of ultrafiltration over bolus diuretic therapy (758, 759). Cost, the need for veno-venous access, provider experience, and nursing support remain concerns about the routine use of ultrafiltration. Consultation with a nephrologist is appropriate before initiating ultrafiltration, especially in circumstances where the non-nephrology provider does not have sufficient experience with ultrafiltration.

See Online Data Supplements 17 and 38 (http://jaccjacc.cardiosource.com/DataSupp/ACCF/2013_HFGL_Evidence_Tables.pdf) for additional data on diuretics versus ultrafiltration in acute decompensated HF and worsening renal function and mortality.

8.6. Parenteral Therapy in Hospitalized HF: Recommendation

Class IIb

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1. **If symptomatic hypotension is absent, intravenous nitroglycerin, nitroprusside, or nesiritide may be considered an adjuvant to diuretic therapy for relief of dyspnea in patients admitted with acutely decompensated HF (760-763).** ***(Level of Evidence: A)***

The different vasodilators include 1) intravenous nitroglycerin, 2) sodium nitroprusside, and 3) nesiritide.

Intravenous nitroglycerin acts primarily through venodilation, lowers preload, and may help to rapidly reduce pulmonary congestion (764, 765). Patients with HF and hypertension, coronary ischemia, or significant mitral regurgitation are often cited as ideal candidates for the use of intravenous nitroglycerin. However, tachyphylaxis to nitroglycerin may develop within 24 hours, and up to 20% of those with HF may develop resistance to even high doses (766-768).

Sodium nitroprusside is a balanced preload-reducing venodilator and afterload-reducing arteriodilator that also dilates the pulmonary vasculature (769). Data demonstrating efficacy are limited, and invasive hemodynamic blood pressure monitoring (such as an arterial line) is typically required; in such cases, blood pressure and volume status should be monitored frequently. Nitroprusside has the potential for producing marked hypotension and is usually used in the intensive care setting as well; longer infusions of the drug have been rarely associated with thiocyanate toxicity, particularly in the setting of renal insufficiency. Nitroprusside is potentially of value in severely congested patients with hypertension or severe mitral valve regurgitation complicating LV dysfunction.

Nesiritide (human BNP) reduces LV filling pressure but has variable effects on cardiac output, urinary output, and sodium excretion. An initial study demonstrated that the severity of dyspnea is reduced more rapidly compared with diuretics alone (760). A large randomized trial in patients with acute decompensated HF demonstrated nesiritide had no impact on mortality, rehospitalization, or renal function, a small but statistically significant impact on dyspnea, and an increased risk of hypotension (762). Because nesiritide has a longer effective half-life than nitroglycerin or nitroprusside, adverse effects such as hypotension may persist longer. Overall, presently there are no data that suggest that intravenous vasodilators improve outcomes in the patient hospitalized with HF; as such, use of intravenous vasodilators is limited to the relief of dyspnea in the hospitalized HF patient with intact blood pressure. Administration of intravenous vasodilators in patients with HF*p*EF should be done with caution because these patients are typically more volume sensitive.

The use of inotropic support as indicated for hospitalized HF with shock or impending shock and/or end-organ perfusion limitations is addressed in Section 7.4.4. See Table 26 for drug therapies and Online Data Supplements 32 and 33 *(http://jaccjacc.cardiosource.com/DataSupp/ACCF/2013_HFGL_Evidence_Tables.pdf)* for additional information on inotropic support.

See Online Data Supplement 39 (http://jaccjacc.cardiosource.com/DataSupp/ACCF/2013_HFGL_Evidence_Tables.pdf) for additional data on nesiritide.

8.7. Venous Thromboembolism Prophylaxis in Hospitalized Patients: Recommendation

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Class I

1. **A patient admitted to the hospital with decompensated HF should receive venous thromboembolism prophylaxis with an anticoagulant medication if the risk–benefit ratio is favorable (770-775).** ***(Level of Evidence: B)***

HF has long been recognized as affording additional risk for venous thromboembolic disease, associated with a number of pathophysiologic changes, including reduced cardiac output, increased systemic venous pressure, and chemical changes promoting blood clotting. When patients are hospitalized for decompensated HF or when patients with chronic stable HF are hospitalized for other reasons, they are at increased risk for venous thromboembolic disease, although accurate numerical estimates are lacking in the literature.

Most early data on the effectiveness of different anticoagulant regimens to reduce the incidence of venous thromboembolic disease in hospitalized patients were either observational, retrospective reports (776, 777) or prospective studies using a variety of drugs and differing definitions of therapeutic effect and endpoints (774, 778-780), making summary conclusions difficult. Early studies involved patients with far longer hospital lengths of stay than occur presently and were performed well before present standard-of-care treatments and diagnostic tests were available (774, 778-780). Newer trials using presently available antithrombotic drugs often were not limited to patients with HF but included those with other acute illnesses, severe respiratory diseases, or simply a broad spectrum of hospitalized medical patients (771-774, 781). In most studies, patients were categorized as having HF by admitting diagnosis, clinical signs, or functional class, whereas only 1 study (782) provided LVEF data on enrolled study patients. All included trials tried to exclude patients perceived to have an elevated risk of bleeding complications or with an elevated risk of toxicity from the specific agent tested (e.g., enoxaparin in patients with compromised renal function). Patients with HF typically made up a minority of the study cohort, and significance of results were not always reported by the authors, making ACCF/AHA class I recommendations difficult to support using this guideline methodology. In some trials, concurrent aspirin was allowed but not controlled for as a confounding variable (772, 783).

For patients admitted specifically for decompensated HF and with adequate renal function (serum creatinine <2.0 mg/dL), randomized trials suggest that enoxaparin 40 mg subcutaneously once daily (770, 773, 774, 783) or unfractionated heparin 5,000 units subcutaneously every 8 hours (771) will reduce radiographically demonstrable venous thrombosis. Effects on mortality or clinically significant pulmonary embolism rates are unclear. Lower doses of enoxaparin do not appear superior to placebo (770, 773), whereas continuing weight-based enoxaparin therapy up to 3 months after hospital discharge does not appear to provide additional benefit (782).

A single prospective study failed to demonstrate certoparin to be noninferior to unfractionated heparin (783), whereas retrospective analysis of a prospective trial of dalteparin was underpowered to determine benefit

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in its HF cohort (776). Fondaparinux failed to show significant difference from placebo in an RCT that included a subgroup of 160 patients with HF (781).

No adequate trials have evaluated anticoagulant benefit in patients with chronic but stable HF admitted to the hospital for other reasons. However, the MEDENOX (Medical Patients with Enoxaparin) trial suggested that the benefit of enoxaparin may extend to this population (770, 773, 774).

A systematic review (784) failed to demonstrate prophylactic efficacy of graded compression stockings in general medical patients, but significant cutaneous complications were associated with their use. No studies were performed exclusively on patients with HF. Two RCTs in patients with stroke found no efficacy of these devices (785, 786).

See Online Data Supplement 20 (http://jaccjacc.cardiosource.com/DataSupp/ACCF/2013_HFGL_Evidence_Tables.pdf) for additional data on anticoagulation.

8.8. Arginine Vasopressin Antagonists: Recommendation

Class IIb

1. **In patients hospitalized with volume overload, including HF, who have persistent severe hyponatremia and are at risk for or having active cognitive symptoms despite water restriction and maximization of GDMT, vasopressin antagonists may be considered in the short term to improve serum sodium concentration in hypervolemic, hyponatremic states with either a V_2 receptor selective or a nonselective vasopressin antagonist (787, 788).** ***(Level of Evidence: B)***

Even mild hyponatremia may be associated with neurocognitive problems, including falls and attention deficits (789). Treatment of hypervolemic hyponatremia with a V_2-selective vasopressin antagonist (tolvaptan) was associated with a significant improvement in the mental component of the Medical Outcomes Study Short Form General Health Survey (788). Hyponatremia may be treated with water restriction and maximization of GDMT that modulate angiotensin II, leading to improved renal perfusion and decreased thirst. Alternative causes of hyponatremia (e.g., syndrome of inappropriate antidiuretic hormone, hypothyroidism, and hypoaldosteronism) should be assessed. Vasopressin antagonists improve serum sodium in hypervolemic, hyponatremic states (787, 788); however, longer-term therapy with a V_2-selective vasopressin antagonist did not improve mortality in patients with HF (790, 791). Currently, 2 vasopressin antagonists are available for clinical use: conivaptan and tolvaptan. It may be reasonable to use a nonselective vasopressin antagonist to treat hyponatremia in patients with HF with cognitive symptoms due to hyponatremia. However, the long-term safety and benefit of this approach remains unknown. A summary of the recommendations for the hospitalized patient appears in Table 28.

Table 28. Recommendations for Therapies in the Hospitalized HF Patient
TnQTable29COR indicates Class of Recommendation; GDMT, guideline-directed medical therapy; HF, heart failure; HF*r*EF, heart failure with reduced ejection fraction; LOE, Level of Evidence; and N/A, not available.

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8.9. Inpatient and Transitions of Care: Recommendations

See Table 29 for a summary of recommendations from this section.

Class I

1. **The use of performance improvement systems and/or evidence-based systems of care is recommended in the hospital and early postdischarge outpatient setting to identify appropriate HF patients for GDMT, provide clinicians with useful reminders to advance GDMT, and assess the clinical response (82, 365, 706, 792-796). (*Level of Evidence: B*)**
2. **Throughout the hospitalization as appropriate, before hospital discharge, at the first postdischarge visit, and in subsequent follow-up visits, the following should be addressed (204, 795, 797-799). (*Level of Evidence: B*):**
    - **a. initiation of GDMT if not previously established and not contraindicated;**
    - **b. precipitant causes of HF, barriers to optimal care transitions, and limitations in postdischarge support;**
    - **c. assessment of volume status and supine/upright hypotension with adjustment of HF therapy as appropriate;**
    - **d. titration and optimization of chronic oral HF therapy;**
    - **e. assessment of renal function and electrolytes where appropriate;**
    - **f. assessment and management of comorbid conditions;**
    - **g. reinforcement of HF education, self-care, emergency plans, and need for adherence; and**
    - **h. consideration for palliative care or hospice care in selected patients.**
3. **Multidisciplinary HF disease-management programs are recommended for patients at high risk for hospital readmission, to facilitate the implementation of GDMT, to address different barriers to behavioral change, and to reduce the risk of subsequent rehospitalization for HF (82, 800-802). (*Level of Evidence: B*)**

Class IIa

1. **Scheduling an early follow-up visit (within 7 to 14 days) and early telephone follow-up (within 3 days) of hospital discharge is reasonable (101, 803). (*Level of Evidence: B*)**
2. **Use of clinical risk-prediction tools and/or biomarkers to identify patients at higher risk for postdischarge clinical events is reasonable (215). *(Level of Evidence: B)***

Decisions about pharmacological therapies delivered during hospitalization likely can impact postdischarge outcome. Continuation or initiation of HF GDMT prior to hospital discharge is associated with substantially improved clinical outcomes for patients with HF*r*EF. However, caution should be used when initiating beta blockers in patients who have required inotropes during their hospital course or when initiating ACE inhibitors, ARBs, or aldosterone antagonists in those patients who have experienced marked azotemia or are at risk for hyperkalemia. The patient should be transitioned to oral diuretic therapy to verify its effectiveness. Similarly, optimal volume status should be achieved. blood pressure should be adequately controlled, and, in patients with AF, ventricular response should also be well controlled. The hospitalization is a “teachable moment” to reinforce patient and family education and develop a plan of care, which should be communicated to the appropriate healthcare team.

Safety for patients hospitalized with HF is crucial. System changes necessary to achieve safer care include the adoption by all US hospitals of a standardized set of 30 “Safe Practices” endorsed by the National

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Quality Forum (804) and National Patient Safety Goals espoused by The Joint Commission (805). Improved communication between clinicians and nurses, medication reconciliation, carefully planned transitions between care settings, and consistent documentation are examples of patient safety standards that should be ensured for patients with HF discharged from the hospital.

The prognosis of patients hospitalized with HF, and especially those with serial readmissions, is suboptimal. Hence, appropriate levels of symptomatic relief, support, and palliative care for patients with chronic HF should be addressed as an ongoing key component of the plan of care, especially when patients are hospitalized with acute decompensation (806). The appropriateness of discussion about advanced therapy or end-of-life preferences is reviewed in Section 11.

For patients with HF, the transition from inpatient to outpatient care can be an especially vulnerable period because of the progressive nature of the disease state, complex medical regimens, the large number of comorbid conditions, and the multiple clinicians who may be involved. Patient education and written discharge instructions or educational material given to the patient, family members, and/or caregiver during the hospital stay or at discharge to home are essential components of transition care. These should address all of the following: activity level, diet, discharge medications, follow-up appointment, weight monitoring, and what to do if symptoms worsen (297). Thorough discharge planning that includes special emphasis on ensuring adherence to an evidence-based medication regimen (795) is associated with improved patient outcomes (792, 797, 807). More intensive delivery of discharge instructions, coupled tightly with subsequent well-coordinated follow-up care for patients hospitalized with HF, has produced positive results in several studies (82, 793, 800). The addition of a 1-hour, nurse educator–delivered teaching session at the time of hospital discharge, using standardized instructions, resulted in improved clinical outcomes, increased self-care and treatment adherence, and reduced cost of care. Patients receiving the education intervention also had a lower risk of rehospitalization or death and lower costs of care (365). There are ongoing efforts to further develop evidence-based interventions in this population.

Transitional care extends beyond patient education. Care information, especially changes in orders and new diagnostic information, must be transmitted in a timely and clearly understandable form to all of the patient's clinicians who will be delivering follow-up care. Other important components of transitional care include preparation of the patient and caregiver for what to expect at the next site of care, reconciliation of medications, follow-up plans for outstanding tests, and discussions about monitoring signs and symptoms of worsening conditions. Early outpatient follow-up, a central element of transitional care, varies significantly across US hospitals. Early postdischarge follow-up may help minimize gaps in understanding of changes to the care plan or knowledge of test results and has been associated with a lower risk of subsequent rehospitalization (803). A follow-up visit within 7 to 14 days and/or a telephone follow-up within 3 days of hospital discharge are reasonable goals of care.

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Table 29. Recommendations for Hospital Discharge
TnQTable30COR indicates Class of Recommendation; GDMT, guideline-directed medical therapy; HF, heart failure; and LOE, Level of Evidence.

See Online Data Supplement 40 (http://jaccjacc.cardiosource.com/DataSupp/ACCF/2013_HFGL_Evidence_Tables.pdf) for additional data on oral medications for the hospitalized patient.

9. Important Comorbidities in HF

*9.1. Atrial Fibrillation**

Patients with HF are more likely than the general population to develop AF (808). There is a direct relationship between the NYHA class and prevalence of AF in patients with HF progressing from 4% in those who are NYHA class I to 40% in those who are NYHA class IV (809). AF is also a strong independent risk factor for subsequent development of HF (808, 810). In addition to those with HF*r*EF, patients with HF*p*EF are also at greater risk for AF (811). HF and AF can interact to promote their perpetuation and worsening through mechanisms such as rate-dependent worsening of cardiac function, fibrosis, and activation of neurohumoral vasoconstrictors. AF can worsen symptoms in patients with HF, and, conversely, worsened HF can promote a rapid ventricular response in AF.

Similar to other patient populations, for those with AF and HF, the main goals of therapy are prevention of thromboembolism and symptom control. Most patients with AF and HF would be expected to be candidates for systemic anticoagulation unless otherwise contraindicated. General principles of management include correction of underlying causes of AF and HF as well as optimization of HF management (Table 30). As in other patient populations, the issue of rate control versus rhythm control has been investigated. For patients who develop HF as a result of AF, a rhythm control strategy should be pursued. It is important to recognize that AF with a rapid ventricular response is one of the few potentially reversible causes of HF. Because of this, a patient who presents with newly detected HF in the presence of AF with a rapid ventricular response should be presumed to have a rate-related cardiomyopathy until proved otherwise. In this situation, 2 strategies can be considered. One is rate control of the patient's AF and see if HF and EF improve. The other is to try to restore and maintain sinus rhythm. In this situation, it is common practice to initiate amiodarone and then arrange for cardioversion 1 month later. Amiodarone has the advantage of being both an effective rate-control medication and the most effective antiarrhythmic medication with a lower risk of proarrhythmic effect.

In patients with HF who develop AF, a rhythm-control strategy has not been shown to be superior to a rate-control strategy (812). If rhythm control is chosen, limited data suggest that AF catheter ablation in HF patients may lead to improvement in LV function and quality of life but is less likely to be effective than in patients with intact cardiac function (813, 814). Because of their favorable effect on morbidity and mortality in patients with systolic HF, beta-adrenergic blockers are the preferred agents for achieving rate control unless otherwise

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contraindicated. Digoxin may be an effective adjunct to a beta blocker. The nondihydropyridine calcium antagonists, such as diltiazem, should be used with caution in those with depressed EF because of their negative inotropic effect. For those with HF*p*EF, nondihydropyridine calcium antagonists can be effective for achieving rate control but may be more effective when used in combination with digoxin. For those for whom a rate-control strategy is chosen, when rate control cannot be achieved either because of drug inefficacy or intolerance, atrioventricular node ablation and CRT device placement can be useful (78, 116, 595, 596). See Figures 5 and 6 for AF treatment algorithms.

*The "ACC/AHA/ESC 2006 Guidelines for the Management of Patients With Atrial Fibrillation" and the 2 subsequent focused updates from 2011 (815-817) are considered policy at the time of publication of the present HF Guideline; however, a fully revised AF guideline, which will include updated recommendations on AF, is in development, with publication expected in 2013 or 2014.

See Online Data Supplement 41 (http://jaccjacc.cardiosource.com/DataSupp/ACCF/2013_HFGL_Evidence_Tables.pdf) for additional data on AF.

Table 30. Clinical Evaluation in Patients With AF

TnQTable31Type IC refers to the Vaughan Williams classification of antiarrhythmic drugs.
AF indicates atrial fibrillation; AV, atrioventricular; ECG, electrocardiogram; LA, left atrial; LV, left ventricular; MI, myocardial infarction; RA, right atrial; and RV, right ventricular.
Reproduced from Fuster et al (6).

Figure 5. Pharmacological management of patients with newly discovered AF.

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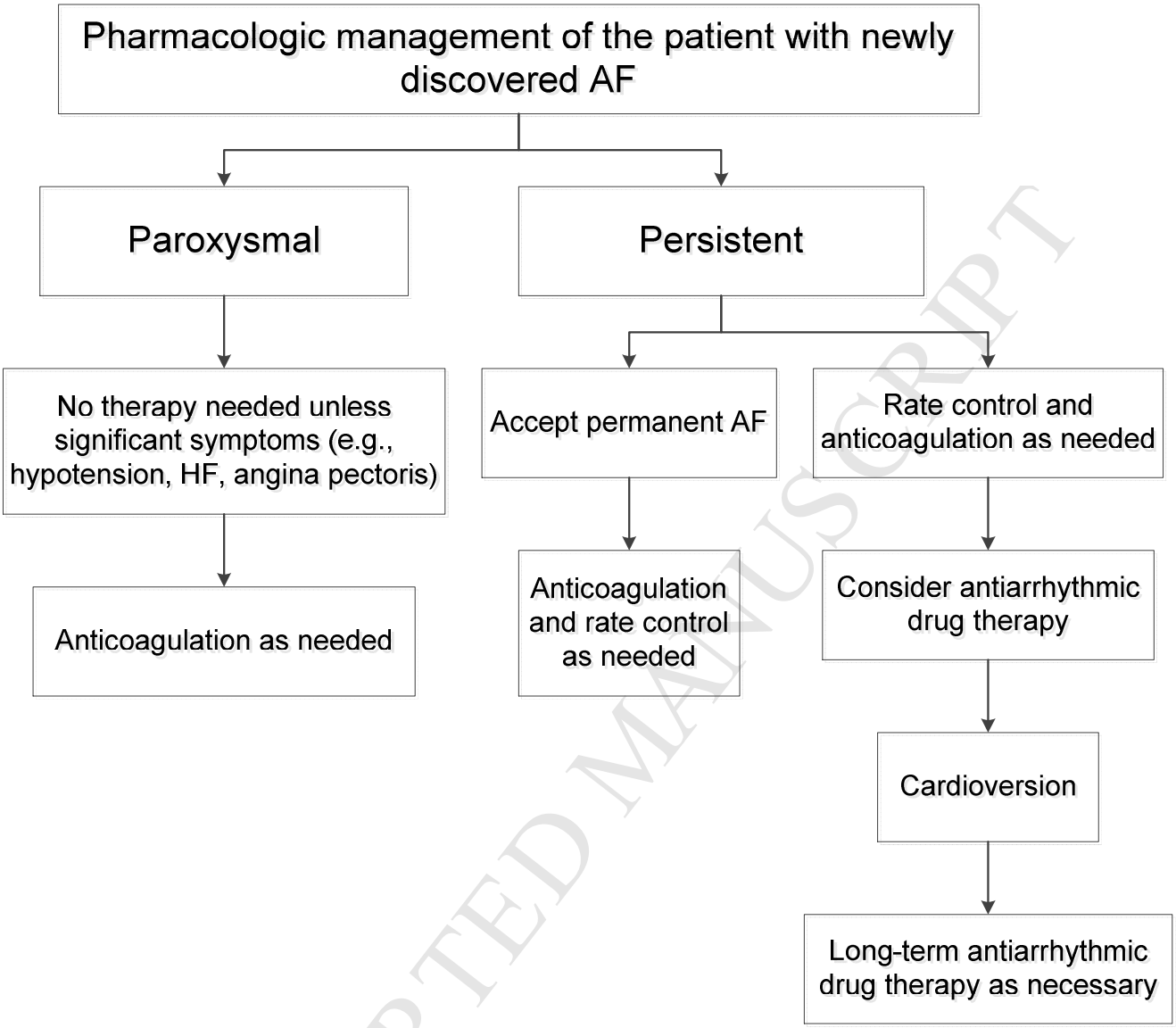

AF indicates atrial fibrillation; and HF, heart failure.
Reproduced from Fuster et al (6).

Figure 6. Pharmacological management of patients with recurrent paroxysmal AF.

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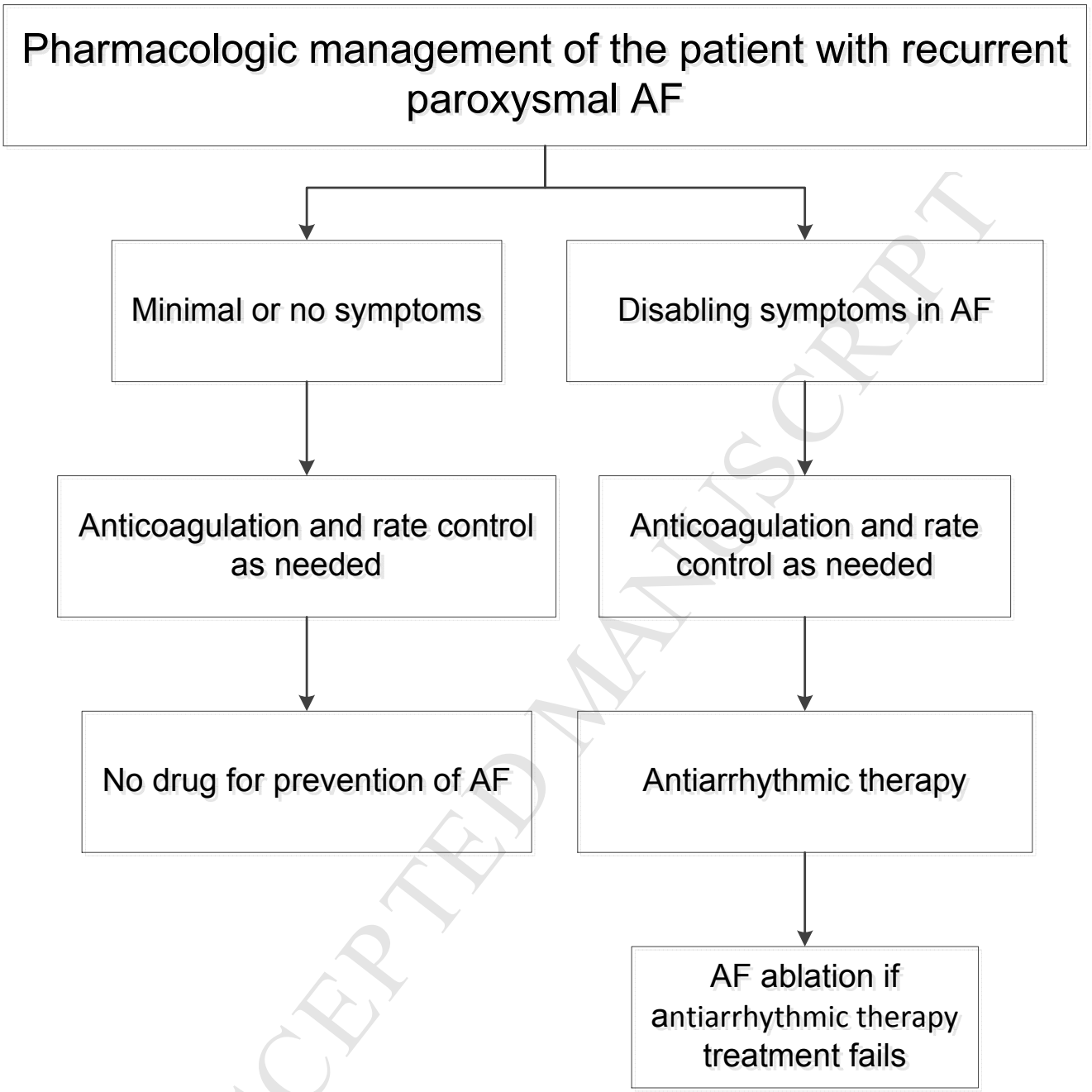

AF indicates atrial fibrillation.
Reproduced from Fuster et al (6).

9.2. Anemia

Anemia is a common finding in patients with chronic HF. Although variably reported, in part due to the lack of consensus on the definition of anemia, the prevalence of anemia among patients with HF increases with HF severity. Anemia is also more common in women and is seen in both patients with HF*r*EF and HF*p*EF (818-823). The World Health Organization defines anemia as a hemoglobin level of <12 g/dL in women and <13 g/dL in men. Registries have reported anemia to be present in 25% to 40% of HF patients (818-820). Anemia is

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associated with an increased mortality risk in HF. In a large study of >150,000 patients, the mortality risk was approximately doubled in anemic HF patients compared with those without anemia, and this risk persisted after controlling for other confounders, including renal dysfunction and HF severity (818). Anemia is also associated with reduced exercise capacity, impaired HRQOL, and a higher risk for hospitalization (225, 819, 824, 825). These risks are inversely and linearly associated with hemoglobin levels, although a U-shaped risk with the highest hemoglobin levels has been reported (822, 826).

Multiple etiological factors, many of which coexist within individual patients, contribute to the development of anemia in HF. Anemia in patients with HF is often normocytic and accompanied by an abnormally low reticulocyte count (825, 827). Evaluation of anemia in HF requires careful consideration of other causes, the most common being secondary causes of iron deficiency anemia.

In persons without identifiable causes of anemia, erythropoiesis-stimulating agents have gained significant interest as potential adjunctive therapy in the patient with HF. In a retrospective study of erythropoiesis-stimulating agents in 26 patients with HF and anemia, the hemoglobin level, LVEF, and functional class improved (828). These patients required lower diuretic doses and were hospitalized less often. Similar findings were also observed in a randomized open-label study of 32 patients (829). A single-blind RCT showed that erythropoietin increased hemoglobin, peak oxygen uptake, and exercise duration in patients with severe HF and anemia (830). Two further studies confirmed these findings; however, none of these were double blind (831, 832).

These positive data led to 2 larger studies. A 165-patient study showed that darbepoetin alfa was associated with improvement in several HRQOL measures with a trend toward improved exercise capacity (6-minute walking distance +34 ±7 m versus +11 ±10 m, p=0.074) (833). In STAMINA-HeFT (Study of Anemia in Heart Failure Trial), 319 patients were randomly assigned to darbepoetin alfa or placebo for 12 months (834). Although darbepoetin alfa did not improve exercise duration, it was well tolerated, and a trend toward improvement in the composite endpoint of all-cause mortality or first hospitalization for HF was seen (hazard ratio: 0.68; 95% confidence interval: 0.43 to 1.08; p=0.10) (834). These favorable data led to the design and initiation of the RED-HF (Phase III Reduction of Events With Darbepoetin alfa in Heart Failure) trial (835).

Two trials in erythropoiesis-stimulating agents, however, later raised concerns that patients treated with an erythropoiesis-stimulating agent may have an increased risk of cardiovascular events (836, 837). Because the populations in these trials differed, the RED-HF trial was continued. Concerns about the use of erythropoiesis-stimulating agents remain. The use of darbepoetin alfa in patients with HF (n=1,347), however, seems safe (838). Also, a substudy of the CHOIR (Correction in Hemoglobin and Outcomes in Renal Insufficiency) trial showed that the increased risk associated with the higher hemoglobin target was not observed in patients with HF at baseline (hazard ratio: 0.99) (839). Finally, a trial using intravenous iron as a supplement in patients with HF*r*EF with iron deficiency showed an improvement in functional status (840). There were no untoward adverse

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effects of iron in this trial. In the absence of a definitive evidence base, the writing committee has deferred a specific treatment recommendation regarding anemia until ongoing randomized trials are completed.

9.3. Depression

Depression is common in patients with HF; those with depressive symptoms have lower HRQOL, poorer self-care, worse clinical outcomes, and more use of healthcare services (841-843). Although it might be assumed that depression occurs only among hospitalized patients (844), a multicenter study demonstrated that even at least 3 months after a hospitalization, 63% of patients with HF reported symptoms of depression (845). Potential pathophysiologic mechanisms proposed to explain the high prevalence of depression in HF include autonomic nervous system dysfunction, inflammation, cardiac arrhythmias, and altered platelet function, but the mechanism remains unclear (846). Although remission from depression may improve cardiovascular outcomes, the most effective intervention strategy is not yet known (842).

9.4. Other Multiple Comorbidities

Although there are additional and important comorbidities that afflict patients with HF as shown in Table 31, how best to generate specific recommendations remains uncertain, given the status of current evidence.

Table 31. Ten Most Common Co-Occurring Chronic Conditions Among Medicare Beneficiaries With Heart Failure (N=4,947,918), 2011

TnQTable32CMS indicates Centers for Medicare and Medicaid Services; and COPD, chronic obstructive pulmonary disease.

10. Surgical/Percutaneous/Transcather Interventional Treatments of HF: Recommendations

See Table 32 for a summary of recommendations from this section.

Class I

1. **Coronary artery revascularization via CABG or percutaneous intervention is indicated for patients (HF*p*EF and HF*r*EF) on GDMT with angina and suitable coronary anatomy, especially for a left main stenosis (>50%) or left main equivalent disease (10, 12, 14, 848). *(Level of Evidence: C)***

Class IIa

1. **CABG to improve survival is reasonable in patients with mild to moderate LV systolic dysfunction (EF 35% to 50%) and significant (≥70% diameter stenosis) multivessel CAD or proximal left anterior descending coronary artery stenosis when viable myocardium is present in the region of intended revascularization (848-850). *(Level of Evidence: B)***
2. **CABG or medical therapy is reasonable to improve morbidity and cardiovascular mortality for patients with severe LV dysfunction (EF <35%), HF, and significant CAD (309, 851). *(Level of Evidence: B)***
3. **Surgical aortic valve replacement is reasonable for patients with critical aortic stenosis and a predicted surgical mortality of no greater than 10% (852). *(Level of Evidence: B)***

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4. **Transcatheter aortic valve replacement after careful candidate consideration is reasonable for patients with critical aortic stenosis who are deemed inoperable (853).** ***(Level of Evidence: B)***

Class IIb

1. **CABG may be considered with the intent of improving survival in patients with ischemic heart disease with severe LV systolic dysfunction (EF <35%) and operable coronary anatomy whether or not viable myocardium is present (307-309).** ***(Level of Evidence: B)***
2. **Transcatheter mitral valve repair or mitral valve surgery for functional mitral insufficiency is of uncertain benefit and should only be considered after careful candidate selection and with a background of GDMT (854-857).** ***(Level of Evidence: B)***
3. **Surgical reverse remodeling or LV aneurysmectomy may be considered in carefully selected patients with HF*r*EF for specific indications, including intractable HF and ventricular arrhythmias (858).** ***(Level of Evidence: B)***

Surgical therapies and percutaneous interventions that are commonly integrated, or at least considered, in HF management include coronary revascularization (e.g., CABG, angioplasty, stenting); aortic valve replacement; mitral valve replacement or repair; septal myectomy or alcohol septal ablation for hypertrophic cardiomyopathy; surgical ablation of ventricular arrhythmia; MCS; and cardiac transplantation (675, 680, 859, 860). Surgical placement of ICDs or LV pacing leads is of historical importance but may be considered in situations where transvenous access is not feasible.

The most common reason for intervention is CAD. Myocardial viability indicates the likelihood of improved outcomes with either surgical or medical therapy but does not identify patients with greater survival benefit from revascularization (304). The dictum of CABG for left main CAD and reduced LV function was considered absolute and subsequently extrapolated to all severities of LV dysfunction without a confirmatory evidence base (848). Newer studies have addressed patients with multivessel CAD, HF, and at least moderately severe to severe LV systolic dysfunction (861, 862). Both surgical and medical therapies have similar outcomes, and decisions about revascularization should be made jointly by the HF team and cardiothoracic surgeon. The most important considerations in the decision to proceed with a surgical or interventional approach include coronary anatomy that is amenable to revascularization and appropriate concomitant GDMT. Valvular heart disease is not an infrequent cause of HF; however, when valvular disease is managed correctly and pre-emptively, its adverse consequences on ventricular mechanics can be ameliorated. The advent of effective transcather approaches to both mitral and aortic disease creates the need for greater considerations of structural interventions for patients with LV systolic dysfunction and valvular heart disease. To date, the surgical or transcather management of functional mitral insufficiency has not been proven superior to medical therapy. A decision to intervene in functional mitral regurgitation should be made on a case-by-case basis, and consideration should be given to participation in clinical trials and/or databases. The surgical or transcather management of critical aortic stenosis is an effective strategy with reasonable outcomes noted even in patients with advanced age (>80 years). Indications for other surgical or percutaneous interventions in the setting of HF are driven by other relevant guidelines or other sections of this guideline, including myomectomy for

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hypertrophic cardiomyopathy, surgical or electrophysiological procedures for AF, nondurable or durable MCS, and heart transplantation.

Several procedures under evaluation hold promise but are not yet appropriate for a guideline-driven indication (Table 33). This includes revascularization as a means to support cellular regenerative therapies. For patients willing to consider regenerative technologies, the ideal strategy is referral to an enrolling clinical trial at a center experienced in both high-risk revascularization and cell-based science (863-865). Surgical reverse-ventricular remodeling (ventricular reconstruction) does not appear to be of benefit but may be considered in carefully selected patients with HF*r*EF for specified indications, including retractable HF and ventricular arrhythmias (858).

Table 32. Recommendations for Surgical/Percutaneous/Transcather Interventional Treatments of HF
TnQTable33CABG indicates coronary artery bypass graft; CAD, coronary artery disease; COR, Class of Recommendation; EF, ejection fraction; GDMT, guideline-directed medical therapy; HF, heart failure; HF*r*EF, heart failure with reduced ejection fraction; LAD, left anterior descending; LOE, Level of Evidence; and LV, left ventricular.

Table 33. Surgical/Percutaneous/Transcatheter Interventions in Patients With HF
TnQTable34AF indicates atrial fibrillation; HF, heart failure; and MCS, mechanical circulatory support.

11. Coordinating Care for Patients With Chronic HF

11.1. Coordinating Care for Patients With Chronic HF: Recommendations

Class I

1. **Effective systems of care coordination with special attention to care transitions should be deployed for every patient with chronic HF that facilitate and ensure effective care that is designed to achieve GDMT and prevent hospitalization (80, 82, 793, 870-884). *(Level of Evidence: B)***
2. **Every patient with HF should have a clear, detailed, and evidence-based plan of care that ensures the achievement of GDMT goals, effective management of comorbid conditions, timely follow-up with the healthcare team, appropriate dietary and physical activities, and compliance with Secondary Prevention Guidelines for cardiovascular disease. This plan of care should be updated regularly and made readily available to all members of each patient's healthcare team (13). *(Level of Evidence: C)***
3. **Palliative and supportive care is effective for patients with symptomatic advanced HF to improve quality of life (30, 885-888). *(Level of Evidence: B)***

Education, support, and involvement of patients with HF and their families are critical and often complex, especially during transitions of care. Failure to understand and follow a detailed and often nuanced plan of care likely contributes to the high rates of HF 30-day rehospitalization and mortality seen across the United States (61, 889). One critical intervention to ensure effective care coordination and transition is the provision of a comprehensive plan of care, with easily understood, culturally sensitive, and evidence-based educational materials, to patients with HF and/or caregivers during both hospital and office-based encounters. A comprehensive plan of care should promote successful patient self-care (870, 884, 890). Hence, the plan of care for patients with HF should continuously address in detail a number of complex issues, including adherence to

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GDMT, timely follow-up with the healthcare professionals who manage the patient's HF and associated comorbidities, appropriate dietary and physical activities, including cardiac rehabilitation, and adherence to an extensive list of secondary prevention recommendations based on established guidelines for cardiovascular disease (Table 34). Clinicians must maintain vigilance about psychosocial, behavioral, and socioeconomic issues that patients with HF and their caregivers face, including access to care, risk of depression, and healthcare disparities (639, 891-895). For example, patients with HF who live in skilled nursing facilities are at higher risk for adverse events, with a 1-year mortality rate >50% (896). Furthermore, community-dwelling patients with HF are often unable to afford the large number of medications prescribed, thereby leading to suboptimal medication adherence (897).

11.2. Systems of Care to Promote Care Coordination for Patients With Chronic HF

Improved communication between clinicians and nurses, medication reconciliation, carefully planned transitions between care settings, and consistent documentation are examples of patient safety standards that should be ensured for all patients with HF. The National Quality Forum has also endorsed a set of patient-centered "Preferred Practices for Care Coordination" (898), which detail comprehensive specifications for successful care coordination for patients and their families.

Systems of care designed to support patients with HF and other cardiac diseases can produce a significant improvement in outcomes. Furthermore, the Centers for Medicare and Medicaid Services is now financially penalizing hospitals for avoidable hospitalizations and readmissions, thereby emphasizing the importance of such systems-based care coordination of patients with HF (899). However, the quality of evidence is mixed for specific components of HF clinical management interventions, such as home-based care (871, 872), disease management (873, 874, 880), and remote telemonitoring programs (80, 875, 876, 878). Unfortunately, numerous and nonstandardized definitions of disease management (873, 879, 880), including the specific elements that compose disease management, impede on efforts to improve the care of patients with HF. Hence, more generic multidisciplinary strategies for improving the quality and cost-effectiveness of systems-based HF care should be evaluated with equal weight to those interventions focused on improving adherence to GDMT. For example, multidisciplinary approaches can reduce rates of hospitalization for HF. Programs involving specialized follow-up by a multidisciplinary team decrease all-cause hospitalizations and mortality; however, this has not been shown for "disease management programs" that focus only on self-care activities (82, 793, 881, 882, 900). Furthermore, patient characteristics may be important predictors of HF and other cardiac disease–related survival and hospitalization. Overall, very few specific interventions have been consistently identified and successfully applied in clinical practice (204, 214, 901-903).

See Online Data Supplements 42 and 43 (http://jaccjacc.cardiosource.com/DataSupp/ACCF/2013_HFGL_Evidence_Tables.pdf) for additional data on disease management and telemonitoring.

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11.3. Palliative Care for Patients With HF

The core elements of comprehensive palliative care for HF delivered by clinicians include expert symptom assessment and management. Ongoing care should address symptom control, psychosocial distress, HRQOL, preferences about end-of-life care, caregiver support, and assurance of access to evidence-based disease-modifying interventions. The HF team can help patients and their families explore treatment options and prognosis. The HF and palliative care teams are best suited to help patients and families decide when end-of-life care (including hospice) is appropriate (30, 885-888, 904). Assessment for frailty and dementia is part of this decision care process offered to the patient and family.

Data suggest that advance directives specifying limitations in end-of-life care are associated with significantly lower levels of Medicare spending, lower likelihood of in-hospital death, and higher use of hospice care in regions characterized by higher levels of end-of-life spending (905). In newly diagnosed cancer patients, palliative care interventions delivered early have had a positive impact on survival and HRQOL. This approach may also be relevant for HF (906). Access to formally trained palliative care specialists may be limited in ambulatory settings. Therefore, cardiologists, primary care physicians, physician assistants, advanced practice nurses, and other members of the HF healthcare team should be familiar with these local treatment options. Evaluation for cardiac transplantation or MCS in experienced centers should include formal palliative care consultation, which can improve advanced care planning and enhance the overall quality of decision making and integrated care for these patients, regardless of the advanced HF therapy selected (907).

Table 34. Plan of Care for Patients With Chronic HF

TnQTable35ACCF indicates American College of Cardiology Foundation; ACCP, American College of Chest Physicians; ACE; angiotensin-converting enzyme; ADA, American Diabetes Association; AHA, American Heart Association; ARB, angiotensin-receptor blocker; ATS, American Thoracic Society; CPR, cardiopulmonary resuscitation; CRT, cardiac resynchronization therapy; ERS, European Respiratory Society; HF, heart failure; HHS, Health and Human Services; ICD, implantable cardioverter-defibrillator; JNC, Joint National Committee; LVAD, left ventricular assist device; QOL, quality of life; SIHD, stable ischemic heart disease; and VAD, ventricular assist device.

12. Quality Metrics/Performance Measures: Recommendations

Class I

1. **Performance measures based on professionally developed clinical practice guidelines should be used with the goal of improving quality of care for HF (706, 801, 917). *(Level of Evidence: B)***

Class IIa

1. **Participation in quality improvement programs and patient registries based on nationally endorsed, clinical practice guideline–based quality and performance measures can be beneficial in improving the quality of HF care (706, 801). *(Level of Evidence: B)***

Quality measurement and accountability have become integral parts of medical practice over the past 2 decades. HF has been a specific target of quality measurement, improvement, and reporting because of its substantial

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impact on population morbidity and mortality. Commonly used performance measures for HF can be considered in 2 distinct categories: process measures and outcomes measures.

Process performance measures focus on the aspects of care that are delivered to a patient (e.g., the prescription of a particular drug such as an ACE inhibitor in patients with LV systolic dysfunction and without contraindications). Process measures derive from the most definitive guideline recommendations (i.e., class I and class III recommendations). A small group of process measures for hospitalized patients with HF have been reported to the public by the Centers for Medicare and Medicaid Services as part of the Hospital Compare program (918).

Measures used to characterize the care of patients with HF should be those developed in a multiorganizational consensus process using an explicit methodology focusing on measurability, validity, reliability, feasibility, and ideally, correlation with patient outcomes (919, 920), and with transparent disclosure and management of possible conflicts of interest. In the case of HF, several national outcome measures are currently in use (Table 35), and the ACCF/AHA/American Medical Association–Physician Consortium for Performance Improvement recently published revised performance measures document includes several process measures for both inpatient and outpatient HF care (Table 36) (921). Of note, the ACCF/AHA distinguish between processes of care that can be considered “Performance Measures” (i.e., suitable for use for accountability purposes) and “Quality Metrics” (i.e., suitable for use for quality improvement but not accountability) (922).

Measures are appealing for several reasons; by definition, they reflect the strongest guideline recommendations. When appropriately specified, they are relatively easy to calculate and they provide a clear target for improvement. However, they do not capture the broader range of care; they apply only to those patients without contraindications to therapy. Evidence of the relation between better performance with respect to process measures and patient outcomes is conflicting, and performance rates for those measures that have been used as part of public reporting programs are generally high for all institutions, limiting the ability of these measures to identify high- and low-performing centers.

These limitations of process measures have generated interest in the use of outcomes measures as a complementary approach to characterize quality. With respect to HF, 30-day mortality and 30-day readmission are reported by the Centers for Medicare and Medicaid Services as part of the Hospital Compare program (Table 35) and are incorporated in the Centers for Medicare and Medicaid Services value-based purchasing program (918). Outcomes measures are appealing because they apply universally to almost all patients, and they provide a perspective on the performance of health systems (923). On the other hand, they are limited by the questionable adequacy of risk adjustment and by the challenges of improvement. The ACCF and AHA have published criteria that characterize the necessary attributes of robust outcomes measures (924).

Table 35. Outcome Measures for HF

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TnQTable36HF indicates heart failure; and NQF, National Quality Forum.

Table 36. ACCF/AHA/AMA-PCPI 2011 HF Measurement Set

TnQTable37*Refer to the complete measures for comprehensive information, including measure exception.
†Test measure designated for use in internal quality improvement programs only. These measures are not appropriate for any other purpose (e.g., pay for performance, physician ranking, or public reporting programs).
‡New measure.
N.B., Regarding test measure no. 8, implantation of ICD must be consistent with published guidelines. This measure is intended to promote counseling only.
ACCF indicates American College of Cardiology Foundation; ACE, angiotensin-converting enzyme; AHA, American Heart Association; AMA-PCPI, American Medical Association–Physician Consortium for Performance Improvement; ARB, angiotensin-receptor blocker; HF, heart failure; ICD, implantable cardioverter-defibrillator; LVEF, left ventricular ejection fraction; and LVSD, left ventricular systolic dysfunction.
Adapted from Bonow et al (921).

See Online Data Supplement 44 (http://jaccjacc.cardiosource.com/DataSupp/ACCF/2013_HFGL_Evidence_Tables.pdf) for additional data on quality metrics and performance measures.

13. Evidence Gaps and Future Research Directions

Despite the objective evidence compiled by the writing committee on the basis of hundreds of clinical trials, there are huge gaps in our knowledge base about many fundamental aspects of HF care. Some key examples include an effective management strategy for patients with HF*p*EF beyond blood pressure control; a convincing method to use biomarkers in the optimization of medical therapy; the recognition and treatment of cardiorenal syndrome; and the critical need for improving patient adherence to therapeutic regimens. Even the widely embraced dictum of sodium restriction in HF is not well supported by current evidence. Moreover, the majority of the clinical trials that inform GDMT were designed around the primary endpoint of mortality, so that there is less certainty about the impact of therapies on the HRQOL of patients. It is also of major concern that the majority of RCTs failed to randomize a sufficient number of the elderly, women, and underrepresented minorities, thus, limiting insight into these important patient cohorts. A growing body of studies on patient-centered outcomes research is likely to address some of these deficiencies, but time will be required.

HF is a syndrome with a high prevalence of comorbidities and multiple chronic conditions, but most guidelines are developed for patients with a single disease. Nevertheless, the coexistence of additional diseases such as arthritis, renal insufficiency, diabetes, or chronic lung disease to the HF syndrome should logically require a modification of treatment, outcome assessment, or follow-up care. About 25% of Americans have multiple chronic conditions; this figure rises to 75% in those >65 years of age, including the diseases referred to above, as well as asthma, hypertension, cognitive disorders, or depression (847). Most RCTs in HF specifically excluded patients with significant other comorbidities from enrollment, thus limiting our ability to generalize

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our recommendations to many real-world patients. Therefore, the clinician must, as always, practice the art of using the best of the guideline recommendations as they apply to a specific patient.

Future research will need to focus on novel pharmacological therapies, especially for hospitalized HF; regenerative cell-based therapies to restore myocardium; and new device platforms that will either improve existing technologies (e.g., CRT, ICD, left VAD) or introduce simpler, less morbid devices that are capable of changing the natural history of HF. What is critically needed is an evidence base that clearly identifies best processes of care, especially in the transition from hospital to home. Finally, preventing the burden of this disease through more successful risk modification, sophisticated screening, perhaps using specific omics technologies (i.e., systems biology) or effective treatment interventions that reduce the progression from stage A to stage B is an urgent need.

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Key Words: ACCF/AHA Practice Guidelines ■ heart failure ■ epidemiology ■ cardio-renal physiology/pathophysiology ■ other heart failure ■ CV surgery: transplantation, ventricular assistance, cardiomyopathy ■ health policy and outcome research ■ congestive heart failure

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Appendix 1. Author Relationships With Industry and Other Entities (Relevant)—2013 ACCF/AHA Guideline for the Management of Heart Failure

TnQTable38This table represents the relationships of committee members with industry and other entities that were determined to be relevant to this document. These relationships were reviewed and updated in conjunction with all meetings and/or conference calls of the writing committee during the document development process. The table does not necessarily reflect relationships with industry at the time of publication. A person is deemed to have a significant interest in a business if the interest represents ownership of ≥5% of the voting stock or share of the business entity, or ownership of ≥$10,000 of the fair market value of the business entity; or if funds received by the person from the business entity exceed 5% of the person's gross income for the previous year. Relationships that exist with no financial benefit are also included for the purpose of transparency. Relationships in this table are modest unless otherwise noted.

According to the ACCF/AHA, a person has a *relevant* relationship IF: a) The *relationship or interest* relates to the same or similar subject matter, intellectual property or asset, topic, or issue addressed in the *document*; or b) The *company/entity* (with whom the relationship exists) makes a drug, drug class, or device addressed in the *document*, or makes a competing drug or device addressed in the *document*; or c) The *person or a member of the person's household*, has a reasonable potential for financial, professional or other personal gain or loss as a result of the issues/content addressed in the *document***.**

*Writing committee members are required to recuse themselves from voting on sections to which their specific relationships with industry and other entities may apply. Section numbers pertain to those in the full-text guideline.
†Indicates significant relationship.

DSMB indicates Data Safety Monitoring Board; EP, electrophysiology; NYU, New York University; PARADIGM, a Multicenter, Randomized, Double-blind, Parallel Group, Active-controlled Study to Evaluate the Efficacy and Safety of LCZ696 Compared to Enalapril on Morbidity and Mortality in Patients With Chronic Heart Failure and Reduced Ejection Fraction; PI, Principal Investigator; SUNY, State University of New York; UCLA, University of California, Los Angeles; and VA, Veterans Affairs.

Appendix 2. Reviewer Relationships With Industry and Other Entities (Relevant)—2013 ACCF/AHA Guideline for the Management of Heart Failure

TnQTable39This table represents the relationships of reviewers with industry and other entities that were disclosed at the time of peer review and determined to be relevant to this document. It does not necessarily reflect relationships with industry at the time of publication. A person is deemed to have a significant interest in a business if the interest represents ownership of ≥5% of the voting stock or share of the business entity, or ownership of ≥$10 000 of the fair market value of the business entity; or if funds received by the person from the business entity exceed 5% of the person's gross income for the previous year. A relationship is considered to be modest if it is less than significant under the preceding definition. Relationships that exist with no financial benefit are also included for the purpose of transparency. Relationships in this table are modest unless otherwise noted. Names are listed in alphabetical order within each category of review.

According to the ACCF/AHA, a person has a *relevant* relationship IF: a) The *relationship or interest* relates to the same or similar subject matter, intellectual property or asset, topic, or issue addressed in the *document*; or b) The *company/entity* (with whom the relationship exists) makes a drug, drug class, or device addressed in the

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document, or makes a competing drug or device addressed in the *document*; or c) The *person or a member of the person's household* has a reasonable potential for financial, professional, or other personal gain or loss as a result of the issues/content addressed in the *document***.**

*Significant relationship.
†No financial benefit.

AAFP indicates American Academy of Family Physicians; ACCF, American College of Cardiology Foundation; ACCP, American College of Chest Physicians; AHA, American Heart Association; DSMB, data safety monitoring board; EP, electrophysiology; HRS, Heart Rhythm Society; ISHLT, International Society for Heart and Lung Transplantation; and VA, Veterans Affairs.

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Appendix 3. Abbreviations

ACE = angiotensin-converting enzyme
ACS = acute coronary syndrome
AF = atrial fibrillation
ARB = angiotensin-receptor blocker
BMI = body mass index
BNP = B-type natriuretic peptide
BTT = bridge to transplantation
CABG = coronary artery bypass graft
CAD = coronary artery disease
CPAP = continuous positive airway pressure
CRT = cardiac resynchronization therapy
DCM = dilated cardiomyopathy
ECG = electrocardiogram
EF = ejection fraction
GDMT = guideline-directed medical therapy
HbA1c = hemoglobin A1c
HF = heart failure
HF*p*EF = heart failure with preserved ejection fraction
HF*r*EF = heart failure with reduced ejection fraction
HRQOL = health-related quality of life
ICD = implantable cardioverter-defibrillator
LBBB = left bundle-branch block
LV = left ventricular
LVEF = left ventricular ejection fraction
MCS = mechanical circulatory support
MI = myocardial infarction
NSAIDs = nonsteroidal anti-inflammatory drugs
NT-proBNP = N-terminal pro-B-type natriuretic peptide
NYHA = New York Heart Association
PUFA = polyunsaturated fatty acids
RCT = randomized controlled trial
SCD = sudden cardiac death
VAD = ventricular assist device

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2013 Heart Failure Guideline Data Supplements

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Data Supplement 1. HFpEF (Section 2.2)

Study Name, Author, Year	Aim of Study	Study Type	Study Size	Patient Population		Endpoints	Statistical Analysis (Results)	Study Limitations	Findings/ Comments
				Inclusion Criteria	*Exclusion Criteria*				
Masoudi JACC 2003;41:217-223 12535812 (1)	To assess factors associated with preserved LVSF in pts with HF	Cross sectional cohort study	19,710	Medicare beneficiary; hospitalized with principal discharge diagnosis of HF; acute care hospitalization; hospitalized between 4/1998-3/1999	No documentation of LVEF	Preserved LVSF	Multivariable logistic regression to assess factors associated with preserved LVSF	Limited to Medicare population; limited to hospitalized pts; missing LVEF in a portion of the population	Factors associated with preserved LVSF, which included gender, advanced age, HTN, AF; and absence of coronary disease
Owan NEJM 2006;355:251-259 16855265 (2)	Define temporal trends in prevalence of HF with preserved LVEF over 15 y period	Retrospective cohort study	4,596	Consecutive pts admitted to Mayo Clinic hospitals; Discharge code for HF; 1987-2001	No documentation of LVEF	Proportion of pts with preserved LVSF; survival	Linear regression and survival analysis	Limited to Olmsted County, MN; limited to hospitalized pts; missing LVEF in a portion of the population	Overall, more than half the population had preserved LVSF; this proportion increased overtime; survival in pts with HFpEF was only slightly better than for those with HFrEF (HR:0.96)
Bhatia NEJM 2006;355:260-269 16855266 (3)	Evaluate the epidemiological features and outcomes of pts with HFpEF vs. HFrEF	Retrospective cohort study	2,802	Pts admitted to 103 Ontario hospitals; 4/1999-3/2001; discharge diagnosis of HF	No documentation of LVEF	Death within 1 y; readmission for HF	Multivariable survival analysis	Limited to Ontario; limited to hospitalized pts; missing LVEF in a portion of the population	31% had HFpEF; HFpEF more often female, older, with AF, and HTN; Unadjusted mortality similar (22% for HFpEF vs. 26% for HFrEF); adjusted mortality also similar (aHR:1.13); readmission rates also similar between groups.
Lee Circulation 2009;119:3070-3077 19506115 (4)	Assess the contribution of risk factors and disease pathogenesis to HFpEF	Retrospective cohort study	534	Framingham participants; incident HF	N/A	Factors associated with HFpEF; Mortality	Multivariable logistic regression (risk factors); multivariable survival analysis (mortality)	Limited to Framingham cohort; relatively small sample size	Factors associated with HFpEF included female gender; elevated SBP; AF; and absence of CAD. Long-term prognosis equally poor (overall cohort median survival of 2.1 y; 5-y mortality 74%).

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Kane JAMA 2011;306:856-863 21862747 (5)	Measure changes in diastolic function and assess the relationship between diastolic abnormalities and HF risk	Retrospective cohort study	2042	Random sample from Olmsted County MN in 1997; age ≥45; participating in baseline and follow up assessments	N/A	Diastolic function grade; incident HF	Multivariable survival analysis	Limited to Olmsted County, MN; limited to those following up for 2nd examination	In 4 y between baseline and follow-up, prevalence of diastolic dysfunction increased from 23.8% to 39.2%. Diastolic dysfunction associated with incident HF (HR:1.81)

AF indicates atrial fibrillation; CAD, coronary artery disease; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HTN, hypertension; LVEF, left ventricular ejection fraction; LVSF, left ventricular systolic function; MN, Minnesota; N/A, not applicable; pts, patients, and SBP, systolic blood pressure.

Data Supplement 2. NYHA and AHA/ACC Class (Section 3)

Study Name, Author, Year	Aim of Study	Study Type	Study Size	Patient Population		Endpoints		Statistical Analysis (Results)	Study Limitations	Findings/ Comments
				Inclusion Criteria	*Exclusion Criteria*	*Primary Endpoint*	*Secondary Endpoint*			
Madsen BK, 1994 8013501 (6)	Predict CHF mortality	Longitudinal registry	190	N/A	Must be ambulatory	Death	N/A	Kaplan-Meier Mortality increased with increased NYHA class and with decreased EF	N/A	Conducted primarily outside U.S.
Holland R, 2010 20142027 (7)	Predict CHF mortality using self-assessed NYHA class	Longitudinal registry	293	Adults with CHF after CHF admission	N/A	Readmission over 6 mo	MLHF questionnaire and death	Survival analysis Readmission rate increased with higher NYHA class	No clinician assessment to compare to pt assessment	Conducted primarily outside U.S.
Anmar KA, 2007 17353436 (8)	Measure association of HF stages with mortality	Cross-sectional cohort	2,029	Residents of Olmsted Co, MN	N/A	5-y survival rates	BNP	Survival analysis HF stages associated with progressively worsening 5-y survival rates	Retrospective classification of stage	N/A
Goldman L, 1981 7296795 (9)	Reproducibility for assessing CV functional class	Longitudinal registry	75	All those referred for treadmill testing	N/A	Reproducibility testing	N/A	NYHA classification	N/A	Reproducibility only 56%

BNP indicates B-type natriuretic peptide; CHF, congestive heart failure; CV, cardiovascular; EF, ejection fraction; HF, heart failure; MLHF, Minnesota Living with Heart Failure; N/A, not applicable; NYHA, New York Heart Association; and pt, patient.

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Data Supplement 3. Prognosis - Mortality (Section 4.1)

Study Name, Author, Year	Aim of Study	Study Type	Study Size	Patient Population		Endpoints		Statistical Analysis (Results)	P Values & 95% CI:	Study Limitations	Findings/ Comments
				Inclusion Criteria	*Exclusion Criteria*	*Primary Endpoint*	*Secondary Endpoint*				
The Seattle HF Model: Prediction of Survival in HF Levy, Wayne Circ 2006 16534009 (10)	Develop and validate a risk model for 1,2,and 3-y mortality	Cohort	Derivation: 1,125 Validation: 9,942	Derivation Cohort: EF <30%, NYHA class III-IV Validation Cohort: EF <40%, NYHA class II-IV Both derivation and validation cohorts primarily out-pts (both clinical trial populations)	N/A	Prediction of 1,2,3-y mortality	N/A	Predicted vs. actual survival for 1, 2, and 3 y: 88.2% vs 87.8%, 79.2% vs 77.6%, 71.8% vs. 68.0%	ROC: 0.729; 95% CI: 0.714-0.744	Population not representative of HF population in general: clinical trial populations, restricted to HF with LVSD. Estimation of risk score is complex and requires computer/calculator.	24 variables included in risk score
Predicting Mortality Among Pts Hospitalized with HF (EFFECT) Lee, Douglas JAMA 2003 14625335 (11)	Develop and validate a risk model for 30-d and 1-y mortality	Cohort	Derivation: 2,624 Validation: 1,407	No EF requirement; Community-based pts hospitalized with HF in Canada (met modified Framingham HF criteria)	Pts who developed HF after admit, transferred from different facility, over 105 y, nonresidents	30-d and 1-y mortality	N/A	Derivation Cohort: in-hospital mortality: 8.9%, 30-d mortality: 10.7%; 1-y mortality: 32.9% Validation cohort: in-hospital mortality: 8.2%, 30-d mortality: 10.4%; 1-y mortality:30.5%	ROC: 0.79 for 30-d mortality; ROC; 0.76 for 1-y mortality	N/A	Variables in Model: age, SBP, resp rate, Na <136, Hbg <10, BUN, CVD, COPD, dementia, cirrhosis, cancer
Predictors of Mortality After Discharge in pts Hospitalized w/ HF (OPTIMIZE-HF) O'Connor, Christopher AHJ 2008 18926148 (12)	Develop models predictive of 60 and 90 d mortality	Cohort study/registry	4,402	No EF criteria (49% with LVSD), pts hospitalized with HF at institutions participating in OPIMIZE-HF performance-improvement program	N/A	Death at 60-90 d	Hospitalization; death or rehospitalization	60-90 d mortality: 8.6%; death or rehospitalization: 36.2%	c index: 0.735; bias-corrected c index: 0.723	Validity - assessed by bootstraping	Developed a nomogram. Variables included in score: Age, weight, SBP, sodium, Cr, liver disease, depression, RAD

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Predictors of Mortality and Morbidity in Pts with Chronic HF Pocock, Stuart EHJ 2006 16219658 (13)	Develop prognostic models for 2-y mortality	Cohorts: used pts in the CHARM program	7,599	No EF criteria; out-pts; symptomatic HF	K >5.5; Cr >265 umol/L; MI or stroke in prior 4 wk; noncardiac disease limiting survival	Mortality	CV death or hospitalization	N/A	ROC:0.75, bias corrected: 0.74; ROC: 0.73 in low EF and in preserved EF cohorts	Population studied not representative of HF in general (pts enrolled in CHARM); validity - assessed by bootstrapping; laboratory data not available.	23 variables included in model
Risk Stratification for Inhospital Mortality in Acutely Decompensated HF: Classification and Regression Tree Analysis Fonarow, Gregg JAMA 2005 15687312 (14)	Estimate mortality risk in pts hospitalized with HF	Cohort/registry	Derivation:33,046 Validation: 32,229	Pts admitted with HF to hospital participating in the ADHERE registry; no EF criteria;	None	In-hospital mortality	N/A	Classification and regression tree analysis; In-hospital mortality: 4.1%; 95% CI:2.1%-21.9%	N/A	N/A	Classifies pts into 5 risk categories. Discriminating nodes: BUN; SBP; Cr
A validated risk score of in-hospital mortality in pts with HF from the AHA GWTG Program Peterson, Pamela CircCQO 2010 20123668 (15)	Develop a risk score for inhospital mortality	Cohort/registry	Derivation:27,850; Validation:11,933	Pts admitted with HF to hospitals participating in the GWTG-HF program	Transfers, missing LVEF data	Inhospital mortality		Inhospital mortality 2.86%; C index 0.75	N/A	Validation cohort from same population. GWTG is a voluntary registry	Variables included in risk score: SBP, BUN, Sodium, age, heart rate, race, COPD
Predictors of inhospital mortality in pts hospitalized for HF. Insights from OPTIMIZE-HF Abraham, William JACC 2008 18652942 (16)	Develop a clinical predictive model of in-hospital mortality	Cohort/registry	40,201	Pts admitted to hospital participating in OPTIMIZE-HF (registry/performance improvement program); no EF criteria (LVSD in 49% of those with measured EF); included those admitted with different diagnosis than the discharge diagnosis of HF	N/A	Inhospital mortality		Inhospital mortality: 3.8%; C index 0.77	N/A	Validity - assessed by bootstrapping	Risk prediction nomogram: age, HR, SBP, sodium, Cr, primary cause for admit, LVSD
Predictors of fatal and non-fatal outcomes in the CORONA:	Develop prognostic models in elderly pts and	Cohort	3,342	Pts enrolled in the CORONA study. Pts ≥60 y; NYHA class II-IV HF; investigator reported	Recent CV event or procedure/operation, acute or chronic liver disease or ALT >2x ULN; BUN >2.5 mg/dL;	Composite: CV mortality, nonfatal MI or nonfatal	All-cause mortality; CV mortality; fatal or nonfatal MI;	Total mortality: C index of 0.719; death due to HF: C index of 0.80;	N/A	Used a clinical trial population; limited to ischemic etiology	Elderly pts on contemporary HF therapy; NT-proBNP added

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incremental value of apolipoprotein A-1, high-sensitivity C-reactive peptide and NT proBNP Wedel, Hans EJHF 2009 19168876 (17)	evaluate the relative prognostic significance of new biomarkers			ischemic etiology; EF ≤40% (or 35% if NYHA II)	chronic muscle disease or unexplained CK >2.5x ULNl; TSH >2x ULN; any condition substantially reducing life expectancy	stroke (time to event)	death from any cause or hospitalization for HF	all-cause mortality or HF hospitalization: C index of 0.701 (all models included NT-proBNP)			predictive information
Comparison of Four Clinical Prediction Rules for Estimating Risk in HF Auble, Thomas E Annals of Emergency Medicine 2007 17449141 (18)	Examine the performance of 4 clinical prediction rules (ADHERE decision tree, ADHERE regression model, EFFECT, Brigham and Women's Hospital rule) for inpatient death, 30-d death, and inhospital death or serious complications	Cohort	33,533	Pts with primary ICD-9 discharge diagnosis of HF admitted at one of 2 Pennsylvania hospitals from the ED	N/A	Inhospital mortality; in-hospital mortality or serious complication; 30-d mortality	N/A	Inhospital mortality: 4.5%; Inhospital mortality or serious medical complication: 11.2%; 30-d mortality: 7.9% ADHERE rules could not be used in 4.1% because BUN or SCr were N/A.	N/A	N/A	Variability among rules in the number of pts assigned to risk groups and the observed mortality within risk group. EFFECT identified pts at the lowest risk, ADHERE tree identified largest proportion of pts in the lowest risk group

ADHERE indicates Acute Decompensated Heart Failure National Registry; AHA, American Heart Association; BUN, blod urea nitrogen; CHARM, Candesartan in Heart Failure: Assessment of Reduction in Mortality and morbidity; COPD, chronic obstructive pulmonary disease; CORONA, Controlled Rosuvastatin Multinational Trial in HF; CV, cardiovascular; CVD, cardiovascular disease; ED, emergency department; EF, ejection fraction; EFFECT, Enhanced Feedback for Effective Cardiac Treatment; GWTG, Get With the Guidelines; HF, heart failure; Hgb, hemoglobin; HR, heart rate; ICD-9, international classification of diseases; LVSD, left ventricular systolic dysfunction; MI, myocardial infarction; Na, sodium, N/A, not applicable; NT-proBNP; n-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; OPIMIZE-HF, Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure; pts, patients; RAD, reactive airway disease; ROC, receiver operating characteristic curve; SBP, systolic blood pressure; SCr, serum creatinine; TSH, thyroid stimulating hormone; ULN, upper limit of normal.

Data Supplement 4. Health-Related Quality of Life and Functional Capacity (Section 4.4)

Study Name, Author, Year	Aim of Study	Study Type	Study Size	Patient Population		Endpoints		Statistical Analysis (Results)	Study Limitations	Findings/Comments
				Inclusion	*Exclusion*	*Primary*	*Secondary*			

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				Criteria	*Criteria*	*Endpoint*	*Endpoint*			
Improvement in HRQoL after hospitalization predicts event-free survival in pts with advanced HF. Moser et al 2009 19879462 (19)	To determine the frequency, durability, and prognostic significance of improved HRQoL after hospitalization for decompensated HF.	Secondary analysis of data from the ESCAPE trial	425	Hospitalized for NYHA class IV, at least 1 sign of fluid overload EF <30% history of prior HF hospitalization or chronic high maintenance diuretic doses survived to discharge from index admission	Significant comorbid condition that could shorten life (e.g. cancer), pulmonary artery catheter, mechanical circulatory or ventilatory support, IV milrinone within 48 h, dobutamine/ dopamine within 24 h, listed for CTX	HRQoL measured with the MLHFQ	Event-free survival	At baseline HRQoL was severely impaired but improved on average at 1 mo (74.2 ± 17.4 vs 56.7 ± 22.7) and improved most at 6 mo. HRQOL worsened in 51 (16.3%) pts and remained the same in 49 (15.7%). OR: 3.3; p<.009 The only characteristic that distinguished among these groups was whether or not the pt was too ill to perform the 6-min walk. There was a group by time interaction; the degree of improvement across time differed between pts who survived without an event and those who died or were rehospitalized by 6 mo. Pts with events between 1 and 6 mo did not experience as much improvement in HRQoL. A decrease in MLHFQ of >5 points predicted better event-free survival. (p<.0001 group time interaction)	Potential for survivor bias. Self-reported HRQoL. Relatively short follow-up period of 6 mo.	In pts hospitalized with severe HF decompensation, HRQoL is seriously impaired but improves substantially within 1 mo for most pts and remains improved for 6 mo. Pts for whom HRQoL does not improve by 1 mo after hospital admission merit specific attention both to improve HRQoL and to address high risk for poor event-free survival
QoL and depressive symptoms in the elderly: a comparison between pts with HF and age and gender matched community controls. Lesman-Leegte et al, 2009. 19181289 (20)	To examine whether there are differences in QoL and depressive symptoms between HF pts and an age and gender matched group of community-dwelling elderly and determine how chronic comorbid conditions qualify the answer	Secondary analysis of COACH trial data plus enrollment of a community sample from Netherlands	781	NYHA II-IV, ≥18 y, structural heart disease. Community sample randomly selected from population ≥55 y and not living at same address. 45% response rate.	Enrollment in a study requiring additional research visits or invasive intervention within last 6 mo or next 3 mo, terminal disease, active psychiatric diagnosis.	QoL measured with Medical Outcome Study 36-item General Health Survey and Cantril Ladder of Life. Depressive symptoms with CES-D.	Chronic conditions abstracted from chart of pts, self-reported by community sample.	QoL significantly impaired in HF pts compared to matched elderly. Largest differences were in physical functioning and vitality. Role limitations due to physical functioning very low in HF pts. QoL was lower in HF pts with COPD or diabetes. Depressive symptoms higher in HF pts (39% vs 21%) all p<0.001.	Manner in which comorbid conditions were assessed differed between HF pts and controls. List used was not all inclusive.	HF has a large impact on QoL and depressive symptoms, especially in women with HF. Differences persist, even in the absence of common comorbidities. Results demonstrate the need for studies of representative HF pts with direct comparisons to age- and gender-matched controls.

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Ethnic Differences in QoL in Persons With HF. Riegel et al 2008 18226772 (21)	To compare HRQoL in non-Hispanic white, black, and Hispanic adults with HF	Longitudinal comparative study with propensity scoring	1,212	Established diagnosis of chronic HF	Recent MI, USA, cognitive impairment, severe psychiatric problems, homeless, or discharged to an extended care or skilled nursing facility	HRQoL measured with the MLHFQ	N/A	HRQoL improved over time (baseline to 3- and 6-mo) in all groups but most dramatically among Hispanics. Hispanics improved more than whites ($p<0.0001$). Hispanics improved more than blacks ($p=0.004$).	Secondary analysis of existing data. Hispanic sample was primarily Mexican so results cannot be generalized to all Hispanics. Samples received different treatments at various sites; treatment was controlled in the analysis. Other factors that could explain these differences were not measured. Cultural bias in the data obtained from the MLHFQ is possible.	Cultural differences in the interpretation of and response to chronic illness may explain why HRQoL improves more over time in Hispanic pts with HF compared with white and black pts.
The impact of chronic HF on HRQoL data acquired in the baseline phase of the CARE-HF study. Calvert, Melanie. 2005 15701474 (22)	To assess the QoL of pts with HF, due to LV dysfunction, taking optimal medical therapy using baseline QoL assessments from the CARE-HF trial, and to evaluate the appropriateness of using the EQ-5D in pts with HF.	RCT	813	NYHA II-IV HF	None specified	QoL Euroquol EQ-5D and MLHFQ	N/A	There is a relationship between the EQ-5D score and gender, on average females enrolled had a worse QoL than male participants. r=-0.08; 95% CI: -0.13 to -04; p=0.00004 Mean EQ-5D score for NYHA III pts was higher than for NYHA IV pts (mean difference 0.17) p<0.0001; 95% CI: 0.08-0.25 Association between MLWHF and EQ-5D scores (increasing MLWFH associated with a decrease in EQ-5D) r=-0.00795; 95% CI: (-0.00885 to -0.00706); p<0.0001 HF is shown to have an important impact on all aspects of QoL but particularly on pts mobility and usual activities and leads to significant reductions in comparison with a representative sample of the UK population.	Pts assessed in the study are not a random sample of pts with severe HF. CARE-HF is an int'l study but used available normative data from a representative sample of the UK population to evaluate burden of disease. A study comparing UK and Spanish time trade-off values for EQ-5D health states demonstrated that although the general pattern of value assignation was similar, there were differences in values assigned to a number of health states	The impact of HF varies amongst pts but the overall burden of disease appears to be comparable to other chronic conditions such as motor neurone or Parkinson's disease. The EQ-5D appears to be an acceptable valid measure for use in pts with HF although further evidence of the responsiveness of this measure in such pts is required.

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Characterization of HRQoL in HF pts with preserved vs low EF in CHARM, Lewis et al, 2007 17188020 (23)	To characterize HRQoL in a large population of HF pts with preserved and low LVEF and to determine the factors associated with worse HRQoL.	Secondary analysis of data from the CHARM trial	2,709	"CHARM-Alternative" pts: LVEF ≤40% and not receiving an ACE-I; "CHARM-Added" pts: LVEF ≤40% and taking ACE-Is. Pts in NYHA class II required admission to hospital with a CV problem in prior 6 mo (which increased proportion of NYHA class III/IV in CHARM-Added. "CHARM-Preserved" pts had LVEF >40% with or without ACEI	N/A	QoL	N/A	9 independent clinical determinants of worse HRQoL: younger age, higher BMI, lower SBP, female sex, worse NYHA class, angina, PND, rest dyspnea, lack of ACE-I. Characteristics did not differ by group. LVEF was NS.	Population was healthy enough to enroll so may have fewer comorbidities. Asymptomatic pts were excluded. Only enrolled in Canada and US. Groups without ACE-I therapy may have affected HRQoL. No gold standard for measuring HRQoL.	Independent factors associated with worse HRQoL in both populations included female sex, younger age, higher BMI, lower SBP, greater symptom burden, and worse functional status.
The enigma of QoL in pts with HF. Dobre D, 2008 17400313 (24)	To review RCTs that assessed the impact of pharmacologic treatments on QoL	Brief communication	N/A	Clinical trials	N/A	QoL	Survival	N/A	N/A	Life prolonging therapies, such as ACE-Is and ARBs improve modestly or only delay the progressive worsening of QoL in HF. Beta blockers do not affect QoL in any way. Therapies that improve QoL (e.g., inotropic agents) do not seem beneficial in relation to survival.

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QoL in individuals with HF. Harrison, Margaret. 2002 12021683 (25)	To evaluate whether the use of usual providers and a reorganization of discharge planning and transition care with improved intersector linkages between nurses, could improve QoL and health services utilization for individuals admitted to hospital with HF.	Prospective randomized trial	192	Admitted to hospital with a diagnosis of CHF Residing in the regional home care radius. Expected to be discharged with home nursing care English or French speaking Admitted for more than 24 h to the nursing units	Cognitively impaired (score ≥8 on Short Portable Mental Status Exam)	HRQoL (MLWHF), symptom distress and function at 6- and 12-wk postdischarge	The no. of all-cause ED visits, hospital readmissions, and QoL measured with a generic measure, Medical Outcome Study Short Form	The overall MLHFQ score was better among the Transitional Care pts than the usual care pts: At 6 wk after hospital discharge (p=0.002) At 12 wk after hospital discharge (p<0.001) The MLHFQ's Physical Dimension subscale score was better among the Transitional Care pts than the usual care pts: At 6 wk after hospital discharge (p=0.01) At 12 wk after hospital discharge (p<0.001) The MLHFQ's Emotional Dimension subscale score was better among the Transitional Care pts than the usual care pts at 6 wk after hospital discharge (p=0.006) 46% of the Usual Care group visited the ED compared with 29% in the Transitional Care group (p=0.03) At 12 wk postdischarge, 31% of the Usual Care pts had been readmitted compared with 23% of the Transitional Care pts (p=0.26).	Conducted the trial in a naturalistic manner in the usual setting of care with usual providers. Possibility of contamination with the hospital nurses providing usual care. Pts may have inadvertently alerted the research coordinators of their assignment to usual care or transitional care. With multiple interventions it's not easy to assess neither the relative contribution of each component nor the synergistic effect of the sum of the parts.	Transitional Care has an important role to play in altering the course of pts hospitalized with HF. Our results suggest that with modest adjustments to usual discharge and transition from hospital-to-home, pts with CHF can experience improved QoL, and decreased use of ED, for 3 mo after hospitalization. This approach will provide the needed adjunct to current management of HF.

ACEI; angiotensin-converting-enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; CARE-HF Cardiac Resynchronisation in Heart Failure; CES-D, Center for Epidemiological Studies-Depression scale; CHARM, Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity; CHF, congestive heart failure; COACH, Comparative study on guideline adherence and patient compliance in heart failure patients; CTX, chest x-ray; CV, cardiovascular; ED, emergency department; EF, ejection fraction; ESCAPE, Evaluation Study of Congestive Heart Failure and PulmonaryArtery Catheterization Effectiveness; HF, heart failure; HRQoL, health-related quality of life; MI, myocardial infarction; MLHFQ score, Minnesota Living With Heart Failure; N/A, not applicable; NYHA, New York Heart Association; pts, patients; PND, Paroxysmal nocturnal dyspnea; QoL, quality of life; RCT, randomized control trial; and SBP, systolic blood pressure.

Data Supplement 5. Stress Testing (Initial and Serial Evaluation) of the HF Patient (Section 6.1.1)

Study Name, Author, Year	Aim of Study	Study Type	Background Therapy	Study Size	Etiology	Patient Population		Severity		Endpoints		Mortality		Trial Duration	Statistical Analysis (Results)	Study Limitations
			Pre-trial standard treatment.	*N (Total) n (Experimental) n (Control)*	*Ischemic/ Non-Ischemic*	*Inclusion Criteria*	*Exclusion Criteria*	*Severity of HF Symptoms*	*Study Entry Sverity Criteria*	*Primary Endpoint*	*Secondary Endpoint*	*Annualized Mortality*	*1st Year Mortality*			

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Defining the Optimal Prognostic Window for CPX in Pts with HF. Arena et al. Circ Heart Fail 2010; 3: 405-411 20200329 (26)	Assess the change in prognostic characteristics of CPX at different time intervals	Cohort	1 year	791	51% ischemic	HF and LV dysfunction		NYHA 2.4 +/- 0.67	N/A	Major cardiac events - mortality, LV device implantation, urgent heart transplant	Cardiac mortality	N/A	75 deaths (of 791)	36 mo FU	For 24 mo post CPX (high vs. low Ve/VCO2): cardiac events p<0.001 (95% CI: 2.1 - 5.5); cardiac mortality p<0.001 (95% CI: 2.2 - 5.8) HR:dichotomous3.4; 3.5	Observational
Value of peak exercise oxygen consumption for optimal timing of cardiac transplantation in ambulatory pts with HF. Mancini et al. Circulation 1991;83;778-786 1999029 (27)	To determine if maximal exercise testing and measurement of PKVO2 identifies pts in whom heart transplant can be safely deferred	Observational prospective cohort	Focus on hemodynamic and NYHA class	122 52 (PKVO2>14) 35 (PKVO2=<14)	46% ischemic	Ambulatory pts referred for heart transplant	Unable to perform exercise testing due to angina	70% NYHA III	N/A	Survival	N/A	N/A	94% survival in those with high PKVO2 vs. 70% for those with low PKVO2	2 y FU	p<0.005	Wide complex tachycardia in 1 pt
Peak Oxygen Consumption as a Predictor of Death in Pts With HF Receiving Beta Blockers. O'Neill JO et al. Circulation 2005;111;2313-2318 15867168 (28)	To determine whether PKVO2 is a reliable indicator of prognosis in the beta blocker era	Observational prospective cohort	Cutoff of 14 mL/kg1	2,105; n=909 on beta blocker; n=1,196 no beta blocker	52% ischemic	Referral for HF with LVEF<35%	Age <20, ESRD, prior OHT	N/A	N/A	Death	Death or transplantation	N/A	N/A	N/A	Pts on beta blockers: Death p<0.001, (95% CI: 1.18–1.36); death and transplant p<0.001, (95% CI: 1.18–1.32) aHR: 1.26; 1.25 per 1-mL/min/kg	N/A

CPX indicates cardiopulmonary exercise testing; EF, ejection fraction; ESRD, end-stage renal disease; FU, follow up; HF, heart failure; pts, patients; LVEF, left ventricular ejection fraction; N/A, not applicable; NYHA, New York Heart Association; OHT, orthotopic heart transplantation; PKVO2; peak oxygen consumption; and RCT, randomized control trial.

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Data Supplement 6. Clinical Evaluation – History (Orthopnea) (Section 6.1.1)

Study Name, Author, Year	Study Type	Study Size	Patient Population	Utility in Detecting Elevated PCWP
Stevenson, LW; Perloff JAMA 1989:261:884-888 2913385 (29)	Single center, prospective	50	Stage D	Orthopnea within preceding wk 91% of 43 pts with PCWP ≥22 0/7 pts with PCWP <22
Chakko et al; Am J Medicine 1991:90:353-9 1825901 (30)	Single center, prospective	42	Stage D	For PCWP >20 Sensitivity 66%, Specificity 47%, PPV 61%, NPV 37%
Drazner et al Circ HF 2008:1:170-177 19675681 (31)	Multicenter substudy of ESCAPE	194 (with PAC)	Stage D	Orthopnea (≥ 2 pillows) OR 2.1 (95% CI: 1.0-4.4); PPV 66%, NPV 51%; +LR 1.15, (-) LR 1.8; all for PCWP>22 OR 3.6 (95% CI: 1.02 -12.8) for PCWP>30

ESCAPE indicates Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness; LR, likelihood ratio; NPV, negative predictive value; OR, odds ratio; PAC, pulmonary artery catheter; PCWP, Pulmonary Capillary Wedge Pressure; PPV, positive predictive value; and pts, patients.

Data Supplement 7. Clinical Evaluation - Examination (Section 6.1.1)

Study Name, Author, Year	Study Type	Study Size	Patient Population	Utility in Detecting Elevated PCWP
Jugular venous pressure for assessing right atrial pressure				
Stevenson, LW; Perloff JAMA 1989:261:884-888 2913385 (29)	Single center, prospective	50	Stage D	21/28 (75%) of pts with RAP ≥10 had elevated JVP
Butman et al JACC 1993:22:968-974 8409071 (32)	Single center, prospective	52	Stage D	RAP associated with JVD and HJR –HJR,-JVD: RAP 4 (2) +HJR, -JVD: RAP 8 (5) +HJR, +JVD: RAP 13 (5)
Stein et al AJC 1997;80:1615-1618 9416951 (33)	Single center	25	Class 3-4	RAP estimated from JVP vs. measured RA: r=0.92. Clinical estimates underestimate elevated JVP. Interaction between utility of estimated RAP and measured RAP (more of an underestimate as measured RAP increased). Bias 0.1 (RAP 0-8), 3.6 (RAP 9-14), 5 (RAP ≥15).
Drazner et al Circ HF 2008:1:170-177 19675681 (31)	Multicenter substudy of ESCAPE	194 (with PAC)	Stage D	Estimated RAP for RAP >12 AUC 0.74

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Jugular Venous Pressure for Detecting Elevated PCWP				
Stevenson, LW; Perloff JAMA 1989:261:884-888 2913385 (29)	Single center, prospective	50	Stage D	Elevated JVP associated with PCWP ≥22 58% sensitivity 100% specificity (0/7 with PCWP ≤18 mm Hg) However 8/18 pts with PCWP ≥35 mm Hg without elevated JVP
Chakko et al Am J Medicine 1991;90:353-359 1825901 (30)	Single center, prospective	52	Stage D	"High JVP" for PCWP >20 mm Hg Sensitivity 70%, Specificity 79%, PPV 85%, NPV 62%
Butman et al JACC 1993:22:968-974 8409071 (32)	Single center, prospective	52	Stage D	JVD at rest or with HJR for PCWP>18 mm Hg: Sens 81%, Spec 80%, PPV 91%, NPV 63%
Badgett et al JAMA 1997; 277:1712-1719 9169900 (34)	Literature review "Rational Clinical Examination" series	NA	Stage D citing above 3 studies	Suggested algorithm: If known low LVEF, and population with high prevalence of increased filling pressure, then elevated JVP is "very helpful" and associated with >90% chance of elevated filling pressures
Drazner et al Circ HF 2008:1:170-177 19675681 (31)	Multicenter substudy of ESCAPE	194 (with PAC)	Stage D	JVP≥12 mm Hg for PCWP>22 Sensitivity: 65%, Specificity: 64%, PPV 75%, NPV 52%, +LR 1.79, (-)LR 1.8
Prognostic Utility of JVP				
Drazner et al NEJM 2001;345:574-81 11529211 (35)	Retrospective analysis of SOLVD Treatment Trial	2569	Stage C	Multivariate analysis for elevated JVP Mean f/u 32 months Death RR 1.15 (95% CI: 0.95-1.38) HF hospitalization 1.32 (95% CI: 1.08-1.62) Death/HF hospitalization 1.30 (95% CI: 1.11-1.53)
Drazner et al Am J Med 2003;114:431-437 12727575 (36)	Retrospective analysis of SOLVD Prevention Trial	4102	Stage B	Multivariate analysis for elevated JVD Mean follow-up 34 mo Development of HF RR 1.38 (95% CI: 1.1-1.7) Death or Development of HF RR 1.34 (95% CI: 1-1,1.6)

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Drazner et al Circ HF 2008:1:170-177 19675681 (31)	Multicenter substudy of ESCAPE	194 (with PAC)	Stage D	Multivariate analysis Enrollment estimated RAP associated with survival outside hospital at 6 mo (Referent RAP<13) RAP 13-16 HR 1.2 (95% CI: 0.96-1.5) RAP >16 HR 1.6 (95% CI: 1.2-2.1)
Meyer et al AJC 2009 103:839-844 19268742 (37)	Retrospective analysis of DIG trial	7788	Stage C	Mean follow-up 34 mo Univariate analysis Elevated JVP associated with Death: HR 1.7 (95% CI: 1.54-1.88) All-cause hosp: HR 1.35 (95% CI: 1.25-1.47) After adjusting for propensity score associations no longer significant; aHR: 0.95 (death), aHR:0.97 (hosp), p>0.5
Utility of Valsalva Maneuver for Detecting Elevated PCWP				
Schmidt et al AJC 1993;71:462-5 8430644 (38)	Prospective single center	38	Unknown (%HF not stated)	Utility of square wave for LVEDP ≥15 mm Hg: sens 100%, spec 91%, PPV 82%, NPV 100%
Rocca et al Chest 1999; 116:861-7 10531144 (39)	Single center, prospective study	45	Stage C	Pulse amplitude ratio by Valsalva correlated with BNP (r=0.6, p<0.001)
Givertz et al AJC 2001 1213-1215 11356404 (40)	Single center, prospective study of Vericor system	30 men	Class 3/4	Predicted PCWP by Valsalva vs measured PCWP: r=0.9, p<0.001. Mean difference 0.07 ±2.9 mm Hg Predicted PCWP had sensitivity: 91%, specificity: 100% for PCWP ≥18 mm Hg
Sharma et al Arch Intern Med 2002:162:2084-2088 12374516 (41)	Prospective study of commercial device (VeriCor) at 2 centers	57 pts (2 women)	Unknown Majority pts with CAD	Pulse amplitude ratio correlated with LVEDP (r=0.86) 84% of measurements within 4 mm Hg of LVEDP
Felker et al Am J Medicine 2006;119:117-132 16443410 (42)	Review paper	N/A	N/A	Significant correlation between CV response to Valsalva and LV filling pressures

AUC indicates area under the concentration curve; BNP, B-Type Natriuretic Peptide; CAD, coronary artery disease; CV, cardiovascular; DIG, Digitalis Investigation Group; f/u, follow-up; ESCAPE, Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness HJR, hepatojugular reflux; LVEF, left ventricular ejection fraction; LVEDP, Left Ventricular End-Diastolic Pressure; JVD, jugular venous distension; JVP, jugular venous pressure; N/A, not applicable; NPV, negative predictive value; PCWP, Pulmonary Capillary Wedge Pressure; PPV, positive predictive value, Pts, patients; r, Pearson's correlation coefficient; RAP, right arterial pressure; and SOLVD, Studies of left ventricular dysfunction.

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Data Supplement 8. Clinical Evaluation – Risk Scoring (Section 6.1.2)

Study Name, Author, Year	Study Type	Study Size	Patient population	Variables	Utility
Stage C					
Levy et al Circulation 2006;113:1424-1433 Seattle HF score 16534009 (10)	Derivation cohort (PRAISE 1); then tested in 5 additional trial databases	1125 (Derivation) 9942 (Validation)	Largely Stage C	Available on website	2 year survival for scores 0, 1,2,3,4 was: 93%, 89%, 78% 58%, 30%, 11% AUC 0.729 (0.71 to 0.74)
Pocock et al Eur Heart J 2006;27:65-75 CHARM 16219658 (13)	Analysis of CHARM	7,599	Stage C HF	21 variables	2 year mortality Lowest to highest deciles 2.5% to 44% C statistic 0.75
Stage D					
Aaronson et al Circulation 1997;95:2660-7 HF Survival Score 9193435 (2)	Derivation and Validation 2 transplant centers	268 (Derivation) 199 (Validation)	Stage D	Ischemic cardiomyopathy, resting heart rate, LVEF, IVCD (QRS duration 0.12 sec of any cause), mean resting BP, peak O2, and serum sodium PCWP (invasive)	3 strata Event-free survival rates at 1 y for the low-, medium-, and high-risk HFSS strata were 93±2%, 72±5%, and 43±7% AUC 1 y 0.76-0.79
Lucas et al Am Heart J 2000;140:840-7 “Congestion Score” 11099986 (43)	Retrospective, single center	146	Stage D	Congestion score: orthopnea, JVD, edema, weight gain, new increase diuretics	Post discharge (4-6 wk) score vs. 2 y death 0: 54% 1-2: 67% 3-5: 41%
Nohria et al JACC 2003:41:1797-1804 “Stevenson profiles” 12767667 (44)	Prospective, single center	452 pts	Stage D	Stevenson classification Profiles A,B,C,L	Profile B associated with death+urgent transplant in multivariate analysis (HR: 2.5, p=0.003).
Drazner et al Circ HF 2008;1:170-7 “Stevenson profiles” 19675681 (31)	Substudy of ESCAPE	388	Stage D	Stevenson classification	Discharge profile “wet or cold” HR 1.5 (1.1, 2.1) for number of d alive outside hosp at 6 mo in multivariate analysis
Levy et al J Heart Lung Tx	Retrospective analysis of REMATCH	129 REMATCH	Stage D	Seattle HF Score	The 1-y ROC was 0.71 (95% CI: 0.62-0.80).

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2009:28: 231-236. Seattle HF Score 19285613 (45)					
Gorodeski et al Circ Heart Fail 2010;3:706-714 Seattle HF Score 20798278 (46)	Single center study of ambulatory pts presented to transplant committee	215 (between 2004-2007)	Stage D	Seattle HF score	ACM, VAD, Urgent HT 2 y f/u C index 0.68 (1 yr), 0.65 (2 yr) Calibration overestimated survival among UNOS 2 pts
Hospitalized Patients					
Lee et al JAMA 2003:290:2581-2587 14625335 (11)	Retrospective study of multiple hospitals in Ontario Canada	2624 (derivation 1999-2001) 1407 (validation 1997-1999)	Hospitalized pts	Age, SBP, RR, Na<136, Hgb <10, BUN, CVA, Dementia, COPD, cirrhosis, Cancer	Predicted and observed mortality rates matched well 30 d mortality AUC derivation 0.82 Validation 0.79 1 y mortality AUC Derivation 0.77 Validation 0.76
Fonarow et al JAMA 2005:293:572-580 ADHERE 15687312 (14)	CART analysis of ADHERE national registry 2001-2003	33,046 (derivation) 32,229 (Validation)	Hospitalized pts	BUN ≥43, SBP<115, SCr ≥2.75	In-hospital mortality AUC 67-69% Morality ranges from 1.8(low risk) to ~25% (high risk)
Rohde et al J Cardiac Failure 2006;12:587-593 "HF Revised Score" 17045176 (47)	Single center study 2000-2004	779	Hospitalized pts	Cancer, SBP ≤124, Cr >1,4m BUN>37, Na <136, Age>70	In-hospital mortality Bootstrap C=0.77 (0.689-0.85) 6 increasing groups: 0,5%, 7%, 10%, 29%, 83%
Abraham et al JACC 2008;52:347-356 OPTIMIZE-HF 18652942 (16)	Analysis of OPTIMIZE-HF registry 2003-2004	48,612 pts Validated in ADHERE	Hospitalized pts	19 variables	In-hospital mortality C statistic 0.77 Validation C statistic 0.746 Excellent reliability for mortality

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Peterson et al Circ Cardiovasc Qual Outcomes 2010:3:25-32 GWTG 20123668 (15)	Analysis of GWTG admitted 2005-2007	27,850 (Derivation) 11,933 (Validation)	Hospitalized pts	Age, SBP, BUN, HR, Na, COPD, nonblack race	In-hospital mortality C index 0.75 Predicted probability mortality over deciles ranged from 0.4% - 9.7% and corresponded with true mortality
Other					
Gheorghiade et al Eur J of Heart Failure 2010:12:423-433 ESC Congestion Score 20354029 (48)	Scientific Statement from Acute HF Committee of HF Association of ESC	N/A	N/A	Congestion score Bedside assessment (Orthopnea, JVD, HM, Edema) Lab (BNP or NT proBNP) Orthostatic BP 6 min walk test Valsalva	Needs to be tested

ACM indicates all cause mortality; ADHERE, Acute Decompensated Heart Failure National Registry; AUC, area under the curve; BNP, B-type natriuretic peptide; BP, blood pressure; BUN, blood urea nitrogen; CART, Classification and regression trees; CHARM, Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity; COPD, chronic obstructive pulmonary disease; CVA, Cerebrovascular Accident; ESC, European Society of Cardiology; ESCAPE, Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness; GWTG, Get With the Guidelines; HF, heart failure; HFSS, heart failure survival score; Hgb, hemoglobin; HR, heart rate; HT, heart transplantation; HM, hepatomegaly; IVCD, intraventricular conduction delay; JVD, jugular venous distension; LVEF, left ventricular ejection fraction; N/A, not applicable; Na, sodium; NT proBNP, n-terminal pro-B-type natriuretic peptide; OPTIMIZE-HF, Organized Program to Initiate Lifesaving Treatment in Hospitalized Pts with HF; PCWP, Pulmonary Capillary Wedge Pressure; PRAISE, Prospective Randomized Amlodipine Survival Evaluation; pts, patients; REMATCH, Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure; ROC, receiver operating characteristic curve; RR, respiratory rate; SBP, systolic blood pressure; SCr, serum creatinine; UNOS, United Network of Organ Sharing; and VAD, ventricular assist device.

Data Supplement 9. Imaging Echocardiography (Section 6.4)

Study Name, Author, Year	Aim of Study	Study Type	Study Size	Patient Population		Endpoints	Statistical Analysis (Results)	Study Limitations
				Inclusion Criteria	*Exclusion Criteria*			
IS. Syed 2010 20159642 (49)	Evaluate LGE-CMR in identifying CA; investigate associations between LGE and clinical, morphologic, functional, and biochemical features.	Observational	120 (35 with positive cardiac histology, 49 without cardiac histology but with echo evidence of CA, 36 without histology or echo evidence of CA)	Histologically proven amyloidosis and, in the case of AL amyloidosis, confirmatory evidence of monoclonal protein in the serum or urine and/or a monoclonal population of plasma cells in the bone marrow.	Prior MI, myocarditis, prior peripheral blood stem cell transplantation, or prior heart transplantation	LGE-CMR presentation in pts with amyloidosis; associations between LGE and clinical, morphologic, functional, and biochemical features.	Of the 35 pts with histology, abnormal LGE was present in 97% of the 49 with echo evidence, abnormal LGE was present in 86% of the 36 without histology or ECHO evidence of CA, abnormal LGE was present in 47%. In all pts, LGE presence and pattern was associated with NYHA functional class, ECG voltage, LV mass index, RV wall thickness, troponin-T, and BNP levels.	No control group, cardiac histology was only present in a subset of pts contraindication to the use of Gd

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V Rizzello 2009 19443475 (50)	Evaluate the prognosis of viable pts with and without improvement of LVEF after coronary revascularisation.	Observational	90; group 1: viable pts with LVEF improvement (n=27); group 2, viable pts without LVEF improvement (n=15), group 3, non-viable pts (n=48)	Pts were already scheduled for coronary revascularization according to clinical criteria of reduced LVEF (40%), symptoms of HF and/or angina, presence/absence of ischemia and presence of critical coronary disease at angiography. Only pts who had undergone coronary revascularisation alone were included in the study	Pts who had undergone mitral valvuloplasty or aneurismectomy in association with revascularisation were excluded.	Cardiac events were evaluated during a 4-y follow-up (cardiac death, new MI, admission to hospital for HF)	Cardiac event rate was low (4%) in group 1, intermediate (21%) in group 2 and high (33%) in group 3. After revascularization, the mean (SD) LVEF improved from 32 (9)% to 42 (10)% in group 1, but did not change significantly in group 2 and in group 3, p,0.001 by ANOVA. HF symptoms improved in both groups 1 (mean (SD) NYHA class from 3.1 (0.9) to 1.7 (0.7)) and 2 (from 3.2 (0.7)-1.7 (0.9)), but not in group 3 (from 2.8 (1.0)-2.7 (0.5)), p=0.001 by ANOVA. The difference in event rate was not statistically significant between groups 1 and 2 -small number of pts- but it was significant between the 3 groups using Kaplan–Meier p=0.01	N/A
Kevin C Allman 2002 11923039 (51)	Examines late survival with revascularization vs medical therapy after myocardial viability testing in pts with severe CAD and LV dysfunction	Meta-analysis of observational studies	3,088 (viability demonstrated in 42%)	Pts with CAD and LV dysfunction who were tested for myocardial viability with cardiac imaging procedures from 24 viability studies reporting pt survival using thallium perfusion imaging, F-18 fluorodeoxyglucose metabolic imaging or dobutamine ECHO.	Those not reporting deaths or where deaths could not be apportioned to pts with vs without viability were excluded	Annual mortality rates, pts followed for 25±10 mo.	For pts with defined myocardial viability, annual mortality rate was 16% in medically treated pts but only 3.2% in revascularized pts (χ^2 =147, p<0.0001). This represents a 79.6% relative reduction in risk of death for revascularized pts. For pts without viability, annual mortality was not significantly different by treatment method: 7.7% with revascularization vs 6.2% for medical therapy (p=NS).	The individual studies are observational, nonrandomized, unblinded and subject to publication and other biases. In this metaanalysis, viability could only be interpreted as “present” or “absent” based on individual studies’ definitions
Beanlands RS. 2002 12446055 (52)	Whether the extent of viability or scar is important in the amount of recovery of LV function and to develop a model for predicting recovery after revascularization that could be tested in a randomized trial.	Prospective multicenter cohort	82; Complete follow-up was available on 70 pts.	Pts CAD and severe LV dysfunction with EF 35% by any quantitative technique, who were being scheduled for revascularization	PTs with MI within the preceding 6 wk, severe valve disease requiring valve replacement, requirement for aneurysm resection, and inability to obtain informed consent.	Absolute change in EF determined by radionuclide angiograms 3 mo postrevascularization	Amount of scar was a significant independent predictor of LV function recovery after revascularization. Across tertiles of scar scores (I, small: 0% to 16%; II, moderate: 16% to 27.5%; III, large: 27.5% to 47%), the changes in EFs were 9.0±1.9%, 3.7±1.6%, and 1.3±1.5% (p=0.003: I vs. III), respectively.	Pt population in this study included pts who were predominantly men, predominately between 53-71 y of age (1 SD from the mean), had multivessel disease, and had bypassable vessels. Although improvement in LV function has been noted at 3 mo of follow-up in many previous studies, recent data suggest that more recovery may be observed with longer follow-up time

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Paul R. Pagley 1997 9264484 (53)	Hypothesized that pts with poor ventricular function and predominantly viable myocardium have a better outcome after bypass surgery compared with those with less viability.	Retrospective cohort	70	Pts with EFs <40% without significant valvular disease who were referred for a first coronary bypass surgery and underwent preoperative quantitative planar 201Tl imaging for viability determination.	Prior CABG, coexisting valvular disease and underwent concurrent aortic or MV replacement, or those with SPECT imaging	CV death or cardiac transplantation; median time to follow-up was 1177 d (range, 590 to 1826)	The viability index was significantly related to 3-y survival free of cardiac event (cardiac death or heart transplant) after bypass surgery (p=0.011) and was independent of age, EF, and number of diseased coronary vessels. Survival free of cardiac death or transplantation was significantly better in group 1 pts on Kaplan-Meier analysis (p=0.018).	N/A
Senior R, 1999 10362184 (54)	To evaluate the effect of revascularization on survival in pts with CHF due to ischemic LV systolic dysfunction based on the presence of myocardial viability	Observational prospective	87	CHF (NYHA class II-IV) for at least 3 mo that was treated medically; LVEF ≤35%; clinical evidence of CAD	Significant valvular disease, unstable angina, MI within three months, sustained ventricular tachycardia or AF	Cardiac deaths were defined as those resulting from acute MI, refractory CHF or occurring suddenly and not being attributed to other known causes after a mean follow-up of 40 ± 17 mo	Pts with at least 5 segments showing myocardial viability underwent revascularization, mortality was reduced by an average of 93% which was associated with improvement in NYHA class as well as LVEF. Pts with <5 segments showing myocardial viability who underwent revascularization (and thus, showing mostly scar), and those with at least 5 segments demonstrating myocardial viability who were treated medically, had a much higher mortality. (95% CI: 22%-99%)	Single-center study where selection bias is unavoidable. Selection bias may have favored taking one group to surgery over another.
Kwon DH 2009 19356530 (55)	To determine whether the extent of LV scar, measured with DHE-CMR predicts survival in pts with ischemic cardiomyopathy ICM and severely reduced LVEF.	Observational	349	Pts with documented ICM (on the basis of 70% stenosis in at least 1 epicardial coronary vessel on angiography and/or history of MI or coronary revascularization), who were referred for the assessment of myocardial viability with CMR	Pts with standard CMR contraindications including severe claustrophobia, AF, and the presence of pacemakers, defibrillators, or aneurysm clips	All-cause mortality was ascertained by social security death index after a mean of follow-up 2.6 ± 1.2 y (median 2.4 y)	Mean scar percentage and transmurality score were higher in pts with events vs those without (39±22 vs 30±20, p=0.003, and 9.7±5 vs. 7.8±5, p=0.004). *On Cox proportional hazard survival analysis, quantified scar was greater than the median (30% of total myocardium), and female gender predicted events (RR: 1.75; 95% CI: 1.02-3.03 and RR:1.83; 95% CI: 1.06-3.16, respectively, both p=0.03).	Selection bias of an observational study conducted at a large tertiary referral center. Only the pts with no contraindications to CMR underwent the examination.
Ordovas KG. 2011 22012903 (56)	N/A	Review paper	N/A	N/A	N/A	N/A	An international multicenter study (54) reported a sensitivity of 99% for detection of acute infarction and 94% for detection of chronic infarction. Delayed enhancement occurs in both acute and chronic (scar) infarctions and in an array of other myocardial processes that cause myocardial necrosis, infiltration, or fibrosis. These include myocarditis, hypertrophic cardiomyopathy, amyloidosis, sarcoidosis, and other myocardial conditions. In several of these diseases, the presence and extent of delayed enhancement has prognostic implications.	N/A

AF, atrial fibrillation; AL, Amyloid Light-chain; ANOVA, analysis of variance; CA, cardiac amyloidosis; CABG, coronary artery bypass graft; CAD, coronary artery disease; CHF, congestive heart failure; CMR, cardiovascular magnetic resonance; CV, cardiovascular; DHE-CMR, delayed hyperenhancement cardiac magnetic resonance; ECHO, echocardiography; EF, ejection fraction; Gd, gadolinium; ICM, ischemic cardiomyopathy; LGE-CMR, late gadolinium enhancement cardiac magnetic resonance; LV, left ventricular; LVEF, left ventricular ejection fraction; MI, myocardial infarction; N/A, not applicable; NS, not significant; NYHA, New York Heart Association; pts, patients; RV, right ventricular; SD, standard deviation; and SPECT, single-photon emission computed tomography.

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Data Supplement 10. Biopsy (Section 6.5.3)

Study Name, Author, Year	Aim of Study	Study Type	Study Size	Patient Population	Results
Cooper LT, Baughman KL, Feldman AM et al. The role of endomyocardial biopsy in the management of CV disease: Circulation 2007 November 6;116(19):2216-33. 17959655 (57)	Role of endomyocadial biopsy for management of CV disease	A scientific statement from the AHA, ACC, & ESC	N/A	N/A	N/A
Kasper EK, Agema WR, Hutchins GM, Deckers JW, Hare JM, Baughman KL. The causes of dilated cardiomyopathy: a clinicopathologic review of 673 consecutive pts. *J Am Coll Cardiol* 1994 March 1;23(3):586-90. 8113538 (58)	To document causes of DCM in a large group of adult HF pts	Retrospective Cohort	673	DCM pts with symptoms within 6 mo, evaluated at Johns Hopkins Hospital 1982-1991	Most common causes of DCM: idiopathic (47%), myocarditis (12%) and CAD (11%), other causes (31%)
Fowles RE, Mason JW. Endomyocardial biopsy. Ann Intern Med 1982 December;97(6):885-94. 6756241 (59)	Complication risk with RV biopsies	Review	N/A	N/A	Complication rate of 1% in 4000 biopsies (performed in transplantation and CMP pts) 4 tamponade (0.14%), 3 pneumothorax, 3 AF, 1 ventricular arrhythmia, and 3 focal neurological complications
Deckers JW, Hare JM, Baughman KL. Complications of transvenous right ventricular endomyocardial biopsy in adult pts with cardiomyopathy: a seven-year survey of 546 consecutive diagnostic procedures in a tertiary referral center. *J Am Coll Cardiol* 1992 January;19(1):43-7. 1729344 (60)	To determine the incidence, nature and subsequent management of complications occurring during RV endomyocardial biopsy in pts with cardiomyopathy	Prospective Cohort	546	546 consecutive biopsies for DCM pts at single center,	33 total complications (6%): 15 (2.7%) during catheter insertion: 12 arterial punctures (2%), 2 vasovagal reactions (0.4%) and 1 prolonged bleeding (0.2%), 18 (3.3%) during biopsy: 6 arrhythmias (1.1%), 5 conduction abnormalities (1%), 4 possible perforations (0.7%) and 3 definite perforations (0.5%). 2 (0.4%) of the 3 pts with a perforation died
Ardehali H, Qasim A, Cappola T et al. Endomyocardial biopsy plays a role in diagnosing pts with unexplained cardiomyopathy. Am Heart J 2004 May;147(5):919-23. 15131552 (61)	To evaluate the utility of RV biopsy in confirming or excluding a clinically suspected diagnosis	Retrospetive chart review	845	Pts with initially unexplained cardiomyopathy (1982-1997) at The Johns Hopkins Hospital.	Clinical assessment of the etiology inaccurate in 31% EMBx helps establish the final diagnosis in most
Holzmann M, Nicko A, Ku¨hl U, et al. Complication rate of right ventricular endomyocardial biopsy via the femoral approach. A retrospective and prospective study analyzing 3048 diagnostic procedures over an 11-year period. Circulation 2008;118:1722–8.	To determine complication rate of RV biopsy	Cohort	2415	1919 pts underwent 2505 endomyocardial biopsy retrospectively (1995-2003), and 496 pts underwent 543	Major complications cardiac tamponade requiring pericardiocentesis or complete AV block requiring permanent pacing rare: 0.12% in the retrospective study and 0% in the prospective study. Minor complications such as pericardial effusion, conduction abnormalities, or arrhythmias in 0.20% in the retrospective study

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18838566 (62)				endomyocardial biopsy prospectively (2004-2005) to evaluate unexplained LV dysfunction	and 5.5% in the prospective study
Elliott P, Arbustini E. The role of endomyocardial biopsy in the management of CV disease: a commentary on joint AHA/ACC/ESC guidelines. *Heart* 2009 May;95(9):759-760. 19221107 (63)	N/A	Commentary	N/A	N/A	Emphasizes genetic causes of CMP

ACC indicates American College of Cardiology; AHA, American Heart Association; AF, atrial fibrillation; AV, atrioventricular; CAD, coronary artery disease; CMP, cardiomyopathy; DCM, dilated cardiomyopathy; EMBx, endomyocardial biopsy; ESC, European Society of Cardiology; LV, left ventricular; N/A, not applicable; pts, patients; and RV, right ventricular.

Data Supplement 11. Stage A: Prevention of HF (Section 7.1)

Study Name, Author, Year	Aim of Study	Study Type	Study Size	Patient Population		Endpoints	Trial Duration (Years)	Statistical Analysis (Results)	Study Limitations
			N (Total) *n (Experimental)* *n (Control)*	*Inclusion Criteria*	*Exclusion Criteria*				
Lloyd-Jones et al, The lifetime risk for developing HF; Circulation, 2002; 106:3068-3072 12473553 (64)	Examine lifetime risk of developing CHF among those without incident or prevalent disease	Prospective cohort	8229	Free of CHF at baseline	N/A	N/A	N/A	Lifetime risk is 1 in 5 for men and women; significant association between MI and HTN in lifetime risk of CHF.	Subjects mostly white and results not generalizable to other races.
Vasan et al, Residual lifetime risk for developing HTN in middle-aged women and men; JAMA, 2002:287:1003-1010. 11866648 (65)	Quantify risk of HTN development	Prospective cohort	1298	Ages 55-65 y and free of HTN at baseline.	N/A	N/A	N/A	Residual lifetime risk for developing HTN was 90%. Risk did not differ by sex or age, lifetime risk for women vs men aged 55 y, HR: 0.91 (95% CI, 0.80-1.04); for those aged 65 y, HR:0.88 (95% CI, 0.76-1.04)	Measured HTN in middle age, when a large portion of people develop HTN at younger ages so actual risk may be different for younger people. Did not take into account other risks for HTN like obesity, family history of high BP, dietary sodium and potassium intake, and alcohol consumption
Levy et al, The progression from HTN to CHF; JAMA, 1996;275:1557-62 8622246 (66)	Analysis of expected rates of HF associated with diagnosis of HTN	Prospective cohort	5,143	Free of CHF at baseline.	N/A	Development of HF	20	Those with HTN at a higher risk for CHF: Men, HR: 2.04; 95% CI: 1.50-2.78; Women, HR: 3.21; 95% CI: 2.20-4.67	Subjects mostly white and results not generalizable to other races. Possible misclassification bias as some subjects diagnosed w/HTN before use of echocardiography.

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								PAR for CHF in those with HTN: 39% for men and 59% in women.	
Wilhelmsen et al, HF in the general population of men: morbidity, risk factors, and prognosis; J Intern Med 2001;249:253-261 11285045 (67)	Identification of risk associated with HTN	Population-based intervention trial	7,495	N/A	N/A	Development of HF	27	CAD and HTN were the most common concomitant diseases in HF pts (79.1%).	N/A
Kostis, et al, Prevention of HF by antihypertensive drug treatment in older persons with isolated systolic HTN; JAMA 1997;278:212-216. 9218667 (68)	To assess the effect of antihypertensive care on the incidence of HF in older pts with systolic HTN	RCT	4,736; 2,365; 2,371	Age ≥60y, Isolated systolic HTN: SBP 160-219 mm Hg with DBP <90 mm Hg.	Recent MI, CABG, DM, alcohol abuse, demential stroke, AF, AV block, multiform premature ventricular contractions, bradycardia <50 beats/min; diuretic therapy.	Fatal and non-fatal HF	4.5	49% reduction RR: 0.51; 95% CI: 0.37-0.71; p<.001	Noteworthy that pts with prior MI had an 80% risk reduction.
Staessen, Wang and Thijs; CV prevention and BP reduction: a quantitative overview updated until 1 March 2003; J Hypertens 2003;21:1055-1076 12777939 (69)	Assessment of various drugs and their reduction of HF	Meta analysis	120,574	N/A	N/A	CV events	N/A	CCB, resulted in better stroke protection than older drugs: including (-8%, p=0.07) or excluding verapamil (-10%, p=0.02), as well as ARB (-24%, p=0.0002). The opposite trend was observed for ACEI (+10%, Pp=0.03). The risk of HFwas higher (p< 0.0001) on CCB (+33%) and alpha blockers (+102%) than on conventional therapy involving diuretics	N/A
Sciaretta, et al; Antihypertensive treatment and development of HF in hypertension: a Bayesian network meta-analysis of studies in pts with HTN and high CV risk. Arch Intern Med. 2011 Mar 14;171(5):384-94. 21059964 (70)	Compare various drugs and risk for HF	Meta analysis	223,313	Studies had to be RCTs from 1997-2009; pts with HTN or a population characterized as having a "high" CV risk profile and a predominance of pts with HTN (>65%); the sample size ≥200 pts; and information on the absolute incidence of HF and	N/A	HF	N/A	Diuretics vs. placebo: OR: 0.59; 95% CrI: 0.47-0.73; ACE-I vs. placebo: OR: 0.71; 95% CrI: 0.59-0.85; ARB: OR: 0.71; 95% CrI: 0.59-0.85. Beta blockers and CCB less effective	N/A

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				other major CV events					
Lind et al, Glycaemic control and incidence of HF in 20985 pts with type 1 diabetes: an observational study. Lancet 2011; Jun 24. 21705065 (71)	Assessment of glycemic control and risk for HF	Meta analysis	20,985 or higher A1C <6.5%	Type 1 DM	N/A	HF	N/A	A1C ≥10.5% vs A1C <6.5%: aHR: 3.98; 95% CI: 2.23-7.14; p<.001;	Used hospital admissions and did not include asymptomatic HF pts, so true incidence of HF underestimated.
Pfister, et al, A clinical risk score for HF in pts with type 2 diabetes and macrovascular disease: an analysis of the PROactive study. Int J Cardiol. 2011;May 31. 21636144 (72)	Identification of risk associated with DM	RCT	4,951	Type 2 DM	N/A	HF	3	Medium risk: HR: 3.5; 95% CI: 2.0-6.2; p<0.0001 High risk: HR: 10.5; 95% CI: 6.3-17.6; p<0.0001	HF was pre-defined by investigator, but rather reported as SAE in the trial. Trial population may not be generalizable to clinical population.
Kenchaiah et al, Obesity and the risk of HF. NEJM, 2002;347:305-313. 12151467 (73)	Assessment of HF risk associated with obesity	Prospective cohort	5,881	≥30 y; BMI ≥18.5;free of HF at baseline	N/A	HF	14	Women, HR: 2.12; 95% CI: 1.51-2.97 Men, HR: 1.90; 95% CI: 1.30-2.79	Possible misclassification of HF and subjects mostly white and results not generalizable to other races.
Kenchaiah, Sesso, Gaziano, Body mass index and vigorous physical activity and the risk of HF among men. Circulation, 2009;119:44-52. 19103991 (74)	Assessment of risk associated with obesity and effect of exercise	Prospective cohort, secondary analysis of RCT	21,094	Free of known heart disease at baseline.	N/A	Incidence of HF	20.5	Every 1 kg/m2 increase in BMI is associated with 11% (95% CI: 9-13) increase in risk of HF. Compared to lean active men: Lean inactive: HR:1.19; 95% CI: 0.94-1.51, Overweight active: HR:1.49; 95% CI: 1.30-1.71), Overweight inactive: HR: 1.78; 95% CI: 1.43- 2.23), Obese active: HR: 2.68; 95% CI: 2.08-3.45, Obese inactive: HR: 3.93; 95% CI: 2.60-5.96	Low incidence of HF as cohort comprised of physicians who are healthier than the general population. BMI measures and physical activity were self-reported. These measures were only taken at baseline and tend to change over time. This cohort consisted only of men and results not generalizable to women.

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Verdecchia et al, Effects of telmisartan, ramipril and their combination on LVH in individuals at high vascular risk in ONTARGET and TRANSCEND. Circulation 2009;120:1380-1389. 19770395 (75)	Evaluate effects of ACE, ARB, or both on development of LVH in pts with atherosclerotic disease.	RCT	23,165 for ONTARGET, 5,343 in TRANSCEND	Hx of CAD, PAD, cerebrovascular disease.	N/A	LVH	5	Telmisartan vs placebo: OR: 0.79; 95% CI: 0.68-0.91; p=0.0017. Telmisartan vs. ramipril: OR: 0.92; 95% CI; 0.83-1.01; p=0.07 Telmisartan + ramipril vs. ramipril: OR: 0.93; 95% CI: 0.84-1.02; *p*=0.12) Telmisartan vs telmisartan + ramipril: OR: 1.01; 95% CI: 0.91-1.12	Diagnosis of LVH was based on ECG, which is less sensitive than echocardiography and was binary (yes/no) instead of quantitative.
Braunwald et al; ACE inhibition in stable coronary artery disease. NEJM 2004;351:2058-2068. 15531767 (76)	Evaluate the effect of trandolapril on vascular events	RCT	8,290; 4,158 (trandolpril); 4,132 (placebo)	Stable CAD	N/A	Major CV events	4.8	HR: 0.95; 95% CI: 0.88-1.06; p=0.43	Results not significant possibly because the pts enrolled were at lower risk for CV events compared to other trials of ACEI.
Mills et al, Primary prevention of cardiovascualr mortality and events with statin treatments. J Am Coll Cardiol; 2008;52:1769-1781 19022156 (77)	Evaluation of primary prevention of CV events with statins	Meta analysis	53,371	N/A	N/A	Major CV events	N/A	RR: 0.84; 95% CI: 0.77-0.95; p=0.004	N/A
Taylor et al, Statins for the primary prevention of CV disease. Cocrane Database Syst Rev, 2011; CD004816 21249663 (78)	Assess benefit and risk of statins for prevention of CVD	Meta analysis	34,272	RCTs of statins with minimum duration of 1 y and f/u of 6 mo, in adults with no restrictions on their total LDL or HDL cholesterol levels, and where ≤10% had a hx of CVD, were included.	N/A	All-cause mortality and fatal/nonfatal CVD	N/A	All-cause mortality: RR: 0.84; 95% CI: 0.73-0.96) Fatal/non-fatal CVD: RR: 0.70, 95% CI: 0.61-0.79	N/A
Abramson et al; Moderate alcohol consumption and risk fo HF among older persons. JAMA, 2001;285:1971-1977. 11308433 (79)	Assessment of risk associated with alcohol use in older adults.	Prospective cohort	2,235	Age ≥65 y; lived in New Haven, Conn, and free of HF at baseline	Heavy alcohol consumption (>70 oz.)	New HF	N/A	No alcohol: aRR: 1.00 (referent), 1-20 oz: aRR: 0.79; 95% CI: 0.60-1.02), 21-70 oz: aRR: 0.53; 95% CI: 0.32-0.88. (p for trend=0.02)	Observational study, could not account for all possible confounders, alcohol consumption was self-reported.

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Walsh et al; Alcohol consumption and risk for CHF in the Framingham Heart Study. Ann Intern Med, 2002; 136:181-191. 11827493 (80)	Assessment of risk associated with alcohol use	Community based cohort	7,223	N/A	N/A	New CHF	N/A	Compared to men who consumed <1 drink/wk, men who consumed 8-14 drinks/wk: HR for CHF: 0.41; 95% CI: 0.21-0.81. In women: those who consumed 3-7 drinks/wk HR: 0.49; 95% CI: 0.25-0.96, compared with those who consumed <1 drink/wk.	Self-reported alcohol consumption.
Choueiri et al, CHF risk in pts with breast cancer treaated with bevacizumab. J Clin Oncol, 2011; 29:632-638. 21205755 (81)	Risk of CHF pts with breast cancer receiving bevacizumab	Meta analysis	3,784	RCTs published between January 1966-March 2010 in English.	N/A	New CHF	N/A	RR: 4.74; 95% CI; 1.84-12.19; p=0.001)	Data on other risk factors for CHF were not collected or unavailable.
Du et al; Cardiac risk associated with the receipt of anthracycline and trastuzumab in a alarge nationwide cohort of older women with breast cancer, 1998-2005. Med Oncol, 2010;Oct 22. 20967512 (82)	New HF	Registry	47,806	Women with breast cancer ≥65 y	N/A	New HF	N/A	HR: 1.19 anthracycline alone, HR: 1.97 trastuzumab alone, HR: 2.37 combo	N/A
Sawaya et al; Early detection and prediction of cardiotoxicity in chemotherapy treated pts. Am J Cardiol, 2011; 107:1375-80. 21371685 (83)	To assess whether early ECHO measurements of myocardial deformation and biomarkers (hsTnI and NT-proBNP) could predict the development of chemotherapy-induced cardiotoxicity in pts treated with anthracyclines and trastuzumab.	Prospective cohort	43	>18 y of age diagnosed with HER-2-overexpressing breast cancer and either scheduled to receive treatment including anthracyclines and trastuzumab or scheduled to receive trastuzumab after previous anthracycline treatment.	Pts with LVEFs ≤50%	Cardiotoxicity	N/A	Elevated hsTnI at 3 mo (p =0.02) and a decrease in longitudinal strain between baseline and 3 mo (p =0.02) remained independent predictors of later cardiotoxicity. Neither the change in NT-proBNP between baseline and 3 mo nor an NT-proBNP level higher than normal limits at 3 mo predicted cardiotoxicity	Small sample size

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McKie et al; The prognostic value of NT-proBNP for death and CV events in healthy normal and stage A/B HF subjects. J Am Coll Cardiol, 2010;55:2140-2147. 20447539 (84)	NT-proBNP as a predictor of death, CV events	Cohort	1,991	Age ≥45 y, lives in Olmsted County, Minnesota	Symptomatic HF (stages C and D HF)	Death, HF, CVA, MI	8.9 years	HR:1.26 per log increase in fully adjusted model in stage A/B pts (95% CI: 1.05–1.51; p=0.015). NT-proBNP was not predictive of death or CV events in the healthy normal subgroup.	Underpowered to detect association of NT-proBNP with adverse outcomes in the healthy normal subgroup.
Velagaleti et al; Multimarker approach for the prediction of HF incidence in the community. Circulation, 2010;122:1700-1706. 20937976 (85)	Evaluation of markers for HF development in the community	Cohort	2,754	Free of HF	N/A	HF	N/A	BNP: aHR: 1.52; 95% CI: 1.24–1.87; p<0.0001 UACR: aHR: 1.35; 95% CI: 1.11–1.66; p=0.004	Subjects mostly white and results not generalizable to other races.
Blecker et al; High normal albuminuria and risk of HF in the community. Am J Kidney Dis, 2011; 58:47-55. 21549463 (86)	Evaluation of albuminuria as risk for new HF	Cohort	10,975	Free of HF	N/A	HF	8.3	aHR: 1.54 (95% CI,:1.12-2.11) UACR normal to intermediate-normal; aHR: 1.91 (95% CI: 1.38-2.66) high-normal; aHR: 2.49 (95% CI: 1.77-3.50) micro; aHR: 3.47 (95% CI: 2.10-5.72) macro (p<0.001)	N/A
deFilippi et al; Association of serial measures of cardiac troponin T using a sensitive assay with incident HF and CV mortality in older adults. JAMA, 2010; 304:2494-2502. 21078811 (87)	Assessment as to whether baseline cTnT or changes predict HF	Cohort	4,221	N/A	N/A	HF	11.8	Complex >99th percentile at baseline: 6.4; change from neg to pos: 1.61 increase.	Samples were available in ~3/4 of the cohort at baseline, and differential absence of cTnT measures may have introduced bias into the estimates of associations with HF and CV death.
Heidenreich, et al, Cost-effectiveness of screening with BNP to identify pts with reduced LVEF. J Am Coll Cardiol, 2004;43:1019-1026. 15028361 (88)	Cost effectiveness of BNP screening	Cost benefit analysis	N/A	Asymptomatic pts.	N/A	N/A	N/A	BNP testing followed by echocardiography is a cost-effective screening strategy for men and possibly women at age 60 y - for every 125 men screened,1 y of life would be gained at a cost of $23,500.	Did not evaluate other blood tests such as pro-BNP as prevalence and outcome data were not available.

ACEI indicates angiotensin-converting-enzyme inhibitor; AF, atrial fibrillation; AV, atrioventricular; BMI, body mass index; BP, blood pressure; CABG, coronary artery bypass graft; CAD, coronary artery disease; CCB, calcium channel blocker; CHF, congestive heart failure; cTnT, cardiac troponin T; CV, cardiovascular; CVA, cerebrovascular accident; CVD, cardiovascular disease; DM, diabetes mellitus; DBP, diastolic blood pressure; ECG, electrocardiography; HDL, high density lipoprotein; HF, heart failure; hsTnI,

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high-sensitivity troponin I; HTN, hypertension; LDL, low density lipoprotein; Hx, history; LVH, left ventricular hypertrophy; MI, myocardial infarction; N/A, not applicable; N-terminal pro–B-type natriuretic peptide; ONTARGET, Ongoing Telmisartan Along and in Combination with Ramipril Global Endpoint Trial; PAD, peripheral arterial disease; PAR, population attributable risk; pro-BNP, pro–B-type natriuretic peptide; pts, patients; RCT, randomized clinical trial; SAE, serious adverse event; SBP, systolic blood pressure; TRANSCEND, Telmisartan Randomized Assessment Study in ACE Intolerant Subjects with CV Disease; and UACR, urinary albumin-to-creatinine ratio.

Data Supplement 12. Stage B: Preventing the Syndrome of Clinical HF With Low EF (Section 7.2)

Study Name, Author, Year	Aim of Study	Study Type	Study Size	Patient Population		Endpoints		Statistical Analysis (Results)	P Values & 95% CI:	OR: HR: RR:	Study Limitations	Findings/ Comments
				Inclusion Criteria	*Exclusion Criteria*	*Primary Endpoint*	*Secondary Endpoint*					
ACE Inhibitors												
Effect of Captopril on Mortality and Morbidity in Pts with LVD after MI Pfeffer, Marc A; NEJM 1992 (SAVE) 1386652 (89)	Investigate whether captopril could reduce morbidity and mortality in pts with LVSD after an MI	RCT	2,331	Within 3-60 d of MI; EF ≤40%; no overt HF or ischemic symptoms; age 21-80 y;	Cr > 2.5 mg/dL; relative contraindication to ACEI; need for ACEI to treat symptomatic HF or HTN; other conditions limiting survival; "unstable course" after MI	All-cause mortality; CV mortality; mortality & derease in EF of 9 units; development of overt HF (despite diuretics and digoxin therapy); hospitalization for HF; fatal or nonfatal MI; mean f/u 42 months	N/A	N/A	Risk Reduction: All-cause mortality 19% (95% CI: 3-32% p=0.019); death from CV cause 21% (95% CI: 5-35%; p<0.001); development of severe HF 37% (95% CI: 20-50%; p<0.001); HF hospitalization 22% (95% CI: 4-37%; p= 0.019); recurrent MI 25% (95% CI: 5-40%; p=0.015)	Low rate of beta blocker use; Recruitment 1987-1990: significant changes in revascularization strategies	Reduction in severe HF and HF hospitalization among pts with MI and LVSD without symptoms of HF
Effect of Enalapril on Mortality and the Development of HF in Asymptomatic Pts with Reduced LVEF. The SOLVD Investigators. NEJM 1992 (SOLVD Prevention) 1463530 (90)	Study the effect of an ACEI, enalapril, on outcomes in pts with LVSD not receiving drug therapy for HF	RCT	4228	EF≤35%; not receiving diuretics, digoxin or vasodilators for HF (asymptomatic LVSD)	N/A	All-cause mortality; mean f/u 37.4 months	Development of HF & mortality; HF hospitalization & mortality	N/A	Risk Reduction: All-cause mortality 8% (95% CI: 95% CI -8 - 21%; p=0.3); CV mortality 12% (95% CI: -3 - 26%; p=0.12); mortality & development of HF 29% (95% CI: 21-36%; p<0.001); mortality & HF hospitalization 20% (95% CI: 9-30%; p<0.001)	Low rate of beta-blocker use	Reduction in combined endpoints of development of HF & mortality and HF hospitalization and mortality among pts with asymptomatic LVSD

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Effect of enalapril on 12-y survival and life expectancy in pts with LVSD: a follow-up study. Jong, P Lancet 2003 12788569 (91)	12-y follow-up of SOLVD to establish if the mortality reduction with enalapril among pts with HF was sustained and wheather susequent reduction in mortality would emerge among those with asymptomatic ventricular dysfunction	Cohort	5,165	SOLVED prevention and treatment trial populations alive at completion of RCTs	N/A	All-cause mortality	N/A	In combined trials (Prevention and Treatment), enalapril extended median survival 9.4 mo (95% CI 2.8-16.5; p=0.004)	In the Prevention Trial mortality 50.9% in enalapril group vs. 56.4% in placebo group; p=0.001. In overall cohort, HR for mortality 0.9 (0.84-0.95); p=0.0003 for enalapril vs. placebo	N/A	Mortality benefit of enalapril among pts with asymptomatic LVSD
Statins											
Intensive Statin Therapy and the Risk of Hospitalization for HF After an ACS in the PROVE IT-TIMI 22 Study Scirica, Benjamin M JACC 2006 16750703 (92)	Determine whether intensive satin therapy reduces hospitalization for HF in high risk pts (intensive statin therapy simvastatin 80 vs. moderate statin therapy pravastatin 40mg)	RCT	4,162	ACS (AMI or high-risk UA) within 10 d; total cholesterol <240 mg/dL; stable condition;	Life-expectancy <2 y; PCI within the prior 6 mo (other than for qualifying event); CABG within 2 mo; planned CABG	Hospitalization for HF (time to first HF hospitalization that occurred 30 d or longer after randomization)	MI	Meta-analysis of 4 large RCTs of statin therapy (TNT, A to Z, IDEAL, PROVE-IT) N=27,546 Reduction in HF hospitalization: OR: 0.73; 95% CI: 0.63-0.84; p<0.001 [x2 for heterogeneity = 2.25, p=0.523)	Atorvastatin 80mg associated with reduction in HF hospitalization: 1.6% vs. 3.1%; HR 0.55; 95% CI: 0.35-0.85; p=0.008 when adjusted for history or prior HF HR 0.55; 95% CI: 0.35-0.36; p=0.008	Sub-study of PROVE IT-TIMI 22. Did not exclude those with prior HF (low rates)	In pts with ACS, intensive statin therapy reduced new onset HF Also perfomred meta-analysis of 4 large statin trials (2 ACS, 1 hx of MI, 1 clinically evident CHD) demonstrating benefit of intensive stating therapy in preventing HF hospitalizaiton
Early Intensive vs a Delayed Conservative Simvastatin Strategy in Pts with ACS. Phase Z of the A to Z Trial.	To compare early initiation of an intensive statin regimen with delayed initiation of a less intensive regimen in pts	RCT	4,479	STEMI or NSTEMI; total cholesterol ≤250 mg/dL; age 21-80; at least 1 high-risk characteristic (>70, DM, hx of CAD, PVD or	Receiving statin therapy, planned CABG, PCI planned within 2 wks of enrollment, ALT level >20% ULN, Cr >2.0mg/dL,	Composite: CV death, non-fatal MI, readmission for ACS, stroke	Individual components of primary endpoint and reascularization due to documented ischemia, all-cause	N/A	New onset HF reduced with intensive therapy: 5% vs 3.7%; HR 0.72; 95% CI: 0.53-0.98; p=0.04 Primary endpoint did not achieve significance: 16.7% vs 14.4%; HR 0.89; 95% CI: 0.76-1.04; p=0.14	Development of HF was a secondary endpoint Did not achieve primary endpoint	In pts with ACS, intensive statin therapy reduced new onset HF

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de Lemos, James A. JAMA 2004 15337732 (93)	with ACS			stroke, elevated CKMB or trooponin levels, recurrent angina with ST changes, ECG evidence of ischemia on pre-discharge stress test, multivessel disease)	concomitant therapy with agents known to enhance myopathy risk; prior hx of non-exercise related elevations in CK or nontraumatic rhabdomyolysis		mortality, new-onset HF (requiring medications or hospitalization), CV hosptialization				

ACEI indicates angiotensin-converting-enzyme inhibitor; ACS acute coronary syndrome; ALT, alanine aminotransferase; AMI, acute myocardial infarction; CABG, coronary artery bypass surgery; CAD, coronary artery disease; CHD, chronic heart disease; CKMB, creatine kinase-MB; Cr, creatinine; CV, cardiovascular; DM, diabetes mellitus; ESG, electrocardiogram; EF, ejection fraction; f/u, follow-up; HF, heart failure; HTN, hypertension; hx, history; LVSD, left ventricular systolic dysfunction; LVD, left ventricular dysfunction; MI, myocardial infarction; NSTEMI, non-ST elevation mysocardial infarction; PCI, Percutaneous coronary intervention; PROVE IT-TIMI 22, Pravastatin or Atorvastatin Evaluation and Infection Therapy -- Thrombolysis in Myocardial Infarction 22; Pts, patients; PVD, Peripheral artery disease; RCT, randomized control trial; SAVE, The Survival and Ventricular Enlargement trial; SOVLD, Studies of Left Ventricular Dysfunction; STEMI, ST elevation myocardial infarction; UA, unstable angina; and ULN, upper limit of normal.

Data Supplement 13. Stage C: Factors Associated With Outcomes, All Patients (Section 7.3)

Study Name, Author, Year	Aim of Study	Study Type	Study Size	Patient Population		Endpoints		Statistical Analysis (Results)	Study Limitations	Findings/Comments
				Inclusion Criteria	*Exclusion Criteria*	*Primary Endpoint*	*Secondary Endpoint*			
Education										

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Long-term prospective RCT using repetitive education at 6-mo intervals and monitoring for the adherence in HF outpt (The REMADHE Trial). Bocchi, Edimar Alcides. 2008 12196335 (94)	To determine whether a disease management program with repeated multidisciplinary education and telephone monitoring benefits HF outpt already under the care of a with HF experience cardiologist.	RCT	350	Diagnosed with HF	N/A	Combined death or unplanned first hospitalization and QoL changes	Hospitalization, death and adherence.	In the intervention group: QoL improved and Lower: deaths (p<0.003) or unplanned hospitalizations (p=0.008; 95% CI: 0.43- 0.88) , hospitalizations(p<0.001) , total hospital d during follow-up (p<0.001), and ED visits (p<0.001) No difference in estimated total mortality (p=ns; 95% CI: 0.55-1.13) or death during hospitalization (p=ns; 95%CI: 0.53-1.41)	Absence of blinding. Perception of better QoL in the intervention group due healthcare provider support as needed. Confouding by social conditions.	Despite modest adherence program reduced unplanned hospitalization, total hospital d, the need for emergency care and improved QoL.
Effect of discharge instructions on readmission of hospitalized pts with HF: do all of the joint commission on accreditation of healthcare organizations HF core measures reflect better care? VanSuch, M. 2006 17142589 (95)	To determine whether documentation of compliance with any or all of the 6 required discharge instructions is correlated with readmissions to hospital or mortality.	Retrospective study	782	Age ≥18 y, principal diagnosis of HF, hypertensive heart disease with HF, or hypertensive heart and renal disease with HF, discharged to home, home care or home care with IV treatment	Pts discharged to skilled nursing facilities or other acute-care hospitals.	Time to: death and readmission for HF or readmission for any cause	N/A	68% of pts received all instructions, and 6% received no instructions. Pts with all instructions (compared to those who missed at least one type of instruction) were significantly less likely to be readmitted for any cause or HF (p= 0.003) Documentation of discharge instructions was correlated with reduced readmission rates. No association between documentation of discharge and instructions and mortality.	Discharge instructions given but not documented. Discharge instructions could be a surrogate indicator for another intervention such as higher quality nursing care. Pt factor could have influenced confounding results. Generalizability limited. No active follow-up. Not all quality of care outcomes were assessed.	Documentation of discharge information and pt education appears to be associated with reductions in both mortality and readmissions.

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Discharge education improves clinical outcomes in pts with chronic HF. Koelling, T. 2005 15642765 (96)	To assess whether a pt discharge education program (the study intervention) improves clinical outcomes in chronic HF pts.	RCT	223	Admitted to hospital with a diagnosis of HF and documented left ventricular systolic dysfunction (EF ≤40%)	Evaluation for cardiac surgery, Noncardiac illness likely to increase 6-mo mortality or hospitalization risk, Inpatient cardiac transplantation evaluation	Total number of d hospitalized or dead in the 180-d follow-up period.	Clinical events, symptoms, and self-care practices.	The intervention group versus controls had fewer d hospitalized or dead in the 180-d follow-up period (p= 0.009), lower risk of rehospitalization or death (RR: 0.65; 95% CI: 0.45-0.93, p= 0.018), as well as lower costs of care, including cost of the intervention (lower by $2823 per pt, p= 0.035).	May not be generalizable- only 223 (38%) participated. pts being evaluated for transplantation not studied. Pts followed by the UMHFP not enrolled. Nurse coordinator unblined. Lack of reliability of self-reported self-care measures.	A 1-h teaching session at the time of hospital discharge resulted in improved clinical outcomes, increased self-care and adherence, and reduced cost of care in pts with systolic HF.
Effects of an interactive CD-program on 6 mo readmission rate in pts with HF- a RCT. Linne, A. 2006 16796760 (97)	To evaluate the impact of added CD-ROM education on readmission rate or death during 6 mo.	RCT	230	Diagnosis of HF (either LVEF < 40% by ECHO or at least 2 of these criteria: pulmonary rates, peripheral edema, a 3rd heart sound and signs of HF on chest x-ray).	Somatic disease, physical handicap with difficulty communicating or handling technical equipment, inability to speak Swedish, incompliance due to alcohol/drug abuse or major psychiatric illness, Participation in another trial	Difference in rate of all cause readmission and death within 6 mo after discharge.	N/A	Intervention group achieved better knowledge and a marginally better outcome (p=NS).	Only 37% completed questionnaire, pts had to come twice to the CD-based education, first as inpts, then 2 wk after discharge. Returning to the hospital may have discouraged participation, especially in sicker pts.	Additional education of HF pts with an interactive program had no effect on readmission rate or death within 6 mo after discharge.

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Computer-based education for pts with chronic HF. A randomized, controlled, multicenter trial of the effects on knowledge, compliance and QoL. Stromberg, A. 2006 16469469 (98)	To evaluate the effects of a single-session, interactive computer-based educational program on knowledge, compliance and QoL in HF pts. To assess gender differences.	RCT	154	Diagnosis of HF	None specified	Knowledge of HF, treatment compliance, self-care and QoL.	N/A	Computer-based group (intervention), knowledge increased: After 1 mo: p= 0.07, After 6 mo: p= 0.03 Women: significantly lower QoL and did not improve after 6 mo as men did (p= 0.0001). No differences between groups in compliance, self-care or QoL.	Data on knowledge collected through questionnaire, small sample size.	Computer-based education increased knowledge about HF compared to traditional teaching alone.
Long-term result after a telephone intervention in chronic HF. Ferrante, D. 2010 20650358 (99)	To assess rate of death and hospitalization for HF 1 and 3 y after a randomized trial of telephone intervention with education to improve compliance in stable HF pts with HF.	Follow-up after a RCT	1,518	Outpt with stable, chronic HF	None specified	Death and hospitalization for HF, 1 and 3 y after intervention ended.	Long term benefits	Rate of death or hospitalization for HF lower in the intervention group: 1 y: RR: 0.81; p= 0.013 95% CI: 0.69-0.96 3 y : RR: 0.72; p= 0.0004 95% CI: 0.60-0.87 Benefit caused by a reduction in admission for HF after 3 y Functional capacity better in intervention group Pts who showed improvement in 1 or more of 3 key compliance indicators (diet, weight control, and medication) had lower risks of events (p< 0.0001).	Classification bias of events due to open trial design.	Benefit observed during the intervention period persisted and was sustained 1 and 3 y after the intervention ended. This maybe due to the intervention impact on pt behavior and habits.
HF self-management education: a systematic review of the evidence. Boren, S. 2009 21631856 (100)	To identify educational content and techniques that lead to successful self-management and improve outcomes.	Systematic review of RCTs	7,413 pts from 35 trials	RCTs evaluating a self-management education program with patient-specific outcome measures.	Not randomized, No control group, Not in English, Failure to identify the content of the program, Providing similar educational content in all study arms,	Satisfaction, learning, self-care behavior, medication, clinical improvement, social functioning, hospital admissions and readmissions, mortality, and	N/A	Programs incorporated 20 educational topics in 4 categories- knowledge and self-management, social interaction and support, fluid management, and diet and activity. 113 unique outcomes were measured and 53% showed significant improvement in at least one study. Education on: sodium restriction associated with decreased mortality (p=0.07), appropriate follow-up associated with decreased cost	Unable to combine all the results. Difficult to compare interventions due to poor descriptions, and lack of transparency. All interventions not reproducible.	Review supports the benefits of educational interventions in chronic HF and suggests that some topics are related to certain outcomes.

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					Did not identify educational techniques used, Measured only knowledge as an outcome.	cost.		(p=0.10), management and recognition of worsening function associated with lower social functioning (p= 0.10). Discussion of fluids associated with increased hospitalization (p=0.01) and increased cost (p=0.10).		
Effect of sequential education and monitoring program on QoL components in HF. Cruz, Fatima das Dores. 2010 20670963 (101)	To determine if a DMP applied over the long-term could produce different effects on each of the QoL components.	Retrospective analysis (Extension of REMADHE trial, a RCT)	412	Under ambulatory care in a tertiary referral center and followed by a cardiologist with experience in HF. Age ≥18 Irreversible HF based on the modified Framingham criteria for at least 6-mo	Unable to attend educational sessions or who could not be monitored due to lack of transportation, or social or communication barriers, MI or unstable angina within past 6 mo, cardiac surgery or angioplasty within past 6 mo, hospitalized or recently discharged, any severe systemic disease that could impair expected survival, procedures that could influence follow-up, pregnancy or child-bearing potential	Change in QoL components during follow-up	Influence of the QoL score at baseline on pt survival.	Improved in the DMP intervention group: Global QoL scores: p<0.01 Physical component: p<0.01 Emotional component: p<0.01	QoL can be confounding. Loss of data due to morality during follow-up may have influenced QoL scores. Retrospective analysis of quality of life components.	Improvement of QoL is a fundamental target for the success of treatment of pts with HF. Specific components of the QoL assessment can behave differently over time and should stimulate the identification and development of new strategies and interventions. Targeting male pts and the emotional components of the QoL assessment in DMPs may be important in order to achieve a greater early improvement in QoL.
Social Support										

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Long-term effect of social relationships on mortality in pts with CHF. Murberg, Terje. 2004 15666956 (102)	To evaluate the effects of social relationships on morality risk in pts with stable, symptomatic HF.	Follow-up study	119	Diagnosed with HF	Unable to complete the questionnaires due to mental debilitation, previous heart transplantation	Perceived social support and isolation.	N/A	Social isolation a significant predictor of mortality (controlling for neuroticism, HF severity, functional status, gender, age): RR= 1.36; 95% CI: 1.04-1.78; p<0.03	Small sample size	Perceived social isolation an independent predictor of mortality in HF pts during a 6-y follow-up period. Experience of social isolation seems to be more critical than lack of social support.
The importance and impact of social support on outcomes in pts with HF: An overview of the literature. Luttik, M.L. 2005 15870586 (103)	To review the literature on what is scientifically known about the impact of social support on outcomes in pts with HF.	Review	17 studies	Studies that investigated the relationship between social support and different outcomes in HF.	None specified	Social support and different outcomes in HF (readmission, mortality, QoL and depression).	N/A	4 studies found clear relationships between social support and rehospitalizations and mortality; the relationship between QoL and depression was less clear.	None noted	Social support is a strong predictor of hospital readmissions and mortality in HF pts. Emotional support in particular is important. Some studies show that support is also related to the prevalence of depression and with remission of major depression in HF. Less evidence to support a relationship between social support and QoL.
Social deprivation increases cardiac hospitalisations in chronic HF independent of disease severity and diuretic non-adherence. Struthers, A. 2000 10618326 (104)	To examine whether social deprivation has an independent effect on emergency cardiac hospitalization in pts with chronic HF.	Cohort study	478	Admitted with an MI between January 1989- December 1992 and subsequently admitted for chronic HF between January 1989- December 1992, ≥3 diuretic prescriptions had to have been dispensed between January 1993- January 1994.	None specified	Emergency hospital admissions (all causes and for cardiac causes only)	N/A	Social deprivation significantly associated with an increase in the number of cardiac hospitalizations (p=0.007). Effect mainly caused by increasing the proportion of pts hospitalized in each deprivation category. 26% in deprivation category 1–2 vs. 40% in deprivation category 5–6 (p= 0.03). Effect of deprivation: independent of disease severity (as judged by the dose of prescribed diuretic), death rate, and duration of each hospital stay. Non-adherence with diuretic treatment could not account for these findings either.	Assessed adherence by whether pt had enough tablets in the house to cover the appropriate time period-measuring pt's maximum possible level of adherence. Poor adherence was associated with being male versus female but not with age, social deprivation, or diuretic dose. It is possible that diuretics caused more troublesome urinary symptoms in men because of prostatism, leading to poorer adherence.	Social deprivation increases the chance of rehospitalization independent of disease severity. Possible explanations are that doctors who look after socially deprived pts have a lower threshold for cardiac hospitalization or that social deprivation alters the way a HF pt accesses medical care during decompensation. Understanding how social deprivation influences both doctor and pt behavior in the prehospital phase is crucial to reduce the amplifying effect that social deprivation has

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										cardiac hospitalizations.
Social support and self-care in HF. Gallager, R. 2011 21372734 (105)	To determine the types of social support provided to HF pts and the impact of differing levels of social support on HF pts' self-care	Cross-sectional, descriptive (COACH sub-study)	333	Admitted to hospital for HF at least once before the initial hospitalization of the original study Age ≥18 y NYHA II-IV; evidence of underlying structural heart disease	Undergone cardiac surgery or PCI in the previous 6 mo, or if these procedures or heart transplantation was planned, Unable to participate in the COACH intervention or to complete the data collection forms	Self-care and social support	N/A	High level of support, compared to low or moderate levels reported significantly better self-care (p= .002) High level of social support, compared medium or low levels, significantly more likely to: consult with a health professional for weight gain (p= 0.011), limit fluid intake (p= 0.02), take their medication (p= 0.017), get a flu shot(p= 0.001), and exercise on a regular basis (p< 0.001).	Secondary analysis. Social support not prespecified in COACH trial. The measure and categories of social support have not been used previously either separately or as a composite measure. It is likely that other important factors influence HF self-care behavior as the multivariate model was not adequate.	The presence of social support by a partner is not sufficient to influence HF pts' self-care. Social support provided by partners needs to be of a quality and content that matches HF pts' perception of need to influence self-care.
Comorbidities										
A qualitative meta-analysis of HF self-care practices among individuals with multiple comorbid conditions. Dickson, V. 2011 21549299 (106)	To explore how comorbidity influences HF self-care	Qualitative meta-analysis	99 pts from 3 trials	Mixed method studies. Included pts with HF with at least 1 comorbid condition	None specified	Perceptions about HF and HF selfcare	N/A	Narrative accounts revealed the most challenging self-care skills: adherence to diet, symptom monitoring, and differentiating symptoms of multiple conditions. Emerging themes included: 1) attitudes drive self-care prioritization and 2) fragmented self-care instruction leads to poor self-care integration and self-care skill deficits.	Generalizability limited due to homogeneous sample. Interpretation of findings relied on interview data available from the primary studies. Findings may be baised because samples were recruited from HF specialty settings, possibly better managed clinically than community samples.	Individuals with multiple chronic conditions are vulnerable to poor self-care because of difficulties prioritizing and integrating multiple protocols. Adherence to a low-salt diet, symptom monitoring, and differentiating symptoms of HF from other chronic conditions are particularly challenging. Difficulty integrating self-care of different diseases and fragmented instructions regarding those conditions may contribute to poor outcomes.

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Psychiatric comorbidity and greater hospitalization risk, longer length of stay and higher hospitalization costs in older adults with HF. Sayers, Steven. 2007 17714458 (107)	To explore associations between psychiatric comorbidity and rehospitalization risk, length of hospitalization, and costs in adults with HF.	Cohort study	21429	Medicare beneficiaries hospitalized during 1999.	HF was not a primary cause of any admission during 1999, Comorbid dementia or organic brain syndrome diagnosis	Psychiatric comorbidity and rehospitalization risk, length of hospitalization, and costs.	N/A	Overall, 15.8% of pts hospitalized for HF had a coded psychiatric comorbidity. Most commonly coded comorbid psychiatric disorder was depression (8.5% of the sample) (p< 0.001). Most forms of psychiatric comorbidity were associated with greater inpatient utilization, including risk of additional hospitalizations, d of stay, and hospitalization charges (p< 0.001). Additional hospitalization costs associated with psychiatric comorbidity ranged up to $7,763, and additional length of stay ranged up to 1.4 d (p< 0.001).	Claims usage based administrative data. Information unavailable regarding the severity of HF in the sample. The possibility that outcomes may be worse for pts with coded comorbid psychiatric diagnoses as opposed to the presence of the conditions themselves cannot be excluded. Cross-sectional design.	Psychiatric comorbidity appears in a significant minority of pts hospitalized for HF and may affect their clinical and economic outcomes. The associations between psychiatric comorbidity and use of inpatient care are likely to be underestimated because psychiatric illness is known to be under detected in older adults and in hospitalized medical pts.
The relevance of comorbidities for HF treatment in primary care: A European survey. Sturm, H. 2006 16084761 (108)	To determine the impact of pt characteristics and comorbidities on chronic HF management, and to identify areas of prescribing that could be improved.	Descriptive study	11,062	Diagnosis of chronic HF and/or a history of MI during a 2-mo period in 1999	None specified	Influence of pt characteristics on drug regimens		Combined drug regimens given to 48% of HF pts (2.2 drugs on average). Pt characteristics accounted for 35%, 42% and 10% of the variance in 1-, 2- and 3-drug regimens, respectively. MI, AF, DM, HTN, and lung disease influenced prescribing most (OR=1.3; 95% CI: 1.2-1.4) AF made all combinations containing beta blockers more likely. For single drug regimes, MI increased the likelihood of non-recommended beta blocker monotherapy while for combination therapy, recommended regimes were most likely. For both HTN and DM, ACEI were the most likely single drug, while the most likely second drugs were beta blockers in HTN and digoxin in DM.	Drug regimens defined to make comparisons within levels of similar treatment intensity possible. Adherence rates depend on the indicators used.	Pt characteristics have a clear impact on prescribing in European primary care. Up to 56% of drug regimens were rational, taking pt characteristics into account. Situations of insufficient prescribing, such as pts post MI, need to be addressed specifically.

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Frequent non-cardiac comorbidities in pts with chronic HF. Dahlstrom, Ulf. 2005 15718170 (109)	To discuss in more detail the impact of co-existing HTN, DM, COPD in pts with HF.	Review	37 studies	None specified	None specified	N/A	N/A	About 50% of pts with untreated HTN will develop HF. Pressure overload leads to the development of LV hypertrophy and diastolic dysfunction. DM occurs in about 20–30% of pts with HF. COPD occurs in approximately 20–30% of HF pts. Anemia occurs in 20–30% of HF pts and is associated with functional impairment and increased mortality and morbidity. Combined treatment with erythropoietin and intravenous iron has shown beneficial effects on clinical symptoms and morbidity.	No limitations addressed.	This review of the literature clearly demonstrates that noncardiac comorbidities are common in pts with HF and that it is important to recognize these conditions and take them into consideration when selecting treatment for these pts. Appropriate treatment of the HF as well as the concomitant diseases will improve the prognosis of these pts.

ACEI indicates angiotensin-converting-enzyme inhibitor; AF, atrial fibrillation; CHF, congestive heart failure; COACH, Community Outreach and Cardiovascular Health; DM, diabetes mellitus; DMP, disease management program; ECHO, echocardiogram; ED, emergency department; EF, ejection fraction; HF, heart failure; HTN, hypertension; IV, intravenous; LVEF, left ventricular ejection fraction; MI, myocardial infarction; N/A, not applicable; NS, not significant; NYHA, New York Heart Association; PCI; percutaneous coronary intervention; pts, patients; QoL, quality of life; RCT, randomized control trial; REHMADE, Repetitive Education at Six-Month Intervals and Monitoring for Adherence in Heart Failure; UMHFP, University of Michigan Heart Failure Program

Data Supplement 14. Nonadherence (Section 7.3.1.1)

Study Name, Author, Year	Aim of Study	Study Type	Study Size	Patient Population		Endpoints		Statistical Analysis (Results)	Study Limitations	Findings/ Comments
				Inclusion Criteria	*Exclusion Criteria*	*Primary Endpoint*	*Secondary Endpoint*			
Noncompliance										

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Use of telehealth by older adults to manage HF. Dansky, K. 2008 20078015 (110)	To investigate the influence of telehealth on self-management of HF in older adults.	RCT	284	Admitted to a home health agency, Primary or secondary diagnosis of HF	None specified	Self-management of HF.	N/A	Confidence is a predictor of self-management behaviors. Pts using a video-based telehealth system showed the greatest gain in confidence levels with time (p= 0.035).	Small sample size. The home health agencies may have limited the external validity of the study. Examination of the effects of the telehealth interventions on specific behaviors was not possible.	Confidence is a positive predictor of self-management, which should encourage the development of interventions that focus on building self-care confidence in HF pts. These results contradict the stereotype that older adults are unable or unwilling to use technology.
Characteristics and inhospital outcomes for nonadherent pts with HF: findings from GWTG-HF. Ambardekar, A. 2009 19781426 (111)	To determine the characteristics, treatments, quality of care, and inhospital outcomes of pts nonadherent to dietary and medication advice as precipitating factors for HF hospitalization.	Cohort study	54,322	Ages >18, pts reported in the GWTG-HF database from January 1, 2005-December 30, 2007	Pts with new diagnoses of HF	2 groups: Those in whom nonadherence contributed to HF admission and those without nonadherence.	Hospital outcomes and quality of care among nonadherent pts vs. those who were adherent.	Multivariate analysis of characteristics of nonadherence: Younger age (per y decrease) p<0.0001; 95% CI: 1.019-1.026; Male gender (vs. female) p<0.0001; 95% CI: (1.196-1.358); Nonwhite race (vs. white) p<0.0001; 95% CI: 1.358-1.632 No health insurance (vs. insurance) p<0.0001; 95% CI: 1.236-1.633 Multivariate analysis of outcomes with vs. without nonadherence: Mortality 1.55% v. 3.49%; p<0.0001 95% CI: 0.51-0.86 Mean length of stay 4.99 d vs. 5.63 p= 0.0017; 95% CI: 0.92-0.97	Rates of nonadherence may be underestimated due to self reporting and biased based on pt characteristics. GWTG-HF is a voluntary program so could over-represent high-performing hospitals. Data collected by chart reviews, only in-hospital measures were tracked so long term follow-up unknown.	Nonadherence is a common precipitant for HF admission. Medication nonadherence greater in younger pts, ethnic minorities and uninsured whereas dietary nonadherence was observed in older, overweight and diabetic pts. Nonadherent pts present with evidence of lower EF and greater volume overload yet have an inhospital course characterized by a shorter LOS and lower mortality. Care of nonadherent pts conformed with Joint Commission core measures but at lower rates with other

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										guideline-based therapies.
Utilization of and adherence to drug therapy among Medicaid beneficiaries with CHF. Bagchi, A. 2007 17919558 (112)	To determine the number of Medicaid beneficiaries with HF, identify the rate of HF drug use, estimate adherence rates, examine factors associated with HF drug use and treatment adherence, and explore policy implications.	N/A	45,572	Living in Arkansas, California, Indiana or New Jersey, enrolled in fee-for service Medicaid with pharmacy benefit coverage during 1998 and 1999 or until death HF (hospitalized and diagnosed during 1998 or diagnosed on ≥ 2 ambulatory visits during 1998)	Stays in nursing home facilities at any time during 1999	Adherence based on: MPR (no. of d a pt is supplied with ≥1 HF drug in relation to the no. of dbetween the pt's first and last prescription dates), MP (no.of d of continuous use of HF medications per mo)	N/A	Odds of having a HF prescription claim were higher with people: Age 65-74 vs. <65: p<0.01; 95% CI: 1.193- 1.344 Age 75-84 vs. <65: p<0.01; 95% CI: 1.458- 1.676 Age ≥85 vs. <65: p<0.01; 95% CI: 1.162, 1.353 Dual Eligible : p<0.01; 95% CI: 1.466-1.580 Disabled: p<0.01; 95% CI: 1.388-1.537 Had CAD : p<0.01; 95% CI: 3.309-3.676 Had DM: p<0.01 95% CI: 2.085- 2.284 Hospitalized for HF in 1998: p<0.01; 95% CI: 1.579-1.701 Odds of having a HF prescription claim were lower among - Blacks vs. whites: p<0.01; 95% CI: 0.735-0.795 Other /unknown ethnic group vs. whites: p<0.01 95% CI: 0.840,-0.919 Men vs. women: p<0.01 95% CI: 0.722-0.775 Adherence better among age ≥85 y than <64 y, men than women, racial and ethnic minorities, dual	Measures of use and adherence are proxies based on prescriptions filled versus observations; findings may overestimate adherence to HF medications. Diagnoses recorded in claims may be incomplete, resulting in the omission of some pts from the study. Limited number of states may lead to biased results if Medicaid beneficiaries in study states are different than other states.	15.2% of diagnosed beneficiaries were not using any HF medications. Adults <65 y, men, ethnic minorities with hospital admissions for conditions other than HF, and beneficiaries with high CDPS scores had lower adherence.

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								eligible and disabled, those with CAD or DM, those with HF related hospitalization (p<0.01). Adherence lower among those with larger proportions of claims for generic HF drugs, higher CDPS risk scores and those with non-HF-related Hospitalizations (p<0.01).		
Drug copayment and adherence in chronic HF: effect on cost and outcomes. Cole, A. 2006 16863491 (113)	To measure the associations among prescription copayment, drug adherence and subsequent health outcomes in pts with HF	Retrospective Cohort Study	5,259 receiving ACE inhibitor 5,144 receiving Beta Blockers 2,373 receiving both	In Ingenix Research Data Mart, diagnosed with HF, and enrolled in commercial and/or Medicare supplemental plans in 2002; ≥2 physician visits or hospitalizations related to HF in 2002; $100-10,000 in costs associated with HF diagnoses in 2002; continuously enrolled in health plan for all of 2002 and at least 1 d in 2003. ACEI and/or beta blockers dispensed at least twice.	Receiving 1 dispensing of ACEI, receiving 1 dispensing of beta blockers, had switched ACEI, had switched beta blockers, MPR <20% or >120%, had conflicting data in their dispensing records	Total cost of health care and hospitalization for HF MPR: proportion of d a pt was exposed to a drug while receiving a regimen	N/A	For pts taking ACEI, a $10 increase in copayment was associated with a 2.6% decrease in MPR (95% CI: 2.0 - 3.1%) This change in adherence was associated with: a predicted 0.8% decrease in medical costs (95 %CI: -4.2 - 2.5%) a predicted 6.1% increase in the risk of hospitalization for chronic HF (95% CI: 0.5 - 12%). For pts taking beta blockers, a $10 increase in copayment was associated with a 1.8% decrease in MPR (95% CI: 1.4 - 2.2%) This change in adherence was associated with: a predicted 2.8% decrease in medical costs (95% CI: -5.9 - 0.1%). a predicted 8.7% increase in the risk of hospitalization for chronic HF (95% CI: 3.8 - 13.8%)	Using prescription dispensing data to assess drug adherence eliminates pts to whom a drug is dispensed only once so may have contributed to high adherence observed. Dispensing data does not capture actual usage. ACEI more expensive than beta blockers resulting in higher copayment. Total medical costs might have been insensitive to specific changes in adherence to HF therapies.	Among pts with HF, higher drug copayments were associated with poorer adherence, although the magnitude of change was small and did not affect total health care costs. It was sufficient to increase risk of hospitalization for HF though.

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The impact of perceived adverse effects on medication changes in HF pts. De Smedt, R. 2010 20142025 (114)	To evaluate the impact of perceived adverse HF drug effects	Retrospective Cohort Study	754	Hospitalized for symptomatic HF NYHA class II-IV Age ≥18 Evidence of structural underlying heart disease	Invasive procedures in the mo before or planned within 3 mo after baseline Already enrolled in other studies Follow-up treatment at another HF clinic	Impact of perceived adverse effects on likelihood and type of changes of potential causal cardiovascular medication & initiation of medication to alleviate the adverse effect.		Risk of a related medication change significantly increased after dry cough, nausea, dizziness, or diarrhea. Dry cough showing the highest increase in risk (83%; 95% CI: 1.35-2.49) Pts with gout had a 4-fold higher likelihood of having alleviating medication started or intensified (95% CI: 2.23-8.05) With dry cough, a 10-fold increase in the likelihood of having ACE inhibitor switched to an ARB (95% CI: 3.2-35.55) Pts with gout had a 3-fold higher likelihood of having diuretics temporarily discontinued and reinitiated at a lower dosage (95% CI: 1.09-10.04)	Cannot be certain that the reported problems resulted from medication. Focused on specific medication changes and did not take all possible adequate actions into account. Recall bias possible- pts may not have reported all perceived problems in the questionnaires.	A considerable number of HF pts perceived possible AEs. The likelihood of medication being changed after pts perceived AEs was low. A high number of pts perceive medication AE.
Associations between outpt HF process-of-care measures and mortality. Fonarow, G. 2011 21464053 (115)	To examine the relationships between adherence to several current and emerging outpt HF process measures and clinical outcomes.	Longitudinal/ Registry	15,177	Clinical diagnosis of HF or post-MI, LVEF ≤35%, ≥2 office visits with a cardiologist in the last 2 y	Noncardiovascular medical condition associated with an estimated survival of ≤1 y, received cardiac transplantation	Process-of-care HF measures: ACE inhibitor or ARB use, beta blocker use, aldosterone antagonist use, anticoagulant therapy for AF or flutter, CRT with defibrillator or pacemaker, ICD, and HF education for eligible pts.		Each 10% improvement in composite care was associated with a 13% lower odds of 24-mo mortality (p <0.0001; 95% CI: 0.84-0.90) All process measures, except aldosterone antagonist use, were each independently associated with improved 24-mo survival (p <0.01 for all except aldosterone antagonist use).	Errors and omissions in the medical chart review process could have occurred. NYHA functional status was not quantified in many of the records, and was instead based on qualitative description. This study analyzed medications prescribed rather than actual pt adherence. Follow-up on vital status was not achieved for all pts. Race/ethnicity, socioeconomic status or pt adherence may be confounding variables. Findings may not apply to practices that differ from the IMPROVE HF outpt cardiology practices in this	These data demonstrate that adherence to HF process measures for ACEI/ARB, beta blocker, anticoagulation for AF, and HF education is significantly associated with survival in outpts with HF. These HF measures may be useful for assessing and improving HF care.

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									study.	
A nurse-based management program in HF pts affects females and persons with cognitive dysfunction most. Karlsson, M. 2005 16009290 (116)	To assess the effect of a nurse-based management program aimed at increasing HF pts' knowledge about disease and self-care and to relate the results to gender and cognitive function.	Substudy of the OPTIMAL project- a RCT	208	Age >60 Systolic dysfunction EF <45% NYHA II-IV	None specified	Pt knowledge of HF and self-care.	N/A	At baseline men knew more about HF compared to women (p<0.01). Females in the intervention group increased their knowledge of self-care between baseline and 6 mo compared to the female control group (p <0.05). Pts with cognitive dysfunction (MMSE <24) presented lower scores on knowledge as compared to those with a MMSE of >24 at baseline. These differences disappeared after the intervention (p<0.01).	Some pts were included one d after hospitalization and some the d before discharge; condition improvement may explain low number of pts scoring low on the MMSE; The drop-out rate was high in the MMSE sub-study.	Nurse-based outpt clinic with specially trained nurses effective in increasing pt knowledge about self-care. Females and those with cognitive impairment gain from such programs.

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Pharmacist intervention to improve medication adherence in HF. Murray, M. 2007 10030506 (117)	To determine whether a pharmacist intervention improves medication adherence and health outcomes compared with usual care for low-income pts with HF.	RCT	314	Age ≥50 y, confirmed diagnosis of HF, regularly used at least 1 CV medication for HF, not using or not planning to use a medication container adherence aid, access to a working telephone, and adequate hearing	Dementia	Medication adherence (tracked by using electronic monitors) and clinical exacerbations that required visits to the ED or hospitalization.	Health-related QoL, satisfaction with pharmacy services, and total direct health care costs.	Medication adherence greater in the intervention group 78.8% vs. 67.9% usual care group (95% CI: 5.0-16.7). At 3 mo, adherence decreased 70.6% in intervention and 66.7 in usual care (95% CI: -5.9-6.5). Medications were taken on schedule 47.2% in the usual care and 53.1% in the intervention group (95%CI: 0.4-11.5). At the end of intervention, taking of medication on schedule decreased 48.9% for usual care and 48.6% in intervention (95% CI: -5.9-6.5) ED visits and hospital admissions were 19.4% less in the intervention group (95% CI: 0.73-0.93). Annual direct health care costs were lower in the intervention group (95% CI: $-7603-$1338)	Pts were not permitted to use medication container adherence aids. Intervention involved 1 pharmacist and a single study site that served a large, indigent, inner-city population of pts. Because the intervention had several components, results could not be attributed to a single component.	A pharmacist intervention for outpts with HF can improve adherence to cardiovascular medications and decrease health care use and costs, but the benefit probably requires constant intervention because the effect dissipates when the intervention ceases.
Short and long-term results of a program for the prevention of readmissions and mortality in pts with HF: are effects maintained after stopping the program? Ojeda, S. 2005 16051519 (118)	To evaluate whether improvement obtained during an intervention program were maintained after the program was stopped.	RCT	153	Discharged with a primary diagnosis of HF from the hospital cardiology ward.	Terminal disease, expected survival <6 mo, possibility of specific etiology treatment, wait list for heart transplant	Decrease in readmissions due to HF and in all-cause mortality event-free survival, defined on the basis of time to death or HF readmission.	Changes in pharmacological treatment and changes in quality of life MLHFQ	During the 16 ±8 mo treatment period, intervention group had: Lower rate of HF readmissions (p <0.01), and Less all-cause mortality Improvement in QoL (p=0.03) 1 y after the intervention, there were no differences between the groups (p=0.03).	Results cannot be extrapolated to all HF pts since the study included pts discharged from a cardiology service, who are usually younger and with fewer co-morbidities.	This intervention can reduce HF morbidity and mortality and improve quality of life but favorable effects decrease after program ends. Long-term programs are required to maintain beneficial effects.

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Excessive daytime sleepiness is associated with poor medication adherence in adults with HF. Riegel, et al 2011 21440873 (119)	To determine if medication adherence differs in adults with HF and EDS compared to those without EDS and to test cognition as the mechanism of the effect.	Prospective cohort comparison study	280	Chronic stage C HF confirmed, able to complete the protocol (vision, hearing, English literacy), no more than mild cognitive impairment	Living in a long term care setting, working nights or rotating shifts, renal failure requiring dialysis, imminently terminal illness, plans to move out of the area, history of serious drug or alcohol abuse in prior y, major depression	Self-reported medication adherence	Cognition measured with a battery of neuropsychological tests	62% were nonadherent with medication regimen. Medication nonadherence was significantly more common in those with EDS Subjects with EDS and cognitive decline were >2 times more likely to be nonadherent (aOR 2.36, 95%CI: 1.12-4.99; p=.033). Secondary models using the Epworth Sleepiness score: The odds of nonadherence increased by 11% for each unit increase in ED (aOR 1.11, 95%CI: 1.04-1.19; p=.025). Subjects with EDS and mild cognitive decline were 1.6 times more likely to be nonadherent over 6 mo follow-up (aOR 1.61; 95%CI: 1-03-2.50; p=.001). The group with EDS but without cognitive decline was twice as likely to be nonadherent (p=.014). 9% increase in the odds of nonadherence for each unit increase in EDS (p=.001). Lack of cognitive vigilance associated with nonadherence. (p=.024)	Medication adherence was self-reported.	HF pts who are sleepy have difficulty paying attention and thus forget to take their medications.

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Compliance with non-pharmacological recommendations and outcome in HF pts, van der Wal et al, 2010 20436049 (120)	To investigate the association between compliance with non-pharmacological recommendations (diet, fluid restriction, weighing, exercise) and outcome in pts with HF.	Secondary analysis of data from the COACH trial	830	Recently hospitalized for symptomatic HF, confirmed by the cardiologist, with evidence for underlying heart disease.	Invasive intervention within the last 6 mo or planned for the next 3 mo, inclusion in another study with additional visits to provider, or evaluation of CTX.	Composite of death or HF readmission and the number of unfavorable d.	mortality and readmission for HF	Pts non-compliant with ≥1 recommendations had a higher risk of mortality or HF readmission (p=0.01). Non-compliance with exercise was associated with an increased risk for mortality or HF readmission (p<0.01). Non-compliance with daily weighing was associated with an increased risk of mortality (p=0.02). Non-compliance (overall) and non-compliance with exercise were associated with a higher risk for HF readmission (p<0.05). Pts who were overall non-compliant or with weighing and exercise had more unfavourable d than compliant pts (p= 0.01).	Almost half had a first diagnosis of HF during the index hospitalization and then compliance was evaluated 1 mo after discharge, which could have influenced rates. 'Unfavorable d' difficult to evaluate. Self-report instrument used to measure compliance. Socially desirable responses possible.	HF pts who follow prescribed nonpharmacologic therapy have better outcomes than those who do not. Exercise and monitoring of daily weights are particularly important.
Nonpharmacologic Measures and Drug Compliance in Pts with HF: Data from the EuroHF Survey, Lainscak et al, 2007 17378994 (121)	To describe the recall of and adherence to nonpharmacologic advice of pts enrolled in the European HF Survey	Descriptive survey of pts from 115 hospitals from 24 European countries	2,331	Clinical diagnosis of HF		Self-reported adherence to nonpharmacologic advice		After hospitalization for HF, pts recalled receiving 4.1 ± 2.7 items of advice with some regional differences. Recall of dietary advice was higher (63%) than for influenza vaccination (36%) and avoidance of NSAIDS (17%). Among those who recalled the advice, many did not follow it completely (cholesterol and fat intake 61%; dietary salt 63%; influenza vaccination 75%; avoidance of NSAIDS 80%). A few indicated they ignored the advice completely. Pts who recalled >4 items versus <4 items were younger and more often received ACE-I (71% vs 62%), beta blockers (51% vs 38%), and spironolactone (25% vs 21%).	Younger pts who were more mobile and had greater social support were more likely to attend interview. Possible response bias.	Younger age and prescription of appropriate pharmacologic treatment are associated with higher rates of recall and implementation.

ACEI indicates angiotensin-converting-enzyme inhibitor; AE, adverse event; AF, atrial fibrillation; ARB, angiotensin receptor blocker; CAD, coronary artery disease; CDPS, Chronic illness and disability payment system; CHF, congestive heart failure; COACH, Community Outreach and Cardiovascular Health; CTX, chest x-ray; CRT, Cardiac resynchronization therapy; CV, cardiovascular; DM, diabetes mellitus; ED, emergency department; EDS, excessive daytime sleepiness; EF, ejection fraction; GWTG-HF; Get with the Guidelines-Heart Failure; HF, heart failure; ICD, implantable cardioverter-defibrillator; IMPROVE-HF, The Registry to Improve the Use of Evidence-Based Heart Failure Therapies in the Outpatient Setting; LOS, length of stay; LVEF, left ventricular

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ejection fraction; MI, myocardial infarction; MLHFQ, Minnesota Living with Heart Failure questionnaire; MMSE, Mini Mental State Examination; MP, Medication Persistence; MPR, medication possession ratio, N/A, not applicable; NSAID, nonsteroidal antiinflammatory drugs; NYHA, New York Heart Association; OPTIMAL, optimising congestive heart failure outpatient clinic project; pts, patients; QoL, quality of life; and RCT, randomized clinical trial.

Data Supplement 15. Treatment of Sleep Disorders (Section 7.3.1.4)

Study Name, Author, Year	Aim of study	Study Type	Study Size	Patient Population		Endpoints		Statistical Analysis (Results)	Study Limitations	Findings/ Comments
				Inclusion Criteria	*Exclusion Criteria*	*Primary Endpoint*	*Secondary Endpoint*			
Continuous positive airway pressure for central sleep apnea and HF (CANPAP). Bradley, T.D. et al 2005 16282177 (122)	To test the hypothesis that long-term treatment of CSA with CPAP in HF pts receiving optimal medical therapy reduces the combined rates of death and heart transplant.	11 center RCT	258	18-79 y, NYHA II-IV, HF due to ischemia, HTN, or idiopathic DCM, stable condition, optimal medical therapy for 1+ mo, LVEF <40%, CSA with ≥15 apnea-hypopnea index (AHI) and >50% of AHI had to be central.	Pregnancy, MI, USA, cardiac surgery within prior 3 mo, OSA	Death and heart transplantation	Hospitalizations, EF, exercise capacity, QoL, neurohormones	No difference between control (n=130) and CPAP (n=128) groups in number of hospitalizations, QoL, ANP levels. No difference in overall event rates (p=0.54).	Underpowered because trial stopped early for low enrollment	CPAP did not extend life, decrease transplant rate in CSA but may be indicated for OSA.
Suppresion CSA by CPAP and transplant-free survival in HF. Arzt, M. 2007 17562959 (123)	To investigate whether suppression of CSA below threshold by CPAP would improve LVEF and heart transplant–free survival.	Post-hoc analysis of a randomized trial.	210	Age 18 to 79 y, NYHA II-IV HF due to ischemic, hypertensive, or idiopathic DCM, stabilized with optimal medical therapy for at least 1 month LVEF <40%, Central sleep apnea	Pregnancy, MI, Unstable angina, cardiac surgery within 3 mo of enrollment, OSA	Combined rate of all-cause mortality or heart transplantation	Apnea-hypopnea index (AHI) mean nocturnal SaO2, and LVEF	Despite similar CPAP pressure and hours of use in the 2 groups, CPAP-CSA– suppressed subjects, compared to controls, experienced: A greater increase in LVEF at 3 mo (p=0.001) Significantly better transplant-free survival (HR: 0.37; 95% CI: 0.142-0.967; p=0.043)	Stratification of CPAP-treated pts based on polysomnogram performed 3 mo after randomization. Because suppressed and unsuppressed status could not be ascertained until completion of PSG, events that occurred during the first 3 mo could not be included; more deaths occurred in the pts randomized to CPAP than control (5 vs. 3). The CPAP-CSA–	These results suggest that in HF pts, CPAP may improve both LVEF and heart transplant–free survival if CSA is suppressed soon after it begins.

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									suppressed group was younger, had a lower AHI, and had a slightly lower proportion of central events than the CPAP CSA–unsuppressed group	
Effect of continuous positive airway pressure on sleep structure in heart failure pts with central sleep apnea. Ruttanaumpawan, P. 2009 19189783 (124)	To determine whether attenuation of CSA by CPAP in pts with HF reduces the frequency of arousals from sleep or improves sleep structure.	RCT	205	Age 18 to 79 y; NYHA II -IV HF due to ischemic, hypertensive, oridiopathic DCM, stabilized on optimal medical therapy ≥ 1 mo, LVEF <40% by radionuclide angiography, CSA defined as an AHI ≥ 15, with >50% of apneas and hypopneas central in nature	Pregnancy, MI, UA or cardiac surgery within 3 mo of enrollment, obstructive sleep apnea	Apnea-hypopnea index and frequency of arousals.	N/A	In controls, there no change in AHI or frequency of arousals. In CPAP group, AHI decreased significantly but neither the frequency of arousals nor sleep structure changed significantly (p<0.001).	Did not classify arousals as being respiratory or non-respiratory related, and did not examine their timing.	Attenuation of CSA by CPAP does not reduce arousal frequency in HF pts. Arousals not mainly a consequence of CSA and may not have been a defense mechanism to terminate apneas in the same way they do in OSA.
Relationship between beta blocker treatment and the severity of CSA in chronic HF. Tamura, A. 2007 17218566 (125)	To examine the relationship between use of beta blockers and the severity of CSA in HF.	Cohort study	45	Chronic HF NYHA II-III LVEF <50%.	Previous cerebrovascular disease, Recent (<6 mo) acute coronary syndrome, chronic respiratory disease	Polysomnography, echocardiography, plasma BNP levels	N/A	Pts receiving beta blockers compared to pts not receiving beta blockers had: lower AHI, lower CAI. Negatively correlated with the dose of carvedilol were: AHI CAI Multiple regression analysis selected no use of beta blockers as an independent factor of CAI. In 5 pts with CAI >5 who underwent serial sleep studies, CAI decreased significantly after 6 mo of treatment with carvedilol.	Small sample size. Did not measure central chemosensitivity to CO2.	In pts with chronic HF, CAI was lower according to the dose of beta blockers. No use of beta blockers was independently associated with CAI. 6 mo of treatment with carvedilol decreased CAI. These results suggest that beta blocker therapy may dose-dependently suppress CSA in pts with chronic HF.
Influence of CRT on different types of SDB. Oldenburg, O. 2007 17467333 (126)	To investigate the influence of CRT on SDB in pts with severe HF.	Prospective non-randomized study	77	Eligible for CRT, present with dyspnea, NYHA III-IV LBBB with QRS ≥150	None specified.	Cardiorespiratory polygraphy. NYHA class, frequency of nycturia,	N/A	CSA was documented in 36 (47%) pts, OSA in 26 (34%), and no SDB in 15 (19%).	Categorization of hemodynamic response based on a novel scoring system	In pts with severe HF eligible for CRT, CSA is common and can be influenced by CRT.

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				msec, LVEDD ≥60mm, LVEF of ≤35%, peak VO2 during standardized cardiopulmonary exercise testing, ≤18 ml/kg/min, during initial testing of several LV-lead positions (posterolateral veins), RV-stimulation sites (apex vs. RVOT) and LV vs. biventricular pacing, pulse pressure as a surrogate parameter of haemodynamic acute response had to increase by >10%.		cardiopulmonary exercise, 6-min walk test, and echocardiography parameters.		Sleep disordered parameters improved in CSA pts only: AHI, SaO2min, Desaturation (p< 0.001) Daytime capillary pCO2 was significantly lower in CSA pts compared to those without SDB with a trend towards increase with CRT (p=0.02). After classifying short term clinical and hemodynamic CRT effects, improved SDB parameters in CSA occurred in responders only (p=0.004).	not prospectively validated. Prospectively followed CRT pts without calculating statistical power needed to show results for pts without SDB, those with OSA, or CSA in advance.	Improvement depends on good clinical and hemodynamic response to CRT.

AHI indicates apnea hypopnoea index; ANP, atrial natriuretic peptide; BNP, B-Type natriuretic peptide; CAI, central apnea index; CPAP, continuous positive airway pressure; CRT, cardiac resynchronisation therapy; CSA, central sleep apnea; DM, dilated cardiomyopathy; EF, ejection fraction; HF, heart failure; HTN, hypertension; LBBB, left bundle branch block; LVEDD, left ventricular end diastolic diameter; LVEF, left ventricular ejection fraction; MI, myocardial infarction; N/A, not applicable; NYHA, New York Heart Association; OSA, obstructive sleep apnea; pts, patients; QoL, quality of life; RV, right ventricular; RVOT, right ventricular outflow tract; SDB, sleep disordered breathing; UA, unstable angina.

Data Supplement 16. Cardiac Rehabilitation-Exercise (Section 7.3.1.6)

Study Name, Author, Year	Aim of Study	Study Type	Study Size	Patient Population		Endpoints		Statistical Analysis (Results)	Findings/Comments
				Inclusion Criteria	*Exclusion Criteria*	*Primary Endpoint*	*Secondary Endpoint*		

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Antiremodeling effect of long-term exercise training in pts with stable chronic HF. Giannuzzi, Pantaleo. 2003 12860904 (127)	To determine whether long-term exercise training may influence LV volume and function in a large cohort of pts with stable chronic HF.	RCT	90	HF secondary to idiopathic DCM, IHD or valvular disease LVEF ≤35% by ECHO. Clinical stability for at least 3 mo under optimized therapy NYHA II-III Peak oxygen uptake (VO2) < 20mL/kg/min at ergospirometry Echocardiographic images of adequate quality for quantitative analysis	Any systemic disease limiting exercise, hypertrophic cardiomyopathy, Valvular disease requiring surgery, Angina pectoris, Sustained ventricular arrhythmias, Severe hypertension, Excess variability >10% at baseline cardiopulmonary exercise test	Cardiopulmonary exercise testing, 6MWT, echocardiography, and QoL.	N/A	Differences from baseline to 6 mo improved in the intervention group for: EF (p<0.001); Work capacity (p<0.001); Peak VO2 (p<0.006); Walking distance (p<0.001); QoL (p<0.01); LV volumes (diminished) (p<0.001); Trend to fewer readmissions for worsening dyspnea (p< 0.05) LV volumes increased in control group (p= 0.05)	In stable chronic HF, long-term moderate exercise training has no detrimental effect on left ventricular volumes and function; rather, it attenuates abnormal remodeling. Furthermore, exercise training is safe and effective in improving exercise tolerance and QoL.
Combined endurance-resistance training vs. endurance training in pts with chronic HF: a prospective randomized study. Beckers, Paul. 2008 18515805 (128)	To compare the effects of combined endurance-resistance training with endurance training only on submaximal and maximal exercise capacity, ventilatory prognostic parameters, safety issues, and QoL in pts with chronic HF.	Prospective randomized study	58	Chronic HF due to ischemic or dilated cardiomyopathy LVEF ≤40% NYHA II-III. Optimal and stable pharmacological treatment	Recent ACS or revascularization in the past 3 mo, actively listed on the transplant list, logistic problems, exercise limited by angina or peripheral arterial occlusive disease, cerebrovascular or musculoskeletal disease preventing exercise training, respiratory limitation	Steady-state workload	VO_2 peak, ventilatory prognostic parameters, upper and lower limb strength, and QoL	In the combined endurance-resistance training (compared to the endurance training group): SSW increased: p=0.007; Decrease in heart rate at SSW: p=0.002; VO_2 peak halftime was reduced: p=0.001 Maximal strength in upper limbs increased: p<0.001 HRQoL improved (reported decrease of cardiac symptoms): p= 0.003; 95% CI: 1.11-12.46.	In chronic HF pts, combined endurance-resistance training had a more pronounced effect on submaximal exercise capacity, muscle strength, and quality of life. The absence of unfavorable effects on left ventricular remodelling and outcome parameters is reassuring and might facilitate further implementation of this particular training modality.

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Comparison of hospital-based versus home-based exercise training in pts with HF: effects on functional capacity, QoL, psyhcological symptoms, and hemodynamic parameters. Karapolat, Hale. 2009 19641843 (129)	To compare the effects of home-based and hospital-based exercise programs on exercise capacity, QoL, psychological symptoms, and hemodynamic parameters in HF pts.	Randomized study	74	Diagnosed with HF for at least 3 mo, HF as a result of ischemic and dilated cardiomyopathy, clinical stability for at least 3 mo, LVEF ≤40% NYHA II-III, optimal and standard pharmacological treatment, ability to speak and understand Turkish, absence of psychiatric disease, ability to remain stable during exercise tests	Neurological, orthopedic, peripheral vascular, or severe pulmonary disease, NYHA class IV, UA pectoris, poorly controlled or exercise-induced cardiac arrhythmias, recent ACS or revascularization (≤3 mo), significant valvular heart disease, AF, uncontrolled arterial HTN, performing exercise training at regular intervals during the previous 6 wk.	Exercise capacity, QoL, psychological symptoms, and hemodynamic parameters	N/A	After the exercise programs, significant improvement was observed in both groups (all p<0.05) including: Peak VO_2; 6MWT; Subscales of physical function, general health, and vitality of short form 36 Beck Depression Inventory LVEF A comparison of the 2 exercise groups revealed no significant differences between them regarding the analyzed variables.	Both the hospital-based and home-based exercise groups improved significantly in functional capacity, QoL, depression symptoms, and LVEF. Based on these results, we believe that physicians can recommend home-based exercise under strict supervision for stable HF pts.
Endurance exercise training in older pts with HF: results from a randomized, controlled, single-blind trial. Brubaker, Peter. 2009 20121952 (130)	To determine whether exercise training improves exercise capacity and HRQoL in older persons with HFrEF.	RCT	59	Age ≥60 y, diagnosed with HfrEF, LVEF ≤45%	Valvular disease as the primary etiology of HFrEF, recent stroke or MI, uncontrolled HTN, any other condition limiting exercise duration	Exercise performance, LV structure and function, neuroendocrine activation and HRQoL.	N/A	Better in Exercise Training Group: Mean cycle ergometer distance per session (p=0.001) Combined walking & cycling distance (p=0.001) Peak exercise workload (watts) (p=0.007) Exercise time (seconds) on the bike (p=0.002) All other outcome measures did not show significance.	Failed to produce consistent benefits in a cohort or elderly pts with HFrEF that included a significant portion of women. Exercise time and peak workload increased but VO_2 peak, the primary outcome, did not. Exercise training failed to provide benefits in any of the 4 primary endpoints.

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Effects of exercise training on health status in pts with chronic HF. Flynn, Kathryn. 2009 19351942 (131)	To test the effects of exercise training on health status among pts with HF.	RCT	2,331	Medically stable, HF outpt, LVEF ≤35%, NYHA II-IV, ability and willingness to undergo exercise training	Unable to exercise, already exercising regularly (>1/wk), had experienced a major CV event in the previous 6 wk	Health status (assessed by the KCCQ)		At 3 mo the KCCQ overall summary score improved by a greater degree in the exercise training group (p< 0.001; 95% CI: 0.84-3.01) At 3 mo there were no further significant changes in KCCQ score for either group (p= 0.85), resulting in sustained, greater improvement overall for the exercise group (p< 0.001). Changes from baseline to 12 mo in the KCCQ overall summary score were associated with changes in exercise time: Cardiopulmonary exercise test: (r=0.28; p< 0.001) Peak O2 consumption: (r=0.21; p< 0.001) 6-min walk distance (r=0.18; p<0.001) Based on these relationships, a 49.7-m change in distance walked corresponds to an individual's change of 5 points on the KCCQ overall summary score.	Exercise training conferred modest but statistically significant improvements in self-reported health status compared with usual care without training. Improvements occurred early and persisted over time.
Resistance training increases 6-min walk distance in people with chronic HF: a systematic review. Hwang, Chueh-Lung. 2010 20482475 (132)	To determine if resistance training improves heart function, exercise capacity and QoL in people with chronic HF more than no intervention or usual care.	Systematic review with meta-analysis of randomized trials	241 pts from 8 trials	Adults with chronic HF Diagnosis based on clinical signs or LVEF <40%	None specified	Cardiac function, exercise capacity, QoL.	N/A	Resistance training significantly increased 6-min walk distance: WMD: 52m; 95% CI: 19-85	Resistance training increased 6-min walk distance compared to no training, but had no other benefits on cardiac function, exercise capacity, or QoL if used along or as an adjunct to aerobic training in people with chronic HF.

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A randomized trial of the addition of home-based exercise to specialist HF nurse care: the Birmingham Rehabilitation Uptake Maximization study for pts with CHF (BRUM-CHF) study. Jolly, Kate. 2009 19168520 (133)	To assess the effectiveness of a home-based exercise program in addition to specialist HF nurse care.	RCT	169	LVEF ≤40% on ECHO; had a severity of at least NYHA II in the previous 24 mo; clinically stable for 4 wk; in receipt of optimal medical treatment and in the care of a specialist HF nurse team from 2 acute hospital trusts and 1 primary care trust in the West-Midlands region, UK; not considered high-risk for a home-based exercise program.	NYHA IV MI; revascularization within the past 4 mo; hypotension; UA; ventricular or symptomatic arrhythmias; obstructive aortic valvular disease; COPD; hypertrophic obstructive cardiomyopathy; severe musculoskeletal problems preventing exercise; case-note reported dementia; current severe psychiatric disorder	Disease-specific QoL measured by the MLHFQ	Composite outcome of death or admission with HF or myocardial infarction. Psychological wellbeing, self-reported physical activity, blood pressure, generic HRQoL, and health care utilization.	At 6 mo, there was no between-group difference in the disease-specific QoL MLHFQ (95% CI: -7.87-2.80) At 12 mo, there was no between-group difference in the disease-specific QoL MLHFQ (95% CI: -5.87-4.76) The only secondary outcomes significant for exercise group: Higher generic QoL scores at 6 mo (95% CI: 0.04-0.18) Lower hospital anxiety and depression scale score at 12 mo (95% CI: -2.00 - -0.14) At 6 mo, the control group showed deterioration in physical activity, exercise capacity and generic QoL.	This study failed to demonstrate a benefit from the addition of a home-based exercise program in a community-based HF population. Further evidence is needed to assess the suitability of home-based exercise programs in this population.
Exercise training in older pts with HF and preserved EF. Kitzman, Dalane. 2010 20852060 (134)	To test the hypothesis that supervised exercise training in older pts with HFpEF would improve the primary outcome of peak exercise VO_2 and the secondary outcome of disease-specific QoL.	RCT	53	Stable with no medication changes for >6 wk; HFpEF defined as history, symptoms and signs of HF Preserved LVEF (≥50%); no evidence of significant coronary, valvular or pulmonary disease or any other medical condition that could mimic HF symptoms.	Contraindication to exercise testing or training; unable to perform a valid baseline exercise test; currently exercising regularly; had known cancer; significant renal dysfunction; substance abuse; uncontrolled diabetes; dementia, History of noncompliance; any other disorder that would preclude participation in the intervention and follow-up.	Peak exercise oxygen uptake	QoL; LV morphology and function, and neuroendocrine function	Peak exercise oxygen uptake increased significantly in the exercise treatment group compared to the control group (p= 0.0002). There were significant improvements in peak power output, exercise time, 6-minute walk distance, and ventilatory anaerobic threshold (all p< 0.002). There was improvement in the physical quality of life score (but not in the total score) (p= 0.03).	This randomized, controlled, single-blind study showed that 16 wk of exercise training was safe and significantly improved peak and submaximal exercise performance in older pts with HFpEF. These results suggest that this nonpharmacological intervention may be a worthwhile consideration for pts with this common and increasingly prevalent disorder.

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Effects of exercise training in pts with HF: the exercise rehabilitation trial (EXERT). McKelvie, Robert. 2002 12094184 (135)	To examine the effects of exercise training on functional capacity in pts with HF.	RCT	181	Documented clinical signs and symptoms of HF LVEF <40%, NYHA I-III, 6MWT distance <500 meters	Inability to attend regular exercise training sessions; exercise testing limited by angina or leg claudication; abnormal blood pressure response to exercise testing; cerebrovascular or musculoskeletal disease preventing exercise testing or training; respiratory limitation; poorly controlled cardiac arrhythmias; any noncardiac condition affecting regular exercise training or decreasing survival.	6MWT	Peak oxygen uptake, dynamic muscle strength, QoL, and cardiac function	Significant increase in 6-min walk distance at 3 and 12 mo (p= 0.026) but no between-group differences (p= 0.081). Incremental peak oxygen uptake increased in the exercise group compared with control group: At 3 mo: (p=0.014); At 12 mo: (p=0.014) At 3 mo, compared with the control group, increases were seen in exercise group for: Arm Curl and Knee Extension: (p=0.014) No significant changes observed in cardiac function or QoL.	Exercise training improves peak oxygen uptake and strength during supervised training. Over the final 9 mo of the study, there was little further improvement, suggesting that some supervision is required for these pts. There were no adverse effects on cardiac function or clinical events.

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Combined endurance and muscle strength training in female and male pts with chronic HF. Miche, Eckart. 2008 18432395 (136)	To evaluate the effect of a combined endurance and muscle strength training program on clinical performance data and health-related psychosocial factors in women and men.	Non-randomized study of men vs. women.	285	Stable chronic HF; LVEF <45%; Peak VO2 <20 ml/min/kg; capable of answering questions on HRQoL and psychological well-being.	Severe pulmonary disorders; neurological deficits; cognitive disorders and physical disabilities which prevented pts from participating in a training program.	LVEF, cardiopulmonary performance, QoL	N/A	Women had a diagnosis of non-IHD and valvular heart disease more commonly than men. LVEF increased: Female: p<0.001 Male: p<0.001 LVEDV decreased: Female: p<0.05 Male: p<0.05 LVESV: Female: p<0.001 Male: p<0.001 Peak VO2: Female: p NS Male: p<0.001 Wattmax (W): Female: p<0.001 Male: p<0.001 6MWT (m): Female: p<0.001 Male: p<0.001 Muscle strength training: Female: p<0.001 Male: p<0.001 Physical Health: Female: p<0.001 Male: p<0.001 Mental Health: Female: p<0.01 Male: p<0.05	The results of our study confirm the feasibility of a combined endurance and resistance program, especially for women. Our findings show a considerably reduced cardiopulmonary performance, negatively affecting physical health. In contrast, no essential restrictions were reported by our groups regarding mental health. This underlines the importance of a physical training program and its continuation at home following the hospital stay in order to influence performance data favorably.

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Long-term effects of a group-based high-intensity aerobic interval-training program in pts with chronic HF. Nilsson, Birgitta. 2008 18940296 (137)	To evaluate the long-term effects of a 4-mo, group-based, high-intensity aerobic interval training program on functional capacity and the QoL in pts with chronic HF.	RCT	80	Stable chronic HF; NYHA II-IIIB; receiving optimal medical treatment; LVEF <40% or ≥40% with clinical symptoms of diastolic HF	Acute MI within 4 wk; UA pectoris; serious rhythm disturbance; symptomatic peripheral vascular disease; severe obstructive pulmonary disease; 6MWT <550 m; workload on the cycle ergometer test >110 W; significant comorbidities that would prevent study entry due to terminal disease or an inability to exercise In a long-term care establishment	Functional capacity, evaluated by 6-min walking distance.	QoL	After 4 mo, in the exercise group: Functional capacity improved (p<0.001), QoL improved (p<0.001). After 12 mo, in the exercise group: Functional capacity still improved (p<0.001). QoL still improved (p=0.003).	The results support the implementation of a group-based aerobic interval training program to improve long-term effects on functional capacity and the QoL in pts with chronic HF.
Efficacy and safety of exercise training in pts with chronic HF. O'Connor, Christopher. 2009 19351941 (138)	To test the efficacy and safety of exercise training among pts with HF.	RCT	2331	HF LVEF ≤35%, NYHA II-IV,despite optimal HF therapy for at least 6 wk	Major comorbidities or limitations that could interfere with exercise training, recent or planned major CV events or procedures, performance of regular exercise training, use of devices that limited the ability to achieve target heart rates.	Composite of all-cause mortality or all-cause hospitalization.	All-cause mortality, the composite of CV mortality or CV hospitalization, and the composite of CV mortality or HF hospitalization.	NS reductions in primary or secondary endpoints. In prespecificed supplementary analyses adjusting for highly prognostic baseline characteristics there were reductions in the exercise training group for: All-cause mortality or hospitalization: (p=0.03; 95% CI: 0.81-0.99) CV mortality or HF hospitalization: (p=0.03; 95% CI: 0.74-0.99)	Regular exercise training in pts with systolic HF was safe. In the protocol-specified primary analysis, exercise training resulted in nonsignificant reductions in the primary endpoint of all-cause mortality or hospitalization and in secondary endpoints. After adjustment for highly prognostic predictors of the primary endpoint, exercise training was associated with modest significant reductions for both all-cause mortality or hospitalization and CV mortality or HF hospitalization.

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Exercise training meta-analysis of trials in pts with chronic HF (ExTraMATCH). Piepoli. 2004 14729656 (139)	To determine the effect of exercise training on survival in pts with HF due to LV systolic dysfunction.	Collaborative meta-analysis	801 pts from 9 trials	Randomized parallel group controlled trials, evaluate exercise training without any other simultaneous intervention, study pts with stable HF (3 mo or more of stability) due to left systolic ventricular dysfunction (LVEF <50%), have an exercise program lasting 8 wks or more, utilize training involving at least both legs, have survival follow up of ≥3 mo.	Trials of arm or single leg training were excluded	Time to death.	Death or time to admission to hospital.	Exercise training significantly reduce mortality (p=0.0015; 95% CI: 0.46-0.92) Exercise training significantly reduced death or admission to hospital (p=0.01 95% CI: 0.56-0.93).	Meta-analysis of randomized trials gives no evidence that properly supervised medical training programs for pts with HF might be dangerous, and indeed there is clear evidence of an overall reduction in mortality.
Randomized trial of progressive resistance training to counteract the myopathy of chronic HF. Pu, Charles. 2001 11356801 (140)	To evaluate whether strength training in elderly pts with chronic HF would be well tolerated and result in improved overall exercise performance without changes in central cardiac function.	RCT	96 (16 HF 80 control)	Community-dwelling, female, age ≥65 mild to moderate, stable systolic HF, NYHA I-III, resting LVEF ≤45%	NYHA class IV, MI within 6 mo, hospitalization for chronic HF within 2 mo, change of HF therapy within 1 mo, UA pectoris, fixed ventricular rate pacemaker, abdominal aortic aneurysm >4 cm, major limb amputation, symptomatic abdominal or inguinal hernias Folstein mini-mental state examination score <23, significant abnormalities on maximal treadmill testing or screening strength testing	Overall exercise capacity (6-min walk distance) and muscle function.	Muscle metabolism and histology, body composition, maximal oxygen consumption, and cardiac function,	Women with chronic HF had significantly lower muscle strength than women without chronic HF (p<0.0001). In resistance trainers (vs. controls): Strength improved (p<0.0001); Muscle endurance improved (p<0.0001); 6-minute walk distance increased (p<0.0003). Increases in type 1 fiber area and citrate synthase activity in skeletal muscle were independently predictive of improved 6-min walk distance (r^2 = 0.78; p=0.0024).	High-intensity progressive resistance training improves impaired skeletal muscle characteristics and overall exercise performance in older women with chronic HF. These gains are largely explained by skeletal muscle and not resting cardiac adaptations.

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The effects of physical training on workload, upper leg muscle function and muscle areas in pts with chronic HF. Senden, Jeff. 2005 15823638 (141)	To investigate the effect of physical training on upper leg muscle area, muscle strength and muscle endurance expressed as upper leg muscle function in relation to exercise performance.	RCT	77	Chronic HF for at least 6 mo, NYHA II-III, clinically stable for at least 3 mo, received optimal medical therapy, physically able to visit the outpt clinic, LVEF <35%	Interfering disease such as COPD, fasting glucose <7.0 mmol/L (DM), neuromuscular disorders, HTN	LVEF, body composition, daily physical activity, exercise performance, upper leg muscle area and isokinetic leg muscle variables.	N/A	Workload and peak oxygen consumption decreased in the control group and increased in the training group ($p<0.05$). Hamstrings area decreased in the control group and did not change in the training group ($p<0.05$). Upper leg muscle function improved in the training group and did not change in the control group ($p<0.05$). At baseline and after intervention nearly 60% of the variance in maximal workload was explained by upper leg muscle function and quadriceps muscle area.	In chronic HF pts, home-based training in conjunction with a supervised strength and endurance training program is safe, feasible and effective and does not require complex training equipment. Physical training prevented loss of hamstrings muscle mass and improved exercise performance by enhancing muscle strength and endurance.
Antiremodeling effect of long-term exercise training in pts with stable chronic HF. Giannuzzi, Pantaleo. 2003 12860904 (127)	To determine whether long-term exercise training may influence LV volume and function in a large cohort of pts with stable CHF.	RCT	90	HF secondary to idiopathic DCM, IHD or valvular disease, LVEF ≤35% by ECHO, clinical stability for at least 3 mo under optimized therapy, NYHA II-III, peak oxygen uptake (VO_2) <20mL/kg/min at ergospirometry, echocardiographic images of adequate quality for quantitative analysis	Any systemic disease limiting exercise, hypertrophic cardiomyopathy, valvular disease requiring surgery, angina pectoris, sustained ventricular arrhythmias, severe HTN, excess variability >10% at baseline cardiopulmonary exercise test	Cardiopulmonary exercise testing, 6MWT, ECHO, and QoL.	N/A	Differences from baseline to 6 mo improved in the intervention group for: EF ($p<0.001$), Work capacity ($p<0.001$), Peak VO_2 ($p<0.006$), Walking distance ($p<0.001$), QoL ($p<0.01$), LV volumes (diminished) ($p<0.006$), Trend to fewer readmissions for worsening dyspnea (EDV $p<0.05$ ESV) LV volumes increased in control group ($p<0.0.01$ EDV ESV)	In stable chronic HF, long-term moderate exercise training has no detrimental effect on LV volumes and function; rather, it attenuates abnormal remodeling. Furthermore, exercise training is safe and effective in improving exercise tolerance and QoL.

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Exercise training reduces circulating adiponectin levels in pts with chronic HF. Van Berendoncks, An. 2010 19656085 (142)	To assess circulating adiponectin concentrations in chronic HF pts, compare with controls, and evaluate the effects of a 4-mo exercise training program.	Prospective, non-randomized trial	80	LVEF <30%, NYHA II-III, symptoms had been stable on medical treatment for at least 1 mo prior to inclusion	Recent ACS or revascularization, valvular disease requiring surgery, exercise-induced myocardial ischemia or malignant ventricular arrhythmia, acute myocarditis or pericarditis, cerebrovascular or musculoskeletal disease preventing exercise testing or training, acute or chronic infections, allergies, cancer or inflammatory disease, DM.	Circulating adiponectin concentrations, exercise capacity, anthropometric data and NT-proBNP levels.	N/A	At baseline, adiponectin levels were significantly higher in chronic HF pts compared with healthy subjects (p=0.015). At baseline, stratification of pts according to tertiles of NT-proBNP revealed an increase in adiponectin with disease severity (p<0.001). Exercise training significantly reduced circulating adiponectin levels in the trained chronic HF group (compared to sedentary chronic HF group) (p=0.008)	Circulating adiponectin concentrations are higher in chronic HF pts compared with healthy subjects and increase with disease severity. Exercise training for 4 mo lowers circulating adiponectin levels. The present findings, together with those from other studies, suggest that dysregulation of the adiponectin pathway contributes to the observed metabolic impairment in chronic HF
Effects of exercise training on cardiac performance, exercise capacity and QoL in pts with HF. Van Tol, Benno. 2006 16713337 (143)	To determine the effect of exercise training in pts with chronic HF on cardiac performance, exercise capacity and HRQoL.	Meta-analysis of RCTs	35 trials	RCTs, included pts with chronic HF in the control and in the intervention group (diagnosis based on clinical findings or LVEF <40%), included at least 1 treatment group receiving exercise training and 1 control group which received standard medical treatment w/o additional exercise training, evaluated outcome measures in terms of cardiac performance, exercise capacity and/or HRQoL, exercise training had to include at least one of the following training modalities: walking, cycling or resistive training of peripheral muscles.	Studies in which only respiratory muscles or one isolated muscle group was trained.	Cardiac performance, exercise capacity and HRQoL.	N/A	During maximal exercise, significant summary effect sizes were found for: SBP (p=0.03), Heart rate (p=0.011), Cardiac output (p=0.004), Peak oxygen uptake (p=0.00), Anaerobic threshold (p=0.00), 6MWT (p=0.00). The MLHFQ improved by an average of 9.7 points (p=0.00).	Exercise training has clinically important effects on exercise capacity and health-related quality of life, and may have small positive effects on cardiac performance during exercise.

6MWT indicates 6 minute walk test; ACS acute coronary syndrome; AF, atrial fibrillation; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; CV, cardiovascular; DCM, dilated cardiomyopathy; DM, diabetes mellitus; ECHO, echocardiography; EF, ejection fraction; EXERT, Exercise Rehabilitation Trial; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fration; HRQoL, health related quality of life; HTN,

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hypertension; IHD, ischemic heart disease; KCCQ, Kansas City Cardiomyopathy Questionnaire; LV, left ventricular; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; MI, myocardial infarction; MLHFQ, Minnesota Living with Heart Failure Questionaire; N/A, not applicatble; NT-proBNP, N-terminal pro-B-Type natriuretic peptide; N/A, not applicable; NS, not significant; O2, oygen; pt, patient; QoL, quality of life; r^2, coefficient of determination; RCT, randomized control trial; SSW, Stead-state workload; UA, unstable angina; UK, United Kingdom; and VO2, oxygen volume.

Data Supplement 17. Diuretics Versus Ultrafiltration in Acute Decompensated HF (Section 7.3.2.1)

Study Name, Author, Year	Aim of Study	Study Type	Study Size	Patient Population		Endpoints		Statistical Analysis (Results)	Study Limitations	Findings/ Comments
Diuretic studies				*Inclusion Criteria*	*Exclusion Criteria*	*Primary Endpoint*	*Secondary Endpoint*			
DOSE-AHF, Felker, 2011 21366472 (144)	To compare high and low doses of diuretics administered over longer and shorter periods of time to determine the safest and most effective combination.	RCT	308	Prior clinical diagnosis of HF that was treated with daily oral loop diuretics for at least 1 mo; current diagnosis of HF, as defined by the presence of at least 1 symptom (dyspnea, orthopnea, or edema) and 1 sign (rales on auscultation, peripheral edema, ascites, pulmonary vascular congestion on chest radiography); daily oral dose of furosemide 80 mg-240 mg (or equivalent); identified within 24 h of hospital admission; current treatment plan includes IV loop diuretics for at least 48 h	BNP <250 mg/mL or NT-proBNP <1000 mg/mL; IV vasoactive treatment or ultrafiltration therapy since initial presentation; treatment plan includes IV vasoactive treatment or ultra-filtration; substantial diuretic response to prerandomization diuretic dosing such that higher doses of diuretics would be medically inadvisable; SBP <90 mm Hg; SCr >3.0 mg/dL at baseline or currently undergoing renal replacement therapy; hemodynamically significant arrhythmias; ACS within 4 wk prior to study entry; active myocarditis; hypertrophic obstructive cardiomyopathy; severe stenotic valvular disease; restrictive or constrictive cardiomyopathy; complex congenital heart disease; constrictive pericarditis;. non-cardiac pulmonary edema; clinical evidence of digoxin toxicity; need for mechanical hemodynamic support; sepsis; terminal illness (other than HF) with expected survival time of <1 y; history of adverse reaction to the study drugs; use of IV iodinated radiocontrast material within 72 h prior to study entry or planned during hospitalization; enrollment	Pt well-being, as determined by VAS; change in SCr	Weight loss; Proportion of pt free of congestion; change in the bivariate relationship of creatinine vs. weight loss; dyspnea, as determined by VAS; pt global assessment, as determined by VAS; change in SCr; Change in cystatin C; worsening or persistent HF, defined as a need for rescue therapy; development of cardio-renal syndrome, defined as an increase in the SCr level >0.3 mg/dL; net fluid loss; time from study entry to discharge during index hospitalization; death or total days hospitalized for	Comparison of bolus vs. continuous infusion: no significant difference in either pts' global assessment of symptoms (mean AUC, 4236±1440 in the bolus vs 4373±1404 in the infusion group, p=0.47) Mean change in creatinine level (0.05±0.3 mg/dL in the bolus vs 0.07±0.3 mg/dL in the infusion group, p=0.45) Secondary Endpoints: No significant differences, including SCr and cystatin C levels during index hospitalization and at 60 d. Comparison of high-dose vs. low-dose strategy: no significant difference in pts' global assessment of symptoms, although there was a nonsignificant trend toward greater improvement in the high-dose group (mean AUC, 4430±1401 vs. 4171±1436; p=0.06; mean change in creatinine level (0.08±0.3 mg/dL with the high-dose strategy and 0.04±0.3 mg/dL with the low-dose strategy, p=0.21). Secondary endpoints: The high-dose strategy was associated with greater diuresis (net fluid loss and weight loss) and greater relief from dyspnea but also with transient worsening of renal function (occured in 23% of pts in the high-dose vs 14% in the low-dose group, p=0.04)	N/A	N/A

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					or planned enrollment in another clinical trial during hospitalization; inability to comply with planned study procedures		HF; death or re-hospitalization	Clinical composite endpoint of death, rehospitalization, or ED visit during the 60-d follow-up period: HR with continuous infusion: 1.15; 95% CI: 0.83-1.60; p=0.41, HR with high-dose strategy, 0.83; 95% CI: 0.60-1.16; p=0.28		
PROTECT, Massie, 2010 20925544 (145)	Rolofylline, an adenosine A1-receptor antagonist, would improve dyspnea, reduce the risk of WRF, and lead to a more favorable clinical course in pt with acute HF	RCT	2,033	Persistent dyspnea at rest or with minimal activity, impaired renal function (an estimated CrCl of 20-80 mL/min with the use of the Cockcroft−Gault equation), a BNP level of ≥500 pg/mL or more or an NT-pBNP level ≥2000 pg/mL, ongoing IV loop-diuretic therapy, and enrollment within 24 h after admission.	Pregnant or breast feeding; acute contrast induced nephropathy, sepsis, serum potassium <3.5mEq/L; ongoing or planned IV therapy for acute HF with positive inotropic agents, vasopressors, vasodilators, or mechanical support, with the exception of IV nitrates, BNP<500; ongoing or planned UF, hemofiltration or dialysis; severe pulmonary disease; significant stenotic valvular disease, heart transplant recipient or admitted for cardiac transplantation	Primary end point was treatment success, treatment failure, or no change in the pt's condition. Success defined as pt-reported moderate or marked improvement in dyspnea both 24 and 48 h after administration of the study drug, in the absence of any criterion for failure. Failure defined as the occurrence of any of the following: death or readmission for HF through d 7, worsening symptoms and signs of HF occurring >24 h after the initiation of the study drug requiring intervention by d 7 or discharge (if earlier), or persistent WRF, defined as an increase in the SCr level ≥0.3 mg/dL (26.5 μmolL) from randomization to d 7, confirmed at d 14, or the initiation of hemofiltration or dialysis during the period from initiation of the study drug through d 7. Pts were classified as having unchanged treatment status if they met neither the criteria for treatment success nor the criteria for treatment failure.	Two secondary outcomes were prespecified: death from any cause or rehospitalization for cardiovascular or renal causes through d 60 and the proportion of pts with persistent renal impairment, defined as an increase in the SCr level ≥0.3 mg/dL by d 7, confirmed at d 14; the initiation of hemofiltration or dialysis through d 7; or death by d 7.	Rolofylline did not provide a benefit with respect to the primary endpoint (OR: 0.92; 95% CI: 0.78-1.09; p=0.35). Persistent renal impairment developed in 15% of pts in the rolofylline group and in 13.7% of pts in the placebo group (OR: 1.11; 95% CI: 0.85-1.46; p=0.44). By 60 d, death or readmission for cardiovascular or renal causes had occurred in similar proportions of pts assigned to rolofylline, 386 of 1356 pts (Kaplan–Meier estimate, 30.7%; 95% CI: 27.8-33.6) as compared with 195 of 677 pts assigned to placebo (Kaplan–Meier estimate: 31.9%; 95% CI: 27.4-36.4) (HR: 0.98; 95% CI: 0.83-1.17; p=0.86). AE rates were similar overall; however, only pts in the rolofylline group had seizures, a known potential adverse effect of A1-receptor antagonists1.	Post hoc selection of the best of 3 dose groups from the pilot trial with multiple small treatment groups carries the risk that an apparent superiority may be the play of chance and may have resulted in the inability to replicate pilot study findings in this more definitive, larger study. Also, clinical relevance of endpoints has been questioned	Rolofylline did not have a favorable effect with respect to the primary clinical composite end point, nor did it improve renal function or 60-d outcomes. It does not show promise in the treatment of acute HF with renal dysfunction

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DAD-HF, Giamouzis, 2010 21111980 (146)	Evaluate the effect of low-dose dopamine and furosemide on diuresis and renal function in pts with acute decompensated HF	RCT	60	Age >18 y; history of HF; deterioration of HF, symptoms of recent onset (<6 h), dyspnea at rest, orthopnea, and paroxysmal nocturnal dyspnea, accompanied by signs of congestion (third heart sound, jugular venous distension, pulmonary rales) on physical examination; levels of serum BNP >400 pg/mL or NT pBNP >1,500 pg/mL; and oxygen saturation <90% on admission.	Acute de novo HF; severe renal failure (admission SCr >215 mmol/L [2.5 mg/dL] or eGFR <30 mL min 1 1.73 m^2); admission SBP <90 mm Hg; severe valvular disease; known adverse reactions to furosemide or dopamine; HF secondary to congenital heart disease; a scheduled procedure with a need for IV contrast dye in the present hospitalization; and a scheduled cardiac surgery within 2 mo.	Incidence of WRF during the first 24 h from randomization. 2 definitions were used for WRF: 1) >0.3 mg/dL rise in SCr level from baseline to 24 h; and 2) >20% decrease in eGFR from baseline to 24 h	Changes in SCr, urea, potassium, and eGFR during the first 24 h from randomization; incidence of WRF over the course of hospitalization; total length of stay; and 60-d mortality or rehospitalization rate (all-cause, cardiovascular, and worsening of HF).	Mean hourly excreted urine volume (272±149mL in high-dose furosemide vs 278±186mL in LDFD plus low-dose dopamine group; p=.965) and changes in dyspnea score (Borg index: 4.4±2.1 in high-dose furosemide group vs 4.7±2.0 in LDFD group; p=.575) during the 8 h of protocol treatment were similar in the two groups. WRF was more frequent in the high-dose furosemide (n=9; 30%) than in the LDFD group (n=2; 6.7%; p=.042). Serum potassium changed from 4.3±0.5 to 3.9±0.4mEq/L at 24 h (p=.003) in the high-dose furosemide group and from4.4±0.5 to 4.2±0.5mEq/L at 24 hours (p=.07) in the LDFD group. Length of stay and 60-d mortality or rehospitalization rates (all-cause, cardiovascular, and worsening HF).	Relatively small study, 2 groups did not receive the same dose of furosemide and did not include a low-dose furosemide only group.	This study shows that LDFD infusions are as effective as high-dose furosemide infusions in terms of clinical and diuretic response in pts hospitalized for acute decompensate d HF. Moreover, LDFD infusion was associated with significantly lower rates of WRF than high-dose furosemide, suggesting a renoprotective effect in this pt population.

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Pilot continuous vs bolus infusion (Duke), L Allen, 2010 20538132 (147)	Pilot study of furosemide by continuous infusion vs twice-d bolus injection. Hypothesis that continuous dosing of IV furosemide provides gradual diuresis with less neurohormonal activation, which would manifest as less renal dysfunction, compared to bolus dosing in the treatment of acute decompensated HF with volume overload	RCT	41	Primary diagnosis of acute decompensated HF; evidence of volume overload; could be randomized <24 h from hospital presentation	End-stage renal disease or anticipated need for renal replacement therapy; were not expected to survive hospitalization; pregnant	Change in SCr from admission to hospital d 3 or hospital discharge	Cumulative urine output and other electrolyte changes from admission to hospital d 3 as well as hospital length of stay	None of the outcomes showed a statistically significant difference between bolus and continuous dosing from admission to hospital d 3. Nonsignificant trend toward improvement in the bolus dosing arm. Decreases in serum potassium, serum sodium, and SBP showed nonsignificant trends in favor of continuous infusion	Smaller study	No statistically significant differences noted between bolus and continuous infusion
Pilot continuous vs bolus infusion (MUSC), Thomson, 2010 20206891 (148)	Pilot study comparing the effectiveness of continuous IV with intermittent IV infusion of furosemide in pt with acute decompensated HF	RCT	56	Admission diagnosis of acute decompensated HF	Pts who had received >2 doses of IV fruosemide before randomization	Net daily urine output	Net daily urine output normalized for amount of furosemide received, total daily urine output normalized for amount of furosemide received, weight loss during the study, need for additional HF therapy, duration of study drug dministration, length of hospitalization	Mean urine output in 24 h was 2,098±1,132 mL in pt receiving continuous vs 1,575±1100 mL in the bolus group (p=0.086). Total urine output was 3726±1121 mL/24 h in the continuous group vs 2,955±1,267 mL/24 h in bolus group (p=0.019). Length of hospital stay was 6.9±3.7 d in the continuous group vs 10.9±8.3 d in the bolus group (p=0.006)	Smaller study	LOS shorter and mean urine output greater in the continuous infusion group vs bolus group
ADHERE, Peacock, 2008 18480204 (149)	To determine the clinical and renal outcomes associated with lower vs higher IV loop diuretic dose in pts hospitalized with acute decompensated	Registry	82,540	Pts in the ADHERE registry who received IV diuretics during a hospitalization for acute decompensated	Pts receiving vasoactive drugs or dialysis. Those who received multiple types of diuretics. Pts with SCr values >6 mg/dL or hospitalizations with LOS <4 h were excluded from the analysis of change in SCr and dialysis	Increase from baseline to last available SCr > 0.5 mg/dL; decrease in GFR >10 mL/min from baseline to discharge; initiation of dialysis during	Inhospital mortality, ICU admission, ICU LOS >3 d, and hospital LOS >4 d	Both before and after risk and propensity adjustments, an increase in SCr >0.5 mg/dL occurred less frequently in LDD admissions than in HDD admissions (both p<0.0001). The prevalence of a >10 mL/min decrease in GFR from baseline to discharge was	ADHERE registry data were retrospective and observational so should be regarded as hypothesis	Among pts in the ADHERE registry, After covariate and propensity adjustments, the inhospital

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	HF. This study analyzed data from the ADHERE registry to look at the impact of diuretic dosing. 62,866 pt receiving <160 mg and 19,674 pts ≥160 mg of furosemide were analyzed.			HF.	initiation. Pt with SCr values >6 mg/dL, GFR values >200 mL/min, or hospitalizations with LOS <24 h were excluded from the analysis of change in GFR.	hospitalization.		significantly lower in LDD vs HDD admissions (p <0.0001). Significant differences between cohorts present after risk and propensity adjustments. LDD treatment was associated with lower prevalence of prolonged ICU LOS (nonsignificant differences). After covariate and propensity adjustments: in-hospital mortality risk of LDD was significantly lower compared to HDD. AUC for adjusted model was 0.78. Unadjusted mortality OR 0.875; 95% CI: 0.787–0.973; p =0.01. After adjustment for covariates known to be associated with mortality – age, BUN, SBP, DBP, sodium, creatinine, heart rate and dyspnea at rest – adjusted OR was 0.888: 95% CI: 0.795–0.993; p =0.0364	generating. Clinical reasons for initiation of IV diuretics was not collected and therefore not considered in analysis.	mortality risk of pts who received LDD was significantly lower compared to those receiving HDD.
Cohort study high vs. low dose (Brigham and Women's) Mielniczuk, 2008 18514930 (150)	This study was a prospective observational analysis of pts in an advanced HF clinic stratified at baseline by diuretic dose (low dose ≤80 mg, high dose >80 mg furosemide equivalent) to evaluate the effect of high/low (or no) diuretic doses on outcomes.	Cohort	183	Eligible pts had to have a primary diagnosis of chronic HF and be followed by a specialist in a tertiary care HF clinic. Pts with either preserved or reduced systolic function were included	Pts were excluded if they required renal replacement therapy, had a concurrent noncardiac diagnosis expected to limit life expectancy to less than 1 y, or were unable to participate in repeat clinical assessments	All pts were followed for 1 y. The primary outcome for the analysis was time to first HF event of HF admission, cardiac transplant, MCS, or death	Secondary outcomes included individual components of the HF composite and WRF, which was defined as an increase in SCr >0.3 mg/dL from baseline	Compared with pts taking LDD (113 pts [62%]), pts taking HDD (70 pts[38%]) had more markers of increased cardiovascular risk (older, ischemic cardiomyopathy, DM and HTN) and were more likely to have a history of recent instability (33% vs 4.4% in low dose, p< .001). SCr significantly higher in pts receiving HDD vs. LDD (1.4 ± 0.5 mg/dL vs 1.1 ± 0.5 mg/dL, respectively, p < .001). 1 y cumulative HF event rates significantly greater in pts taking HDD when to low-dose/no diuretics (HF composite, 29% vs 4.5%, p<.01; HF hospitalization, 26% vs 4.5%, p< .01; MCS or transplant, 7.1% vs 2.7%, P = .02; death, 2.9% vs 0.9%, p= .4; high vs low dose for all). Among pts taking HDD, those with a history of instability had significantly greater HF event rates during a 1-y period compared with pts with recent	Smaller study, observational, single-center	HDD may be more of a marker than a cause of instability. A history of HF stability during the past 6 mo is associated with an 80% lower risk of an HF event during the next y, independently of baseline diuretic dose.

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								clinical stability (HF composite, 47% vs 18%, p =.013) Independently of diuretic dose, pts with a history of clinical stability had an 80% lower risk of developing an HF event . HDD were a strong univariate predictor of subsequent HF events (HR: 3.83, 95% CI: 1.82-8.54); however, after adjustment for clinical stability, diuretic dose no longer remained significant (HR: 1.53, 95% CI: 0.58-4.03).		
PROTECT **pilot**, Cotter, 2008 18926433 (151)	Pilot study was designed to identify an efficacious dose while refining inclusion criteria and endpoints	RCT	301	Hospitalized for acute HF with an estimated CrCl of 20-80 mL/min and elevated natriuretic peptide levels were enrolled within 24 h of presentation	SBP <95 or >160 mm Hg; fever >38°C; acute contrast-induced nephropathy; resistant hypokalemia; ongoing or planned IV therapy with positive inotropic agents, vasopressors, vasodilators with the exception of IV nitrates, or mechanical support (intra-aortic balloon pump, endotracheal intubation, or ventricular assist device); severe pulmonary disease; significant stenotic valvular disease; previous heart transplant or admission for cardiac transplantation; clinical evidence of ACS <2 wk before screening; and acute HF caused by significant arrhythmias; pts at high risk of seizures	The prespecified primary analysis for this pilot phase was a trichotomous classification of pts as "success," "unchanged," or "failure" based on their changes in symptoms and renal function. This pilot phase was not powered to demonstrate statistically significant changes. The major objective was to evaluate the performance of this novel endpoint and refine it on the basis of real-world experience. Treatment success was defined as an improvement in dyspnea (reported by the pt using a 7-point Likert scale as moderately or markedly better compared with study start) determined at 24 and 48 h after the start of study drug (d 2 and 3) or d of discharge if earlier, as long as the pt did not meet any of the criteria for treatment failure. Treatment failure was defined as death, early HF readmission (occurring	Composite of death or all-cause readmission within 60 d	Pts treated with rolofylline more likely to achieve success, as evidenced by improved dyspnea (52.7% vs 37.2%), and less likely to experience failure (manifested by worsening HF, death, or renal impairment) compared with pts treated with placebo (16.2% vs 28.2%). By comparing rolofylline 30 mg with placebo, the OR estimated from the proportional odds model was 0.51 (95% CI: 0.28–0.94). In the prespecified subgroup of pts with higher natriuretic peptide levels, pretreatment BNP level ≥500, or NT pro-BNP ≥2000 pg/mL, most likely representing more severe acute HF, the OR from the proportional odds model was 0.59 (95% CI 0.30–1.17). SCr increased in pts receiving placebo and remained stable or tended to decrease in those receiving rolofylline. On d 14 the absolute differences between placebo and rolofylline for change in creatinine increased with increasing rolofylline dose, reflecting the lesser increase in creatinine in rolofylline-treated pt (r = -0.12, p=.030). Treatment with 30 mg, the dose selected for the pivotal trials, was associated with a trend toward reduced 60-d mortality or readmission for cardiovascular or renal cause (HR: 0.55; 95% CI: 0.28-1.04).	Limited by the study size and number of treatment groups. Study was not powered to quantitatively distinguish between the 3 active doses, although trends emerged suggesting a dose-related preservation of renal function and increase in diuresis, as well as a greater effect on the composite endpoint at the 30 mg dose.	The preservation of renal function associated with rolofylline, a selective renal vasodilator, is the first evidence that an intervention to prevent renal impairment may positively affect acute symptoms and 60-d outcome in pts with acute HF; however, results were not confirmed in the phase III trial.

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						within 7 d of study drug initiation), worsening HF as defined daily by the physician assessment by d 7, or persistent renal impairment as defined above. Unchanged pts were classified as unchanged if neither criteria for success or failure were met.				
DIG, Ahmed, 2008 17532064 (152)	The objective of this propensity-matched study was to determine the effect of diuretics on mortality and hospitalizations in HF pts ≥65 y.	Registry	7,788	Pts who were at ≥21 y of age were eligible for the main trial if they had HF, a LVEF ≤45%, were in normal sinus rhythm, and did not meet any of 20 easily determined, not overly restrictive exclusion criteria	Age <21 yrs; baseline EF not available; MI, cardiac surgery or PTCA within 4 wk; unstable or refractory angina <1 month; II-III AV block without pacemaker; AF or flutter; cor pulmonale; constrictive pericarditis; acute myocarditis; hypertrophic cardiomyopathy; amyloid cardiomyopathy; complex CHD; tx with IV inotropic agents; K+ < 3.2 mmol/L or >5.5 mmol/L; on heart transplant list; noncardiac cause of HF; Creatinine >3.0 mg/dL or severe liver disease; unlikely to comply	All-cause mortality and all-cause hospitalization during 36.7 mo of median follow-up	Mortality and hospitalizations due to cardiovascular causes and HF	All-cause mortality occurred in 173 pts not receiving diuretics and 208 pts receiving diuretics respectively during 2,056 and 1,943 person-y of follow-up (HR:1.36; 95% CI: 1.08-1.71; p=0.009). All-cause hospitalizations occurred in 413 pts not receiving and 438 pts receiving diuretics respectively during 1,255 and 1,144 person-y of follow-up (HR: 1.18; 95% CI: 0.99-1.39; p=0.063). Diuretic use was associated with significant increased risk of cardiovascular mortality (HR:1.50; 95% CI:1.15-1.96; p=0.003) and HF hospitalization (HR:1.48; 95% 95% CI: 1.13-1.94; p=0.005).	Beta blockers were not approved for HF during the DIG trial and data on beta blocker use were not collected	Diuretic use associated with increased mortality among elderly in the DIG trial
EVEREST, Gheorghiade, 2007 17384438 (153)	To evaluate short-term effects of tolvaptan when added to standard therapy in pts hospitalized with HF	RCT	2,048 (trial A) and 2,085 (trial B)	Age ≥18 y with a history of chronic HF (requiring treatment for a minimum of 30 d before hospitalization) who had been hospitalized primarily for worsening CHF and had a LVEF ≤40% (measured at any point within 1 y of admission). Entry required HF	Cardiac surgery within 60 d of enrollment, cardiac mechanical support, biventricular pacemaker placement within the last 60 d, comorbid conditions with an expected survival of less than 6 mo, acute MI at the time of hospitalization, hemodynamically significant uncorrected primary cardiac valvular disease, refractory end-stage HF, hemofiltration or dialysis, supine systolic arterial blood pressure of less than 90 mm Hg, SCr concentration >3.5 mg/dL (>309.4 µmol/L), serum potassium concentration > 5.5 mEq/L, and	Composite of changes in global clinical status based on a visual analog scale and body weight at d 7 or discharge if earlier	Dyspnea (d 1), global clinical status (d 7 or discharge), body weight (d 1 and 7 or discharge), and peripheral edema (d 7 or discharge).	Rank sum analysis of the composite primary endpoint showed greater improvement with tolvaptan vs placebo (trial A, mean [±SD], 1.06 [0.43] vs 0.99 [0.44]; and trial B, 1.07 [0.42] vs 0.97 [0.43]; both trials p<.001). Mean (±SD) body weight reduction was greater with tolvaptan on d 1 (trial A, 1.71 [1.80] vs 0.99 [1.83] kg; p<.001; and trial B, 1.82 [2.01] vs 0.95 [1.85] kg; p<.001) and day 7 or discharge (trial A, 3.35 [3.27] vs 2.73 [3.34] kg; p<.001; and trial B, 3.77 [3.59] vs 2.79 [3.46] kg; p<.001). Improvements in global clinical status were not different between groups. More pts receiving tolvaptan (684	N/A	In pts hospitalized with HF, oral tolvaptan in addition to standard therapy including diuretics improved many, though not all, HF signs and symptoms, without serious AE.

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				symptoms at rest or minimal exertion and signs of congestion (≥2 of the following: dyspnea, jugular venous distention, or peripheral edema) at time of randomization.	hgb of less than 9 g/dL			[76.7%] and 678 [72.1%] for trial A and trial B, respectively) vs pts receiving placebo (646 [70.6%] and 597 [65.3%], respectively) reported improvement in dyspnea at d 1 (both trials p<.001). Edema at d 7 or discharge improved significantly with tolvaptan in trial B (p =0.02) but did not reach significance in trial A (p=0.07). Serious AE frequencies were similar between groups, without excess renal failure or hypotension		
EVEREST, Konstam, 2007 17384437 (154)	To investigate the effects of tolvaptan initiated in pts hospitalized with HF	RCT	4,133	Pts age ≥18 y with reduced LVEF ≤40%, signs of volume expansion, NYHA class III/IV symptoms, and hospitalization for exacerbation of chronic HF no more than 48 h earlier were eligible for the study	Cardiac surgery within 60 d of enrollment, cardiac mechanical support, biventricular pacemaker placement within the last 60 d, comorbid conditions with an expected survival of <6 mo, acute MI at the time of hospitalization, hemodynamically significant uncorrected primary cardiac valvular disease, refractory end-stage HF, hemofiltration or dialysis, supine systolic arterial bp < 90 mm Hg, SCr >3.5 mg/dL (309 μmol/L), K+ level greater than 5.5 mEq/L, and hgb <9 g/dL.	Dual primary endpoints were all-cause mortality (superiority and noninferiority) and cardiovascular death or hospitalization for HF (superiority only)	Composite of cardiovascular mortality or cardiovascular hospitalization; incidence of cardiovascular mortality; and incidence of clinical worsening of HF (death, hospitalization for HF, or unscheduled visit for HF). Additional secondary endpoints included changes from baseline in body weight at d 1, serum sodium level at d 7 or discharge in pts with a baseline serum sodium <134 mEq/L, edema score at d 7 or discharge for those with edema at baseline, pt-assessed dyspnea at d 1 for those	During a median follow-up of 9.9 mo, 537 pts (25.9%) in tolvaptan group and 543 (26.3%) in placebo group died HR for mortality: 0.98; 95% CI, 0.87-1.11; p=.68). Kaplan-Meier estimates of mortality at 1 y were 25.0% in the tolvaptan group and 26.0% in the placebo group. Composite cardiovascular death or hospitalization for HF: 871 tolvaptan group (42.0%) and 829 placebo group (40.2%) HR: 1.04; 95% CI: 0.95-1.14; p=.55). Secondary endpoints of CV mortality, CV death or hospitalization, and worsening HF were also not different. Tolvaptan significantly improved secondary endpoints of d 1 pt-assessed dyspnea (p<.001), with 74.3% of the tolvaptan group and 68.0% of the placebo group demonstrating an improvement in dyspnea score, as well as d 1 body weight, and d 7 edema. In pts with hyponatremia, serum sodium levels significantly increased. The KCCQ overall summary score was not improved at outpt wk 1, but body weight and serum sodium effects persisted long after discharge.	N/A	Tolvaptan initiated for acute treatment of pts hospitalized with HF had no effect on long-term mortality or HF-related morbidity.

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							with dyspnea at baseline, and KCCQ overall summary score at outpt wk 1.			
DIG, Ahmed (UAB), 2006 16709595 (155)	Non-potassium-sparing diuretics are commonly used in HF. They activate the neurohormonal system, and are potentially harmful. Yet, the long-term effects of chronic diuretic use in HF are largely unknown. This study retrospectively analysed the DIG data to determine the effects of diuretics on HF outcomes. Effects of diuretics on mortality and hospitalization at 40 mo of median follow-up were assessed using matched Cox	Registry	2,782	The DIG trial enrolled 7,788 ambulatory chronic systolic (LVEF ≤45%; n=6800) and diastolic (LVEF >45%; n=988) HF pts in normal sinus rhythm, of whom 6,076 (78%) were receiving diuretics	Age <21 y; baseline EF unavailable; MI, cardiac surgery or PTCA within 4 wk; unstable or refractory angina <1 mo; II-III AV block without pacemaker; AF or flutter; cor pulmonale; constrictive pericarditis; acute myocarditis; hypertrophic cardiomyopathy; amyloid cardiomyopathy; complex CHD; tx with IV inotropic agents; K+ < 3.2 mmol/L or > 5.5 mmol/L; on heart transplant list; noncardiac cause of HF; Creatinine > 3.0 mg/dL or severe liver disease; unlikely to comply	All-cause mortality	Mortality from worsening HF, and hospitalizations due to all causes and worsening HF	Propensity scores for diuretic use were calculated for each of the 7,788 DIG participants using a non-parsimonious multivariable logistic regression model, and were used to match 1,391 (81%) no-diuretic pts with 1,391 diuretic pts. Mean survival times for diuretic vs. no-diuretic pts: 47 (95% CI: 46–48) and 50 (95% CI: 49–51) mo. All-cause mortality was 21% for no-diuretic pts and 29% for diuretic pts (HR: 1.31; 95% CI: 1.11-1.55; p=0.002). HF hospitalizations occurred in 18% of no-diuretic pts and 23% of diuretic pts (HR: 1.37; 95% CI: 1.13-1.65; p=0.001). Mortality due to HF occurred in 6% of pts in the no-diuretic group and 9% of those in the diuretic group (HR: 1.36; 95% CI 0.99–1.87; p=0.056). Compared with 8% deaths among pts never receiving diuretics during the first 24 mo of follow-up, 19% of those who	Based on non-randomized findings, retrospective. Beta-blockers were not approved for HF during the DIG trial and data on beta-blocker use were not collected	Chronic diuretic use was associated with increased long-term mortality and hospitalizations in a wide spectrum of ambulatory chronic systolic and diastolic HF pts

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	regression models							always received diuretics during the same time died from all causes (multivariable adjusted HR: 1.81; 95% CI 1.38–2.38; p<0.0001).		
DIG, Domanski, 2006 16762792 (156)	Investigate the associations between death, cardiovascular death, death from worsening HF, SCD, and HF hospitalization among those taking a PSD, NPSD, or no diuretic in the DIG trial	Registry	6,797	HF and LVEF ≤45% enrolled in the DIG trial. The DIG randomly assigned 6800 pts with HF and LVEF ≤45% to digoxin or placebo in a double-blinded controlled trial	Age <21 y; baseline EF not available; MI, cardiac surgery or PTCA within 4 wk; unstable or refractory angina <1 mo; II-III AV block without pacemaker; AF or flutter; cor pulmonale; constrictive pericarditis; acute myocarditis; hypertrophic cardiomyopathy; amyloid cardiomyopathy; complex CHD; tx with IV inotropic agents; K+ < 3.2 mmol/L or > 5.5 mmol/L; on heart transplant list; noncardiac cause of HF; Creatinine > 3.0 mg/dL or severe liver disease; unlikely to comply	All-cause death, cardiovascular death, death from progressive HF, SCD, and HF hospitalization	N/A	For death from HF or SCD, the incident rates were not significantly different between the pts taking the PSD only versus no-diuretic group (p=.06, and p=.7, respectively); for the other 4 events (hosp for HF, death from CVD, death from all causes, hosp or death from HF), the incidence rates were all significantly lower in the no-diuretic group than in the PSD-only group (p≤.01). For all 6 events, the incidence rates for the NPSD only group were significantly higher than the PSD-only group (p≤.02). The incidence rates for the NPSD-only group and both-diuretic groups were comparable and not significantly different with the p- values ranging from .07 to .6 (date not shown). After multivariate analysis, the risks of all 6 endpoints were increased in pts taking a NPSD, whether or not they were taking a PSD after adjusting for known covariates. There was no significant difference in the risk of any of these events for pts taking only PSD and those taking no diuretics. Compared with not taking diuretic, risk of death (RR: 1.36, 95% CI: 1.17–1.59, p<.0001), cardiovascular death (RR: 1.38, 95% CI: 1.17–1.63; p=.0001), progressive HF death (RR: 1.41, 95% CI: 1.06–1.89, p= .02), SCD (RR: 1.67, 95% CI 1.23–2.27, p=.001), and HF hospitalization (RR: 1.68, 95% CI: 1.41–	Post-hoc study and doses of diuretics were not available for analysis. Also, did not analyze effects of treatment over time. Beta-blockers were not approved for HF during the DIG trial and data on beta blocker use were not collected	Among pts in the DIG trial, compared with pts not taking any diuretic or taking a PSD, pts taking non-PSD had a higher RR of death.

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								1.99, p< .0001) were increased with NPSD. There was no significant difference in any endpoint for pts taking only PSD compared to no diuretic. PSD only subjects were less likely than NPSD subjects to be hospitalized for HF (RR: 0.71, 95% CI: 0.52–0.96, p=.02).		
Cohort study low vs. high dose (Cedars Sinai/ UCLA), Eshaghian, 2006 16765130 (157)	This study sought to determine the dose-dependent relation between loop diuretic use and HF prognosis	Cohort	1,354	Study population consisted of 1,354 consecutive pts with advanced systolic HF referred to a single university medical center for HF management and/or transplant evaluation from 1985 to 2004	Pts with LVEF >40%, those with HF due to valvular disease, and those aged <18 y were excluded from the analysis	All-cause mortality	The composite endpoint of death or urgent transplant (status IA) was analyzed as a secondary endpoint	Pts with HF in the highest diuretic dose quartile were found to have significantly impaired survival compared with pts in the lowest quartile. Survival estimates at 1 y were 91%, 88%, 80%, and 69% for quartiles 1, 2, 3, and 4, respectively (p <0.0001). Survival estimates at 2 y were 83%, 81%, 68%, and 53%, respectively (p <0.0001). Death from any cause: HR: 3.4, 95% CI: 2.4-4.7 death and urgent transplantation: HR 2.7, 95% CI 2.0-3.5 death from progressive HF: HR: 3.8; 95% CI 2.1-6.8 sudden death: HR: 3.6; 95% CI: 1.9-6.8 Univariate analysis- compared with the lowest quartile, increasing loop diuretic dose quartiles were associated with a progressive increase in mortality (second quartile, HR: 1.2; 95% CI: 0.8-1.7; third quartile, HR: 2.1, 95% CI 1.5-2.9; and fourth quartile, HR: 3.4; 95% CI 2.4-4.7). Diuretic dose quartiles were associated with increased mortality independent of other covariates. After adjustment the highest diuretic quartile remained a significant predictor of increased mortality at 1 y (HR: 4.2; 95% CI: 1.5-11.3) and at 2 y (HR: 4.0; 95% CI 1.9-8.4)	Possible selection bias. Diuretic dose was examined at only a single point in time, without considering chnages in doses over time. Baseline characteristics and other HF treatments different among the diuretic dose quartiles. With adjustment for multiple covariates, larger loop diuretic doses could still be a surrogate for other measured and unmeasured variables that reflect more severe HF. Serum potassium and magnesium level information was unavailable. Propensity matching was not performed. So the relation between	This study suggests that in pts with advanced systolic HF, the use of higher doses of loop diuretics is associated with significantly increased all-cause mortality. Although it may appear obvious that pts with HF requiring higher loop diuretic doses to prevent fluid retention and control symptoms might be sicker than pts receiving lower doses, the powerful and independent association with mortality warrants further consideration.

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									loop diuretic dose and increased mortality is causative.	
Cochrane review, 2005 16034890 (158)	To compare the effects and adverse effects of continuous IV infusion of loop diuretics with those of bolus IV administration among pts with HF class III-IV	Meta-analysis	254	RCTs comparing the efficacy of continuous IV infusion versus bolus IV administration of loop diuretics in HF in a total of 8 RCTs.	N/A	(7 studies) urine output, cc/24 h; Electrolyte disturbances (hypokalemia, hypomagnesemia); adverse effects (tinnitus and hearing loss); (single study) duration of hospital stay and cardiac mortality; (2 studies) all cause mortality	N/A	Urine output: the output (as measured in cc/24 h) was noted to be greater in pts given continuous infusion with a WMD of 271 cc/24 h (95%CI: 93.1-449; p<0.01). Electrolyte disturbances were not significantly different in the two treatment groups : RR 1.47; 95%CI: 0.52-4.15; p=0.5. Less adverse effects (tinnitus and hearing loss) were noted with continuous infusion: RR 0.06; 95%CI: 0.01- 0.44; p=0.005. Duration of hospital stay was significantly shortened by 3.1 d with continuous infusion WMD -3.1; 95%CI -4.06 to -2.20; p<0.0001; while cardiac mortality was significantly different in the two treatment groups, RR: 0.47; 95% CI: 0.33 to 0.69; p<0.0001. All-cause mortality was significantly different in the two treatment groups, RR: 0.52; 95% CI: 0.38- 0.71; p<0.0001.	Available data were insufficient to confidently assess the merits of the 2 methods of giving IV diuretics. The existing data did not allow definitive recommendations for clinical practice	Based on small and relatively heterogeneous studies, this review showed greater diuresis and a better safety profile when loop diuretics were given as continuous infusion.
SOLVD, Domanski, 2003 12932605 (159)	Study sought to determine whether NPSDs in the absence of a PSD may result in progressive HF.	Registry	6,797	Symptomatic and asymptomatic pts with a LVEF fraction <0.36 were randomly assigned to double-blinded treatment with enalapril or placebo.	Only drug class was ascertained; specific medications were not recorded.	Rates of hospitalization for HF, death from cardiovascular disease, death from all causes, and either hospitalization or death due to worsening HF	N/A	The risk of hospitalization from worsening HF in those taking a PSD relative to those taking only a non-PSD was 0.74; 95% CI 0.55-0.99; p= 0.047. The RR for cardiovascular death was 0.74; 95% CI 0.59-0.93; p=0.011), for death from all causes 0.73; 95% CI: 0.59-0.90; p=0.004), and for hospitalization for, or death from, HF 0.75; 95% CI: 0.58-0.97; p=0.030). Compared with pts not taking any diuretic, the risk of hospitalization or death due to worsening HF in pts taking	This study is retrospective and, therefore, not definitive proof that NPSDs cause progressive HF. Because the diuretic dosage was not available, we cannot draw conclusions about a dose-response	This study shows that in pts with moderate or severe LV dysfunction, the use of a PSD is associated with a reduced risk of death or hospitalization due to

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								non-PSDs alone was significantly increased (RR:1.31: 95% CI: 1.09-1.57; p=0.0004); this was not observed in pts taking PSDs with or without a NPSD (RR: 0.99; 95% CI: 0.76- 1.30; p=0.95).	relationship. Also, baseline data were used, and diuretic treatment status may have changed over time	progressive HF, relative to pts taking only a non-PSD.
PRAISE, Neuberg, 2002 12094185 (152)	The prognostic importance of diuretic resistance (as evidenced by a high-dose requirement) was retrospectively evaluated in pts with advanced HF who were enrolled in the PRAISE.	Registry	1,153	LVEF <30% and NYHA functional class IIIb/IV HF despite mandatory background treatment with digoxin, diuretics, and ACE inhibitors.	Pts were excluded if their serum potassium level was <3.5 or >5.5 mmol/L and if their SCr level was >3.0 mg/dL (270 >mol/L), and/or if they met other standard exclusion criteria	Death or cardiac transplantation	N/A	HDD were independently associated with mortality, sudden death, and pump failure death (aHR: 1.37 (p=.004), aHR: 1.39 (p=.042), and aHR: 1.51 (p=.034), respectively. Use of metolazone was an independent predictor of total mortality (aHR: 1.37; p=.016) but not of cause-specific mortality. In quartiles of loop diuretic dose, total mortality increased progressively without a clear risk threshold, more than doubling from the lowest-dose group to the highest-dose group (p=.001). Unadjusted mortality rates were 20.7% (n=152), 30.7% (n=313), 36.8% (n=304), and 44.8% (n=84) for increasing dose of furosemide (40 mg, 40-80 mg, 80-120 mg, and 120 mg daily) or bumetanide (1 mg, 1-2 mg, 2-3 mg, and 3 mg daily), respectively. By proportional hazard regression, high diuretic dose was an independent predictor of total mortality (aHR: 1.37; p=0.004), sudden death (a HR: 1.39, p=0.042), and pump failure death (aHR: 1.51, p=0.034).	Retrospectiveolder study as pts enrolled in PRAISE were not on beta blockers.	Found that high doses of loop diuretic (>80mg of furosemide or >2mg of buetanide daily) were independently associated with mortality in pts with advanced HF. When degree of congestion was considered together with its treatment, the associated risks were additive, suggesting that diuretic resistance should be considered an indicatior of prognosis in chronic HF. However, retrospective analysis does not establish harm, nor rule out a long-term

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										benefit of diuretic therapy.
Ultrafiltration										
UNLOAD substudy (Maryland), Rogers, 2008 18226766 (160)	This study was designed to evaluate the consequences of UF and standard IV diuretic (furosemide) therapy on GFR and renal plasma flow in pts with acute decompensated HF.	RCT	19	Pts hospitalized for acute decompensated HF with an EF <40% and ≥2 signs of hypervolemia based on at least 2 of the following findings: ≥2+ pitting edema of the lower extremities, jugular venous pressure ≥10 cm H_2O, pulmonary edema or pleural effusion on chest radiograph consistent with decompensated congestive HF, ascites, paroxysmal nocturnal dyspnea, or ≥2 pillow orthopnea.	Pts with ACS, SCr >3.0 mg/dL, SBP ≤ 90 mm Hg, hematocrit >45%, inability to obtain venous access, or clinical instability likely to require IV nitroprusside or IV pressors, history of administration of IV diuretics and/or vasoactive drugs during the present hospitalization (except for a single dose of IV diuretics administered in the ED before hospitalization), use of iodinated radiocontrast material, contraindication to the use of anticoagulation, systemic infection, or hemodialysis were excluded from the substudy.	Urine output, GFR (as measured by iothalamate), and renal plasma flow (as measured by para-aminohippurate) were assessed before fluid removal and after 48 h.	N/A	19 pts (59 +/- 16 y, 68% were male) were randomized to receive UF (n= 9) or IV diuretics (n= 10). The change in GFR (-3.4 +/- 7.7 mL/min vs -3.6 +/- 11.5 mL/min; p= .966), renal plasma flow (26.6 +/- 62.7 mL/min vs 16.1 +/- 42.0 mL/min; p= .669), and filtration fraction (-6.9 +/- 13.6 mL/min vs -3.9 +/- 13.6 mL/min; p= .644) after treatment were not significantly different between the UF and furosemide treatment groups. No significant difference in net 48-h fluid removal between the groups (-3211 +/- 2345 mL for UF and -2725 +/- 2330 mL for furosemide, p= .682). UF removed 3666 +/- 2402 mL. Urine output during 48 h was significantly greater in the furosemide group (5786 +/- 2587 mL) compared with the UF group (2286 +/- 915 mL, p< .001).	Small single center study. Pts receiving UF tended to have worse GFR at baseline. Renal hemodynamic outcomes were measured during acute fluid removal (48 h). Unknown as to when changes in GFR or RPF occur. The present study does not assess any chronic effects of UF or diuresis.	During a 48-h period, UF did not cause any significant differences in renal hemodynamics compared with the standard treatment of IV diuretics
UNLOAD, MR Costanzo, 2007 17291932 (161)	To compare the safety and efficacy of venovenous UF and standard IV diruetic therapy for hypervolemic HF pts	RCT	200	Pts hospitalized with primary diagnosis of acute decompensated congestive HF; evidence of fluid overload as indicated by: pitting edema (2+) of lower extremities; jugular venous distension; pulmonary edema or pleural effusion; ascites;	ACS; creatinine >3.0; SBP <90 mmHg; hematocrit >45%; prior administration of IV vasoactive drugs in the ED; clinical instability requiring pressors during hospitalization; recent use of iodinated contrast material; severe concomitant disease expected to prolong hospitalization; sepsis; on or	Total weight loss during first 48 h; change in dyspnea score during first 48 h.	Change in global assessment; change in QoL (living with HF); changes in BNP; changes in 6 min walk test; total fluid loss during first 48 h; changes in BUN and creatinine; changes in renin and aldosterone; rate of hospitalizations and	Primary efficacy endpoints: Weight loss was greater in the UF than in the standard-care group (5.0 ± 3.1 kg vs. 3.1 ± 3.5 kg; p=0.0001) Dyspnea scores were similarly improved in the UF and standard-care group at both 8 and 48 h. Primary safety endpoints: Changes in SCr were similar in the 2 groups throughout the study and % of pts with rise in SCr >0.3 mg/dL were	Population not representative of HF pts (better renal function, and excluded pts with hypotention); industry sponsored;	While weight loss was greater and rehospitalization at 90 d was lower in the UF arm, data not available on long-term effects on renal function or resource utilization. The pts in trial represented

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				paroxysmal nocturnal dyspnea or 2-pillow orthopnea	requires renal dialysis; history of cardiac transplant; heparin allergy.		unscheduled clinic and ED visits in the wk after inpt treatment	similar in both groups at 24 h, 48 h and at discharge Serum potassium <3.5 mEq/l occurred in 1% of the UF group and 12% of diuretics group (p=0.018)	small trial; usual care group not very aggressively treated	hemodynamically stable/congested HF pts that respond very well to diuretics and have better outcomes vs. HF population in general.
Case-series (Mayo clinic), Liang, 2006 17174232 (162)	Present data on UF from a series of pts treated at the Mayo clinic who were generally sicker and had failed at least 1 IV treatment	Case-series	11	HF pts admitted to Mayo clinic who have failed at least 1 IV diuresis treatment	Contraindication to UF	Change in creatinine; fluid loss; complications from UF	N/A	5 pts had significant rise in creatinine, 5 required dialysis, overall 6-mo mortality 55%, bleeding and complications related to positional flow were common.	Small study; single institution; pts with much worse prognosis vs general HF population	In high risk populations, (mean GFR of 38 mL/min) UF may not be the most appropriate choice.
RAPID-CHF, Bart, 2005 16325039 (163)	Pilot study which compared a single 8-h UF intervention to usual care in pts admitted with decompensated HF	RCT	40	Hospitalized with primary diagnosis of HF; at least 2+ edema of the lower extremities and at least either JVP >10, pulmonary edema or pleural effusion on CXR, pulmonary rales, pulmonary wedge or LVEDP >20, ascites, or pre-sacral edema	Severe stenotic valvular disease; ACS; SBP <90; hematocrit >40% 5. poor peripheral venous access; hemodynamic instability; use of iodinated radiocontrast within 72 h of consent or anticipated use; severe concomitant disease	24-h weight loss	Total volume removal at 24 and 48 h; global HF and dyspnea assessments; serum electrolytes; and length of hospital stay	No difference in 24-h weight loss (p=0.240), significantly more fluid removal with UF (4,650 mL in UF group vs. 2,838 mL in usual care group, (p=0.001) and improved dyspnea scores (p=0.039) and no change in creatinine. Trend toward greater weight loss at 24 h in the UF group	Small study, pilot	UF group had more fluid removed, with no significant change in creatinine, however no difference in 24 h weight loss.
EUPHORIA, Costanzo, 2005 16325040 (164)	Compared UF to historical controls in order to determine if use of UF before any IV diuretics in pts with decompensated HF and modest renal dysfunction reestablishes euvolemia and permits hospital discharge in ≤3 d, without hypotension, a ≥25% increase in SCr. or other AEs.	Observational study	20	Volume overload; modest degree of renal dysfunction or diuretic resistance (chronic daily PO furosemide ≥80 mg, or torsemide ≥ 40mg, or bumetamide ≥ 2mg and SCr ≥1.5 mg/dl), relatively high diuretic requirement at baseline; <12 h since hospitalization, given no vasoactive drugs and <1 dose IV diuretic	Hematocrit >40%;. end-stage renal disease requiring dialysis; Hypercoagulability; SBP <85 mm Hg; Requirement for IV inotropes; Participation in another research study or previously in this trial	Weight loss; hospital length of stay	Increase in creatinine >25%, hypotension; BNP levels	An average of 8,367 ± 4,232 mL were removed with 2.6 ± 1.2, 8 h UF courses. Of the 19 pts 12 (68%) were discharged in ≤3 d	Small observational study; Single-center series	Concluded that UF decreases length of stay and readmissions. compared the treatment period with the pre-treatment period, rather than with a randomized control cohort.

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Agostoni, 1994 8154506 (165)	Investigated the mechanisms involved in the regulation of salt and water metabolism in pt with HF. Extracorporeal UF was utilized as a nonpharmacologic method for withdrawal of body fluid.	RCT	16	Treated with a combination of digoxin, oral furosemide, and ACE inhibitor (captopril or enalapril) for chronic; sinus rhythm; NYHA II-III	Pts with acute MI (<1 y), angina pectoris, primary valvular disease, intermittent claudication, fibrotic or primary vascular lung diseases, sinus or atrioventricular node dysfunction, effort-induced severe ventricular arrhythmias or an artificial pacemaker	Scores of lung water; exercise test parameters; plasma renin, aldosterone and norepinephrine		3 mo after UF or IV diuretic, the hemodynamic variables examined at rest had returned to the control values in the diuretic group, but not the UF group. In the UF group, right atrial pressure, pulmonary artery pressure and wedge pressure were still as reduced as they had been 24 h after UF. ($p<0.01$, only figures displayed).	Small older study	After UF, improved functional capacity continued for 3 mo after the procedure
Pepi, 1993 8038023 (166)	To investigate the pathophysiological (cardiac function and physical performance) significance of clinically silent interstitial lung water accumulation in pts with moderate HF; to use isolated UF as a means of extravascular fluid reabsorption	RCT	24	NYHA functional class II-III HF and clinically silent by radiologically evident increased lung water; sinus rhythm and EF <35%	Severe tricuspid or mitral regurgitation; pleural, pericardial or abdominal effusion	LVSF (from ultrasonography); Doppler evaluation of mitral, tricuspid, and aortic flow and echo-Doppler determination of cardiac output; radiological score of extravascular lung water; R/LV filling pressures; oxygen consumption at peak exercise and exercise tolerance time in cardiopulmonary tests.		UF decreased radiological score of extravascular lung water (from 15(1)-9(1)) and of right (from 7.1 (2.3)-2.3 (1.7) mm Hg) and left (from 17.6 (8.8)-9.5 (6.4) mm Hg) ventricular filling pressures; an increase in oxygen consumption at peak exercise (from 15.8 (3.3) to 17.6 (2) mL/min/kg) and of tolerance time (from 444 (138) to 508 (134) s); decrease in atrial and ventricular dimensions; no changes in the systolic function of the left ventricle; a reduction of the early to late filling ratio in both ventricles (mitral valve from 2 (2) to 1.1 (1.1)); (tricuspid valve from 1.3 (1.3) to 0.69 (0.18)) and an increase in the deceleration time of mitral and tricuspid flow, reflecting a redistribution of filling to late diastole. Variations in the ventricular filling pattern, lung water content, and functional performance persisted for 3mo in all cases. None of these changes was detected in the control group.	Small older study; single institution	Pathophysiological study involving UF and hemodynamic outcomes.
Agostoni, 1993 8426008 (167)	The aim of this study was to evaluate whether UF is beneficial in pts with moderate congestive HF.	RCT	36	NYHA functional classes II and III; stable clinical condition; receiving drug treatment (stable over last 6 mo) optimized to prevent development of edema and maintain a stable body weight (+/- 1	Pts with acute MI (<1 y), angina pectoris, primary valvular disease, intermittent claudication, fibrotic or primary vascular lung diseases, sinus or atrioventricular node dysfunction, effort-induced	Functional performance was assessed with cardiopulmonary exercise tests	Plasma norepinephrine levels	Significant reductions in UF group right atrial pressure (from 8 ± 1 - 3.4 ± 0.7 mm Hg, pulmonary wedge pressure (from 18 ± 2.5 - 10 ± 1.9 mm Hg) and cardiac index (from 2.8 ± 0.2 -2.3± 0.2 L/min). During the follow-up period, lung function improved, extravascular lung water (X-ray score) decreased and	Small older study	Pathophysiological study involving UF and hemodynamic outcomes.

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				kg in last 6 mo); therapeutic digoxin level (if on digoxin)	severe ventricular arrhythmias or an artificial pacemaker			peak oxygen consumption (mL/min per kg) increased from 15.5 ± 1 (d -1) to 17.6 ± 0.9 (d 4), to 17.8 ±0.9 (d 30), to 18.9 ±1 (d 90) and to 19.1 ±1 (d 180). Oxygen consumption at anaerobic threshold (mL/min per kg) also increased from 11.6 ±0.8 (d -1) to 13 ±0.7 (d 4), to 13.7 ± 0.5 (d 30), to 15.5 ± 0.8 (d 90) and to 15.2 ± 0.8 (d 180). These changes were associated with increased ventilation, tidal volume and dead space/tidal volume ratio at peak exercise. Improvement in exercise performance was associated with a decrease in norepinephrine at rest, a downward shift of norepinephrine kinetics at submaximal exercise and an increase in norepinephrine during orthostatic tilt. None of these changes were recorded in group B.		

ACS indicates acute coronary syndrome; ADHERE, Acute Decompensated Heart Failure National Registry; AE, adverse event; AUC, area under the curve; BNP, B-Type natriuretic peptide; BUN, blood urea nitrogen; CHD, chronic heart disease; CHF, congestive heart failure; CrCl, creatinine clearance; CV, cardiovascular; DAD-HF, Dopamine in Acute Decompensated Heart Failure; DBP, diastolic blood pressure; DIG, Digitalis Investigation Group; DM, diabetes mellitus; ED, emergency department; eGFR, glomerular filtration rate; EUPHORIA, Early Ultrafiltration Therapy in Patients with Decompensated Heart Failure and Observed Resistance to Intervention with Diuretic Agents; EVEREST, Efficacy of Vasopressin Antagonism in hEart failuRE: Outcome Study With Tolvaptan; HDD, high dose diuretics; HF, heart failure; Hgb, hemoglobin; HTN, hypertension; ICU, intensive care unit; IV, intravenous; KCCQ, Kansas City Cardiomyopathy Questionnaire; LDD, low dose diuretics; LDFD, low-dose furosemide; LOS, length of stay; LVEF, left ventricular ejection fraction; MCS, mechanical cardiac support; N/A, not applicable; NPSD, nonpotassium-sparing diuretics; NT-pBNP, N-terminal pro-B-Type natriuretic peptide; PO, per oral; PRAISE, Prospective Randomized Amlodipine Survival Evaluation; PROTECT, Placebo-controlled Randomized study of the selective A(1) adenosine receptor antagonist rolofylline for patients hospitalized with acute heart failure and volume Overload to assess Treatment Effect on Congestion and renal function; PTCA, percutaneous transluminal coronary angioplasty; PSD, potassium-sparing diuretics; pts, patients; RAPID-HF, Relief for Acutely Fluid-Overloaded Patients With Decompensated Congestive Heart Failure; RCT, randomized control trial; SBP, systolic blood pressure; SCD, sudden cardiac death; SCr, serum creatinine; SOLVD, Studies of left ventricular dysfunction; Tx, treatment; UF, ultrafiltration; UNLOAD, Ultrafiltration Versus Intravenous Diuretics for Patients Hospitalized for Acute Decompensated Heart Failure; VAS, visual analog scale, WMD, weighted mean difference; and WRF, worsening renal function.

Data Supplement 18. ACE Inhibitors (Section 7.3.2.2)

Study Name, Author, Year	Aim of Study	Study Type	Background Therapy	Study Size	Etiology	Patient Population		Endpoints		Mortality	Trial Duration (Years)	Absolute Benefit	P Values & 95% CI:
			Pre-trial standard treatment.	*N (Total) n (Experimental) n (Control)*	*Ischemic/ Non-Ischemic*	*Inclusion Criteria*	*Exclusion Criteria*	*Primary Endpoint*	*Secondary Endpoint*	*1st Year Mortality*			

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CONSENSUS 1987 2883575 (168)	To Evaluate influence of enalapril on prognosis of NYHA class IV HF	RCT	Diuretics (spironolactone 53%, mean dose 80mg), digitalis (93%), other vasodilators, except ACEI (ie nitrates 46%)	253; 127;126	CAD 73%	Severe HF/symptoms at rest/NYHA class IV; Increased heart size >600 ml; BP: 120/75; HR: 80; AF 50%	APE; hemodynamically import aortic/MV stenosis; MI w/in prior 2 mo Unstable angina; planned cardiac surgery; right HF b/c of pulm disease; Cr>300 umol/L	Mortality	Change in NYHA-FC, LV size, Cr level	52% placebo group and 36% enalapril group (6 mo mortality: 26% in enalpril group and 44% in placebo group)	0.51 y	N/A	Crude mortality at end of 6 mo (primary endpoint), 26% in enalapril group and 44% in placebo group—40% reduction (p =0.002). Mortality was reduced by 31% at 1 y (p=0.001)
10 y FU of CONSENSUS 1999 10099910 (169)	Report on the survival at the 10-y follow up of the pts randomized in CONSENSUS. (1st study to show prognostic improvement by an ACEI. Pts in NYHA class IV HF treated with enalapril or placebo. After study completion all pts were offered open-label enalapril therapy).	10-y open-label follow-up study (via completion of a questionnaire) on the survival status of pts in CONSENSUS -a RCT.	All pts were offered open-label enalapril therapy	315; 77; 58		253 randomized pts included in analysis of time from randomization to death; Survivors (135) of the double-blind period included in analysis of the time from end of double-blind period to death; Severe, NYHA IV		Mortality			10 y		5 pts, all in the enalapril group, were long-term survivors (p=0.004). Averaged over the trial (double-blind plus open-label extension) risk reduction was 30% (p=0.008), 95% CI: 11% - 46%. At end of double-blind study period, mortality considerably higher among pts not receiving open ACEI therapy

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SOLVD 1991 2057034 (170)	Study the effect of enalapril on mortality and hospitalization in pts with chronic HF and EF ≤35%	RCT	Diuretics + Digoxin	2569; 1285; 1284	Ischemic heart disease 72%	LVEF <35%; Mild to severe (11% class I/<2% class IV); LVEF 25%; BP: 125/77; HR: 80; AF: 8-12%	Age >80 y; Unstable angina; MI w/in past mo; Cr>2.0 mg/dL	Mortality	Hospitalizations; Incidence of MI; Mortality by specific causes; Combined mortality and morbidity from both SOLVD+/SOLVD-	15.70%	3.45 y	Treating 1000 SOLVD+ pts with enalapril for ~3 y would save ~50 premature deaths and 350 hospitalizations.	Reduced mortality by 16%; (95% CI, 5-26%; p=0.0036)
SOLVD 1992 1463530 (90)	Study effect of ACEIs on total mortality and mortality from CV causes, the development of HF, and hospitalization for HF in pts with EF ≤35%	RCT	No drug treatment for HF	4228; 2111; 2117	History of ischemic heart disease 85%	EF <35%; Asymptomatic; NYHA class I (67%) + II; EF: 28%; BP: 126/78; HR: 75; AF: 4%	As per SOLVD+	Mortality; Combined mortality and the incidence of HF and rate of hospitalization for HF	Incidence of HF and rate of hospitalization for HF		3.12 y		Reduced mortality: p=0.30; 95% CI: -8-21%
SOLVD F/U 2003 12788569 (91)	12-y FU of SOLVD to establish if the mortality reduction with enalapril among pts with HF was sustained, and whether a subsequent reduction in mortality would emerge among those with asymptomatic ventricular dysfunction.	12 y f/u of RCTs [SOLVD+ and SOLVD-]	N/A	6784; 3391; 3393	N/A	Participation in SOLVD+ and SOLVD- Asymptomatic to severe; NYHA I-IV	N/A	Mortality	N/A	N/A	N/A	Enalapril extended median survival by 9.4 mo in the combined trials (95% CI: 2.8–16.5, p=0.004).	In the prevention trial, 50.9% of the enalapril group had died c/w 56.4% of the placebo group (p=0.001). In the treatment trial, 79.8% of the enalapril group had died c/w 80.8% of the placebo group (p=0.01). Combined prevention and treatment trials: HR for death was 0.90 for the enalapril group c/w placebo group (95% CI: 0.84–0.95, p=0.0003).

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ATLAS 1999 10587334 (171)	To compare the efficacy and safety of low and high doses of ACEI on the risk of death and hospitalization in chronic HF. than the large doses that have been shown to reduce morbidity and mortality in pts with HF. AIM: Investigate if low doses and high doses of ACEIs have similar benefits.	RCT	N/A	3164; 1596 to the low-dose strategy and 1568 to the high-dose strategy.	CAD 65%	LVEF <=30%; NYHA class II, III, or IV, despite treatment with diuretics for ≥2 mo (Treatment for HF in ED or hospital within 6 mo required for pts in class II); Prior use of digitalis, ACEIs, or vasodilators allowed but not mandated; NYHA II-IV (mainly class II); LVEF 23%; SBP 126 mmHg; HR 80; NYHA class: III (few II and IV)	Acute coronary ischemic event or revascularization procedure within 2 mo; History of sustained or symptomatic ventricular tachycardia; Intolerant of ACEIs; SCr >2.5 mg/dL	Mortality from all causes	Combined risk of all-cause mortality and hospitalization for any reason; CV mortality, CV hospitalizations; All-cause mortality combined with CV hospitalizations; CV mortality combined with CV hospitalizations; Combined risk of fatal and nonfatal MI plus hospitalization for unstable angina		5 y		High-dose group had 8% lower risk of all-cause mortality (p=0.128) and 10% lower risk of CV mortality (p=0.073) than low-dose group. Death or hospitalization for any reason, high-dose group had 12% lower risk than low-dose group, p=0.002. Total number of hospitalizations: high-dose group 13% fewer hospitalizations for any reason (p=0.021), 16% fewer hospitalizations for CV reason (p=0.05), and 24% fewer hospitalizations for HF (p=0.002).
Post-MI ACEI Use													

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SAVE, 1992 1386652 (89)	To test the hypothesis that the long-term administration of captopril to survivors of acute MI who had baseline LV dysfunction but did not have overt HF requiring vasodilator therapy would reduce mortality, lessen deterioration in cardiac performance, and improve clinical outcome.	RCT	Beta-blockers 36%; Digitalis 26%; Nitrates 51%	2231; 1115; 1116	Ischemic 100%	Alive 3 d after MI; LVEF <40%; >21 y of age, but <80; Killip class I — 60% (60% of the ps did not have even transient pulmonary congestion at baseline/the time of their acute MI; EF 31%; BP 113/70; HR 78;	Failure to undergo randomization within 16 d after the MI; Relative contraindication to the use of an ACEIs or the need for such an agent; SCr > 2.5 mg/dl	Mortality from all causes	Mortality from CV causes; Mortality combined with a decrease in the EF of at least 9 units in surviving pts; CV morbidity (development of severe CHF or the recurrence of MI); Combination of CV mortality and morbidity; 2 endpoints of severe HF (treatment failure): 1st, development of overt HF necessitating treatment with ACEI and 2nd, hospitalization to treat CHD.		3.5 y		Mortality from all causes was significantly reduced in the captopril group (228 deaths, or 20%) as c/w the placebo group (275 deaths, or 25%); the RR:19% (95% CI, 3-32%; p= 0.019). RR:21% (95% CI, 5 - 35%; p = 0.014) for death from CV causes, 37% (95% CI, 20-50%; p<0.001) for the development of severe HF, 22% (95% CI, 4-37%; p= 0.019) for CHF requiring hospitalization, and 25% (95% CI, 5-40%; p= 0.015) for recurrent MI.

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AIRE 1993 8104270 (172)	Investigated the effect of therapy with ACEI ramipril, on survival in pts who had shown clinical evidence of HF at any time after an acute MI. Also, to compare the incidences of progression to severe or resistant HF, nonfatal re-infarction and stroke between the 2 groups.	RCT		2006; 1014; 992		Aged ≥18 y, with a definite acute MI 3-10 d before randomization; Clinical evidence of HF at any time since acute MI	Use of an ACEI considered to be mandatory	Mortality from all causes			1.3 y		Mortality from all causes was significantly lower for pts on ramipril compared to pts on placebo. RR: 27%; 95% CI: 11-40%; p = 0.002. Prespecified secondary outcomes: risk reduction of 19% for the 1st validated outcome—namely, death, severe/resistant HF, MI, or stroke (95% CI: 5% - 31%; p=0.008).
TRACE 1995 7477219 (173)	To determine whether pts who LV dysfunction soon after MI benefit from long-term oral ACE inhibition.	RCT	Beta blocker 16%; Calcium antagonist 28%; Diuretic 66%; Nitrates 53%; Digoxin 28%.	1749; 876; 873	Ischemic 100%	Consecutive pts >18 y hospitalized with MI; Criteria for MI: chest pain or electrocardiographic changes, accompanied by >2X increase in one or more cardiac enzymes; LV dysfunction (EF <35%); NYHA class 1 - 41%; BP 121/76; HR 81	Contraindication to ACEI or a definite need for them; Severe, uncontrolled DM; Hyponatremia (<125 mmol/L); Elevated SCr level (2.3 mg/dL)	Death from any cause	Death from a CV cause, sudden death; Progression to severe HF (hospital admission for HF, death due to progressive HF, or HF necessitating open-label ACEI); Recurrent infarction (fatal or nonfatal); Change in the wall-motion index (EF)	The mortality from all causes at 1 y was 24%.		24 lives were saved after one mo of treating 1000 pts	During the study period, 304 pts in the trandolapril group died (34.7%), as did 369 in the placebo group (42.3%). RR: 0.78 (95% CI, 0.67 - 0.91; p=0.001). In every subgroup, treatment with trandolapril was associated with a reduction in risk.

ACEI indicates angiotensin-converting-enzyme inhibitor; AF, atrial fibrillation; AIRE, Acute Infarction Ramipril Efficacy; APE, acute pulmonary embolism; ATLAS, Assessment of Treatment with Lisinopril and Survival; BP, blood pressure; CAD, coronary artery disease; CHD, chronic heart disease; CHF, congestive heart failure; CONSENSUS Cooperative North Scandinavian Enalapril Survival Study; Cr, creatinine; CV, cardiovascular; C/W, compared with; DM, diabetes mellitus; ED, emergency department; FU, follow-up; HF, heart

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failure; HR, heart rate; LV, left ventricular; MI, myocardial infarction; MV, mitral valve; N/A, not applicable; NYHA, New York Heart Association; pts, patients; SAVE, survival and ventricular enlargement trial; SBP, systolic blood pressure; SOLVD, Studies Of Left Ventricular Dysfunction; RCT, randomized control trial; SCr, serum creatinine; and TRACE, Trandolapril Cardiac Evaluation.

Data Supplement 19. ARBs (Section 7.3.2.3)

Study Name, Author, Year	Aim of Study	Study Type	Background Therapy	Study Size	Etiology	Patient Population		Severity	Endpoints		Mortality	Trial Duration (Y)	Statistical Results
			Pre-trial standard treatment.	*N (Total) n (Experimental) n (Control)*	*Ischemic/ Non-Ischemic*	*Inclusion Criteria*	*Exclusion Criteria*		*Primary Endpoint*	*Secondary Endpoint*	*1st Y Mortality*		
CHARM Alternative; Granger et al; (2003) 13678870 (174)	Discover whether ARB could improve outcome in pts not taking an ACEI (intolerant)	RCT	Diuretics, Beta-blockers (55%), spironolactone 24%, Digoxin 45-46%	2028; 1013; 1015	Ischemic 67-70%	Symptomatic HF, EF <40%, no ACEI (b/c of intolerance)		NYHA II-IV; mild to severe (<4% class IV); EF: 30%; BP: 130/70; HR: 74-75; AF: 25-26%	Composite of CV death or hospital admission for CHF	CV death, hospital admission for CHF or non-fatal MI; CV death, CHF admission, non-fatal MI, non-fatal stroke; CV death, CHF admission, non-fatal MI, non-fatal stroke, coronary revascularization; Death (any cause); New DM		2.8 y	Absolute reduction of 7 major events per 100 pts threated - NNT 14 pts to prevent 1 CV death or hospitalization. HR: 0.77 (95% CI: 0.67-0.89); p=0.0004
CHARM-ADDED; McMurray et al; (2003) 13678869 (175)	To investigate if ARB + ACEI in pts with chronic HF improve clincal outcomes	RCT	Beta blocker-55%; spironolactone 17%; Digoxin 58-59%	2548; 1276; 1272	Ischemic 62-63%	Symptomatic HF; EF <40%; Treatment with ACEI; Age >18 y		NYHA class II-IV; mild to severe (<3% class IV) ; EF 28%; BP 125/75; HR 74; AF 27%	Composite of CV death or hospital admission for CHF	CV death, hospital admission for CHF or non-fatal MI; CV death, CHF admission, nonfatal MI, non-fatal stroke; CV death, CHF admission, non-fatal MI, non-fatal stroke, coronary revascularization; Death (any cause); New DM		3.4 y	Absolute reduction of 4.4 pts with events per 100 pts treated- NNT of 23 to prevent 1 first event of CV death or CHF hospitalization. RR: 0.85 (95% CI: 0.75-0.96); p=0.011

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VALIANT; Pfeffer et al; (2003) 14610160 (176)	Compare the effect of an ARB, ACEI and the combination of the 2on mortality	Randomized double blind multicenter trial	Beta-blockers; ASA	14,703 Valsartan:4909 Captopril-: 4909 VAL + CAP: 4885	Ischemic 100% (MI inclusion criteria)	Age >18 y; Acute MI complicated by HF; LV systolic dysfunct (EF <35%), (<40% on radionuclide ventriculography); SBP > 100 mmHg; Cr < 2.5 mg/dL	Prior intolerance or contra-indication to ACEI/ ARB	NYHA I-IV; asymptomatic-severe, EF 35%; BP: 123/72; HR: 76	Death from any cause		12.5% VAL 12.3% VAL--CAP 13.2% CAP	2.1 y	VAL and CAP: 1.0 (97.5% CI-- 0.90-1.11); p= 0.98 ; VAL+CAP and CAP: 0.98 (97.5% CI-- 0.89-1.09); p= 0.73
Val-HeFT; Cohn et al; (2001) 11759645 (177)	Evaluate long term effects of adding ARB to standard therapy for HF	RCT	Diuretics; Digoxin 67%; Beta blocker 35%; ACEI 93%	5010; 2511; 2499	Ischemic 57%	Age>18 y; NYHA II, II, IV; At least 2 wk of background meds including ACEIs; EF <40% and LVID >2.9 cm/BSA		NYHA II-III, IV (only ~2% class IV); Mild to severe; EF 27%; BP 123/76; AF 12%	Mortality; Combined end point of mortality and morbidity	Change in EF; • NYHA class, QoL scores; Signs and symptoms of HF		1.92 y	Mortality similar for the 2 treatment groups. For the combined endpoint: RR: 0.87; 97.5% CI, 0.77-0.97; p=0.009
HEAAL study; Lancet 2009; 374: 1840-48. 19922995 (178)	Compared the effects of high-dose vs low-dose losartan on clinical outcomes in pts with HF.	RCT	Diuretic drugs (77%), beta blockers (72%), and ARBs (38%).	3846 losartan 150 mg (n=1927) or 50 mg daily (n=1919).	IHD 64%	>18 y; NYHA class II–IV; LVEF <40%, with stable CV medical therapy for at least 2 wk; Intolerance to ACEI; Investigators encouraged to start beta blocker and titrate to a maximum, whenever possible	Pregnancy or lactation; known intolerance to ARBs; Systolic arterial blood pressure <90 mm Hg; Significant stenotic valvular heart disease; Active myocarditis; active pericarditis; Planned	NYHA II-IV (70% II); EF: 33%; BP: 124/77; HR: 71; AF; 28%	Death or admission for HF	Composite endpoint of death or CV admission. Additional prespecified outcomes included: death, death or all-cause admission, CV death, all-cause admission, CV admission, admission for HF, and changes in the severity of heart disease		4.7 y median f/u	Treating pts with 150 mg dose instead of 50 mg dose would result in 1 additional pt w/out the primary event at 4 y for every 31 pts treated. Composite: 828 (43%) pts in 150 mg group vs. 889 (46%) in 50 mg group died or admitted for HF (HR: 0.90; 95% CI: 0.82-0.99; p=0.027) • Components: 635 pts in 150 mg group vs. 665 in 50 mg group died (HR: 0.94, 95% CI: 0.84-1.04; p=0.24), and 450 vs. 503 pts admitted for HF (0.87, 0.76–0.98; p=0.025)

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							heart transplantation w/in 6 mo; coronary angioplasty, CABG, acute MI, UA pectoris, cerebrovascular accident, or TIA within the previous 12 wk; Suspected significant renal artery stenosis						
CHARM-Overall 13678868 (179)	Aimed to find out whether the use of an ARB could reduce mortality and morbidity.	RCT-parallel, randomized, double-blind,	Diuretics 83% Beta blockers 55% ACEI 43% Spironolactone 17% Digoxin 43%	7601 pts (7599 with data) 3803 3796		>18 y; NYHA class II–IV for at least 4 wk; 3 distinct populations: pts with LVEF <40% who were not receiving ACEIs (previous intolerance) or who were currently receiving ACE, and pts with LVEF >40%	SCr > 265 µmol/L, serum potassium >5.5 mmol/L Bilateral renal artery stenosis; symptomatic hypotension Women of childbearing potential not using adequate contraception; Critical aortic or mitral stenosis; MI, stroke, or open-heart surgery in	NYHA II-IV NYHA II-IV Only 3% class IV	The primary outcome of the overall program: all-cause mortality; For all the component trials: CV death or hospital admission for CHF.		The annual CV death rate among the placebo group who had reduced LVEF was around 9% and was only 4% in the placebo group of CHARM-Preserved.	3.1 y	886 (23%) pts in candesartan and 945 (25%) in placebo group died (unadjusted HR: 0.91; 95% CI: 0.83–1.00; p=0.055; covariate aHR: 0.90 95% CU: 0.82–0.99; p=0.032) • Fewer CV deaths (691 [18%] vs 769 [20%], unadjusted HR: 0.88; 95% CI: 0.79–0.97; p=0.012; covariate aHR: 0.87; 95% CI: 0.78–0.96; p=0.006) • Hospital admissions for CHF (757 [20%] vs 918 [24%], p<0.0001)

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							the previous 4 wk; Use of an ARB in the previous 2 wk							

ACEI indicates angiotensin-converting-enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blockers; ASA, aspirin; BP, blood pressure; BSA, body surface area; CABG, coronary artery bypass graft; CHARM, Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity; CHD, chronic heart disease; CHF, congestive heart failure; Cr, creatinine; CV, cardiovascular; DM, diabetes mellitus; EF, ejection fraction; FU, follow-up; HEAAL study, effects of high-dose versus low-dose losartan on clinical outcomes in patients with heart failure; HF, heart failure; HR, heart rate; IHD, ischemic heart disease; LV, left ventricular; LVD, left ventricular dilatation; MI, myocardial infarction; MV, mitral valve; N/A, not applicable; NNT, number needed to treat; NYHA, New York Heart Association; QoL, quality of life; pts, patients; SBP, systolic blood pressure; RCT, randomized control trial; SCr, serum creatinine; TIA, transient ischemic attack; UA, unstable angina; Val-HeFT, Valsartan Heart Failure Trial; and VALIANT, Valsartan in Acute Myocardial Infarction.

Data Supplement 20. Beta Blockers (Section 7.3.2.4)

Study Name, Author, Year	Aim of Study	Study Type	Background Therapy	Study Size	Etiology	Patient Population		Severity	Endpoints		Mortality		Trial Duration	Statistical Results
				N (Total) n (Experimental) n (Control)		*Inclusion Criteria*	*Exclusion Criteria*		*Primary Endpoint*	*Secondary Endpoint*	*Annualized Mortality*	*1st Y Mortality*		
CIBIS II CIBIS II investigators and committee members (1999) 10023943 (180)	Investigate the efficacy of bisoprolol in decreasing all-cause mortality in chronic HF	RCT-multicenter double-blind randiomised placebo controlled trial (Europe)	Diuretics + ACEI; [amiodarone allowed--14-l6%]	2647; 1327; 1320	Documented Ischemic 50%	NYHA class lll or lV EF: <35% 18-80 y old	Uncontrolled HTN; MI/UA w/in previous 3 mo; PTCA/CABG w/in previous 6 mo; AV-block >1st degree w/o PPM; Heart rate < 60bpm; resting SBP <100mmHg; renal failure; Reversible obstruct lung disease; Use of beta blocker	Moderate to severe. Mean BP: 130/80; Mean HR: 80; Mean EF: 28%; Mean LVEDD: 6.7 cm; AF: 20%	All-cause mortality	All-cause hospital admissions All CV deaths Combined endpoints Permanent treatment withdrawal	13.2% Placebo group 8.8% Treatm't group	N/A	1.3 y	HR: 0.66 (95% CI: 0.54-0.81); p<0.0001
MERIT-HF; MERIT study Group; (1999) 10376614 (181)	Investigate whether Metoprolol CR/XL lowered mortality in pts with decreased EF and	RCT--multicenter double-blind randiomised placebo controlle	Diuretics + ACEI [Amiodarone NOT allowed]	3991; 1991; 2001	Ischemic 65%	NYHA ll-lV; 40-80 y old; LVEF <40% (36-40 if 6-min walk <450m); HR >68 bpm	MI/UA w/in 28 d; Contra-indication or current use of beta blocker; PTCA/CABG w/in 4 mo Planned transplant or ICD; Heart block > 1st degree w/o PPM;	Mild to severe. Mean BP: 130/78; Mean HR: 78; Mean EF 28%; AF 16-17%	All-cause mortality All-cause mortality in combination with all-cause admission to hospital	N/A	11.0% Placebo group 7.2% Treatm't group	N/A	1 y	Treatment of 27 pt for 1 y can prevent 1 death. 0.66 (95% CI: 0.53-0.81); p=0.00009

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	symptoms of HF	d trial (Europe + USA)					SBP<100mmHg							
COPERNICUS; Packer et al; (2002) 12390947 (182)	Investigate whether Carvadiolo is beneficial in severe HF	RCT--double blind	Diuretics (PO or IV) + ACEI (or ARB); [Amiodarone allowed 17-18%]	2289; 1156; 1133	Ischemic 67%	Euvolumic NYHA class IV; LVEF <25%; No positive inotropes or vasodilators w/in 4 d	Pt requiring hospitalized intensive care; Use of positive inotropes or IV; vasodilators w/in 4-d; Coronary revascularization/MI/CVA/sign VT or VF w/in 2 mo; SBP < 85 mmHg, Heart rate <68, Cr >2.8 mg/dL	Severe Mean BP: 123/76; Mean HR: 83; Mean EF 20%;	All-cause mortality	Combined risk of death or hospitalization-any reason; Combined risk of death or hospitalization--CV reason; Combined risk of death or hospitalization--HF reason; Pt global assessment	19.7% placebo [24.0% in pts with recent or recurrent cardiac decompensations]	18.5% in placebo group 11.4% in Carvedilol group	10.4 mo	Treating 1000 pt for 1 y led to savings of 70 premature deaths p=0.0014
SENIORS; Flather et al; (2005) 15642700 (183)	Assess effects of the beta blocker Nebivolol in pts ≥70 y regardless of EF.	RCT	Diuretics + ACEI (+aldosterone antagonist in 29%)	2128; 1067; 1061	Prior h/o CAD in 69%	Age >70 Chronic HF with one of the following: hospitalization with CHF w/in a year or EF <35% w/in the past 6 months	New HF therapy w/in 6 wk or change in drug therapy w/in 2 wk Contra-indication to beta blockers, current use of beta blockers Significant renal dysfunction CVA w/in 3 mo.	Mild to severe Mean BP: 139/81; Mean HR: 79; Mean EF 36% (1/3 with EF >35%);	Composite of all-cause mortality or CV hospital admission	All-cause mortality Composite of all-cause mortality or all-cause hospital admissions All cause hospital admissions CV hospital admissions CV mortality Composite of CV mortality or CV hospital admissions NYHA class assessment; 6 MWT	N/A	N/A	1.75 y	Absolute risk reduction 4.2%; 24 pts would need to be treated for 21 mo to avoid one event RR: 0.86; 95% CI: 0.74-0.99; p=0.039

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A Trial of the Beta-Blocker Bucindolol in Pt with Advanced Chronic HF The Beta-Blocker Evaluation of Survival Trial Investigators 11386264 (184)	Designed to determine whether bucindolol hydrochloride, a nonselective beta-adrenergic blocker and mild vasodilator, would reduce the rate of death from any cause among pt with advanced HF and to assess its effect in various subgroups defined by ethnic background and demographic criteria — specifically women and members of minority groups.	RCT	ACEIs (if tolerated) [91% ACE; 7% ARB], for at least 1 mo. Before the publication of the results of the DIG trial, 12 digoxin therapies were required, but thereafter its use became discretionary [DIG 94%].	2708; 1354; 1354	Ischemic 59%	NYHA class III or IV HF LVEF <35% >18 y	Reversible cause of HF present Candidates for heart transplantation Cardiac revascularization procedure within the previous 60 d UA Heart rate <50 beats per minute, SBP <80mmHg Decompensated HF.	NYHA III or IV (92% class III) EF 23%; HR 82; BP 117/71; AF 12%	Death from any cause	Death from CV causes (death due to pump failure or an ischemic event or sudden death) Hospitalization for any reason Hospitalization because of HF Composite of death or heart tansplantation LVEF at 3 and 12 mo MI; QoL; and any change in the need for concomitant therapy	For pt in NYHA functional class III, the annual mortality rate was 16% in the placebo group; For pt with NYHA class IV, the annual mortality rate in the placebo group was 28% **Overall**: annual mortality of 17% in placebo group c/w 15% in the bucindolol group.	N/A	~2 y	449 pt in placebo group (33%) died, 411 in the bucindolol group (30%; HR: 0.90; 95% CI, 0.78-1.02; unadjusted p=0.10; adjusted p=0.13)

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COMET; Poole-Wilson et al; (2003) 12853193 (185)	To compare the effects of carvedilol and metoprolol on clinical outcome in pts with HF	RCT	Diuretics, ACEIs	3029; 1511 carvedilol; 1518 metoprolol tartrate	N/A	NYHA class II-IV EF <35% Previous CV admission	N/A	Mild to severe	All-cause mortality Composite endpoint of all-cause mortality, or all-cause admission	N/A	N/A	N/A	4.8 y	All-cause mortality 34% carvedilol and 40% metoprolol (HR: 0.83; 95% CI 0.74-0.93; p=0.0017)
(CIBIS) III; 2005 16143696 (186)	Sufficient data do not currently exist to establish the optimum order of initiating chronic HF therapy (ACEI vs. beta blocker). This was the objective of the CIBIS III trial-- it compared the effect on mortality and hospitalization of initial monotherapy with either bisoprolol or enalapril for 6 mo, followed by their combination for 6 to 24 mo.	Multicenter, prospective, randomized, open-label, blinded end point evaluation (PROBE) trial,24 with 2 parallel groups.	Diuretics 84%; Digoxin 32%	1010 Bisoprolol 505; Enalapril 505	CAD 62%	>65 y, NYHA class II or III, and LVEF <35% (By echo within the 3 mo) Clinically stable HF (without clinically relevant fluid retention or diuretic adjustment within 7 d)	Treatment with an ACEI, an ARB, or a beta blocker for >7 d during the 3 mo before randomization Heart rate at rest <60 beats/min without a functioning pacemaker Supine SBP <100 mm Hg at rest SCr≥220 μmol/L AV block greater than first degree without a functioning pacemaker Obstructive lung disease contraindicating bisoprolol treatment	NYHA II or III; mild to moderate CHF LVEF 29%; Heart rate 79; SBP 134	The primary endpoint was time-to-the-first-event of combined all-cause mortality or all-cause hospitalization	Combined end point at the end of the monotherapy phase and the individual components of the primary end point, at study end and at the end of the monotherapy phase. CV death CV hospitalization	N/A	N/A	Mean of 1.22±0.42 y (maximum of 2.10 y).	In the ITT sample, 178 pt (35.2%) with a primary end point in the bisoprolol-first group, and 186 (36.8%) in the enalapril-first group (absolute difference -1.6%; 95% CI -7.6 to 4.4%; HR: 0.94; 95% CI 0.77 to 1.16; noninferiority for bisoprolol-first versus enalapril-first treatment, p=0.019)

ACEI indicates angiotensin-converting-enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blocker; AV, atrioventricular; BP, blood pressure; CABG, coronary artery bypass graft; CHF, congestive heart failure; CIBIS II, Cardiac Insufficiency Bisoprolol Study II; COMET, Carvedilol Or Metoprolol European Trial; COPERNICUS, carvedilol prospective randomized cumulative survival; Cr, creatinine; CR/XL, controlled release/extended release; CV, cardiovascular; CVA, cerebrovascular accident; c/w, compared with; DIG, Digitalis Investigation Group; EF, ejection fraction; HF, heart failure; h/o, history of; HR, hazard ratio; ICD, ICD, implantable cardioverter defibrillator; ITT, intent to treat; MERIT-HF, Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure;

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MI, myocardial infarction; MWT, minute walk test; NYHA, New York Heart Association; PPM, permanent pacemaker; PTCA, percutaneous transluminal coronary angioplasty; Pts, patients; QoL, quality of life; RCT, randomized control trial; RR, relative risk; SBP, systolic blood pressure; SCr, serum creatinine; UA, unstable angina; USA, United States of America; VF, ventricular fibrillation; VT, ventricular tachycardia; and w/o, without.

Data Supplement 21. Anticoagulation (Section 7.3.2.8.1)

Study Name, Author, Year	Aim of Study	Study Type	Study Size	Study Size (HF Subpopulation)	Patient Population		Endpoints		Statistical Analysis (Results)
					Inclusion Criteria	*Exclusion Criteria*	*Primary Endpoint*	*Secondary Endpoint*	
WARCEF Pullicino 2006, 16500579; Homma 2012, 22551105 (187)	Compare efficacy of warfarin (INR 2.75) vs aspirin (325 mg/d) in HF pt in sinus rhythm	RCT, double blind/double dummy, multicenter, parallel group	N=2305, mean f/u 3.5 y; (69% power to detect ~18% reduction primary endpoint)	N/A	EF≤35%,NYHA I-IV, sinus rhytm, taking ACEI/ARB or H/N, planned treatment with beta blocker	Contraindication to or absolute indication for 1 treatment; MI/PCI/cardiac surgery <3 mo; decompensated HF, life expectancy otherwise <5 y, HF admission or CEA or PPM insertion <1 mo	Efficacy: time to first of (death+ischemic stroke+intracerebral hemorrhage); Safety: major hemorrhage	Efficacy: primary endpoint+MI+HF hospitalization; components of primary composite; Safety: intracerebral+intracranial hemorrhage	Primary Efficacy: 7.47 events (warfarin) vs. 7.93 events (aspirin) /100 person-y. Secondary: ischemic stroke – warfarin, HR: 0.52; Safety major hemorrhage: Warafin 1.78 vs aspirin 0.87/100 person-y. Primary Endpoint: p=0.40: 95% CI: 0.79 - 1.10; ischemic stroke p=0.0005, 95% CI: 0.33 - 0.82; major hemorrhage p<0.001
HELAS Cokkinos 2006 16737850 (188)	Determine if warfarin(INR 2.0-3.0) or aspirin (325 mg/d) reduces thromboemboli in HF	RCT, multicenter, double-blind, placebo-controlled; (converted to pilot study due to inadequate enrollment)	N=194, mean f/u 22 mo; Ischemic (aspirin vs warfarin), N=114; DCM (warfarin vs. placebo), N=80 (stopped at 4% target due to poor recruitment)	N/A	NYHA II-IV; EF <35%; Prespecified subgroups: Ischemic vs DCM	MI <2 mo; "reversible ischemia", mitral disease, HoCM, AF, LV thrombus, pregnancy, uncontr HTN, contra-ind to either study drug, otherwise <2 y expected survival	Efficacy: composite [nonfatal stroke + arterial TEE or PE + MI + rehospitalization + worsened HF + all-cause mortality]; Safety: ICH + "bleeding" on treatment	Need for coronary revascularization; readmission for ischemia	Primary Efficacy (events/100 person-y): Isch/aspirin (14.9), Isch/warfarin (15.7); DCM/warfarin (6); DCM/placebo (10); Safety: Isch/ warfarin (4), DCM/ warfarin (3), others (0). 2.2 events/100 person-y (5 stroke, 2 MI, no arterial TEE or PE).
WASH Cleland 2004 15215806 (189)	Pilot Study: feasibility of study comparing warfarin (INR 2.5) to aspirin (300 mg/d) to placebo	Prospective multicenter placebo-controlled RCT, 3-arm, open-label, blinded endpoint	N=279 pts, mean f/u 27 mo	N/A	Required diuretics; LVEDD >55 mm or >30 mm/m^2 or EF ≤35%; Prespecified subgroups: ischemic vs. DCM	"Definite" indication for warfarin or aspirin, MI < 4 wk, inpt status, contr-ind to either drug	Time to first event (on treatment or within 10 d of stopping treatment): composite [death + nonfatal MI + nonfatal stroke]	Prespecified: death or CV hospitalization; death or all-cause hospitalization; total hospitalizations; death or CV hospitalization or need for increased diuretic dose; worsening HF; MI; stroke; major hemorrhage.	Both ITT an AT: "no difference" PRIMARY ITT: Placebo: 26% (HR: 0.96; 95% CI: 0.60-1.54); Aspirin: 32% (HR: 1.16; 95% CI: 0.74-1.85); Warfarin: 26% (HR: 0.88; 95% CI 0.54-1.43), p=0.22; AT: Placebo: 20% (HR: 1.08 95% CI: 0.65-1.89); Aspirin: 22% (HR: 1.02 95% CI: 0.59-1.75); Warfarin: 18% (HR: 0.89

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									95% CI: 0.50-1.16); Secondar ITT: all-cause hospitalizations (Placebo 48% vs. Aspirin 64% vs. Warfarin 47%); Major hemorrhage "no difference"; minor hemorrhage (Placebo 5% vs. Aspirin 13% vs. Warfarin 17%), p=0.033
WATCH Massie 2009 19289640 (190)	Hypotheses: warfarin superior to aspirin and clopidogrel superior to aspirin for HF pt with reduced LVEF in sinus rhythm	Prospective, multicenter RCT, open label (warfarin) or double blind APT group comparing aspirin (162 mg) vs. clopidogrel (75 mg no load) vs warfarin (target INR 2.5)	N=1587; treatment for 1 y; mean f/u 1.9 y (stopped early due to poor recruitment)	N/A	NYHA II-IV, EF ≤35%; sinus rhythm on entry; on diuretics and ACE-I /ARB or H/N	Reversible HF; contraindicated to any study drug; imminent procedure or surgery; other survival-limiting disease	Efficacy: time to first event of composite [death + nonfatal MI + nonfatal stroke]; Safety: major bleeding	Death; nonfatal MI; nonfatal stroke; hospitalization for HF	Efficacy ITT: Primary - No difference warfarin vs. aspirin vs clopidogrel; Secondary - A group with more total and HF hospital admissions; Safety ITT: warfarin=aspirin, both with more major bleeding than clopidogrel Efficacy PRIMARY: ITT: warfarin vs. aspirin: HR: 0.98; 95% CI: 0.86-1.12; p=0.77. clopidogrel vs. aspirin: HR: 1.08 95% CI: 0.83-1.40; p=0.57. warfarin vs. clopidogrel: HR: 0.89; 95% CI: 0.68-1.16; p=0.39. AT: warfarin superior to aspirin (p=0.0095), warfarin superior to clopidogrel (p=0.0031). SECONDARY endpoints: HF hospitalizations aspirin (22.2%) vs. warfarin (16.5%), p=0.019; Total HF admissions aspirin (218) vs. warfarin (155), p <0.001. Safety PRIMARY: major bleeding warfarin (5.2%) vs. clopidogrel (2.1%), p=0.007; warfarin vs. aspirin (p=NS). POST HOC Ischemic group (N=1163): Strokes warfarin (0) vs. aspirin (1.6), p=0.01; warfarin (0) vs. clopidogrel (2.7%), p=0.0009; Nonischemic group (N=424) Major bleed clopidogrel (0.7%) vs. warfarin (6.3%), p=0.0093. AT analysis (not prespecified): warfarin superior to aspirin (p=0.0095); warfarin superior to clopidogrel (p=0.0031).

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EPICAL Echemann 2002 12413509 (191)	Compare warfarin vs. aspirin vs. both on survival in CHF	Prospective observational population-based, nonrandomized, consecutive hospital survivors of hospitalization, aspirin vs. warfarin at hospital discharge	N=417 with complete data, mean f/u= 5 y; aspirin (30.9%) vs. OAT (28.3%) vs. both (2.4%)	N/A	≥ 1 hospitalization for HF, NYHA II-IV, EF ≤30% or CTR ≥ 0.60, plus hypotension or systemic or pulmonary edema	Failure to meet inclusion criteria (systematic enrollment)	Survival 1 y and 5 y from index hospitalization; stratified by LVEF	None	Both warfarin (RR=0.60) and aspirin (RR=0.70) associated with improved survival Univariate survival: AC (1 y 77.7%; 95% CI: 71.7-82.4), 3 y 55.1%; 95% CI: 48.7-61.5), 5 y 40.4% [95% CI: 34.1-46.8] vs. no AC (1 y 71.5% [95% CI: 64.9-78.1], 3 y 47.0% [95% CI: 39.6-54.3], 5 y 31.0% [95% CI 24.0-38.0; p=0.01] for AC vs no AC; Multivariate: OAT RR:0.60 [95% CI 0.4-0.8], aspirin RR: 0.7 [95% CI 0.5-0.9]
Wojnicz 2006 16996844 (192)	Pilot Study: LMWH effects on clinical endpoints in chronic HF secondary to DCM	Prospective, randomized, active treatment control, open label comparing enoxaparin 1.5 mg/kg BID x 14 d, then 1 daily x 3 mos	N=102 (52 treatment, 50 control) enrolled, data on N=85 for analysis; f/u=1 y	N/A	Stable NYHA II-IV, EF ≤40%; cath to exclude CAD, Biopsy	Contraindicated to any heparin, T1DM, valvular HD, recent heparin exposure, CAD	Composite [mortality + urgent heart transplant + hospital admission for worsening HF] at 6 and 12 mo	Total survival, BNP, LVEF, echo chamber parameters, NYHA class change, VO_2 max, QoL	Primary: no difference Primary: enoxaparin 4 vs. control 8, p=NS; mortality: p=NS; Secondary: BNP reduction enoxaparin (1125-489) p<0.001 vs. no change in control; LVEF improvement: enoxaparin increase 6.5%, p=0.023; 95% CI: 1.01-8.17.
RE-LY Connolly 2009 19717844 (193)	Compare dabigatran vs. warfarin effects on stroke/arterial emboli in pts with AF	Noninferiority, multicenter, prospective RCT, blinded dab (110 or 150 mg BID) or unblinded warfarin (INR 2.0-3.0)	Total N=18,113; median f/u=2.0 y	HF n=5793 (32%): HF on dab 110 mg (n=1937/6015); HF on dab 150 (n=1934/6076); HF on warfarin (n=1922/6022).	AF + ≥1 additional risk factor for stroke (median CHADS2 score 2.1). HF as qualifying criteria req'd LVEF <40% or NYHA Class ≥ II	Excessive bleeding risk, severe valve disease, stroke <14 d/severe stroke <60 mo, creat clear <30 mL/min	Efficacy: composite [stroke or systemic embolism]; Safety: Major hemorrhage (2 y)	Stroke, systemic embolism, death, MI, PE, TIA, hospitalization	ITT, noninferiority with Cox prop hazards. Subsequent analyses for superiority Symptomatic HF: multivariate HR for dab 150 vs warfarin, p=0.33; 150 mg dab vs warfarin: stroke 0.64; 95% CI: 0.51-0.81; p<0.001 (p<0.05 for all stroke subgroups). MI: RR: 1.38; 95% CI1.00-1.91; p=0.048
ACTIVE-W 2006 16765759 (194)	Combination clopidogrel + aspirin vs warfarin in reducing vascular events in AF	Prospective open label noninferiority RCT of [clopidogrel 75 mg + aspirin 75-100 mg] vs warfarin (INR 2.0-3.0)	Total N=6706	HF N=2031 (30%)	AF, LVEF <45%	Other need for warfarin, excessive bleeding risk, prev ICH, platelets <50 K, mitral stenosis	Efficacy: First event of [stroke or arterial TEE or MI or vascular death]; Safety: Major hemorrhage	Efficacy: components of primary; Safety: Minor hemorrhage	KM log-rank (time to event) Total Study: Primary Efficacy: clopidogrel +aspirin: 5.60 events/y vs. warfarin 3.93 events/y; RR: 1.44; 95% CI 1.18-1.76; p=0.0003; stroke RR: 1.72; 95% CI: 1.24-2.37; p=0.001
ARISTOTLE Granger 2011 21870978 (195)	Compare apixaban to warfarin in preventing stroke in pt with AF	Prospective double-blind, double-dummy noninferiority + superiority RCT of AP 5 mg BID to warfarin INR 2-3	Total N=18,201 , median F/u=1.8 y	HF n=6451 (35.5%), apixaban=3235, warfarin=3216	≥2 episodes AF or flutter, CHADS2 ≥2 (HF criteria: symptomatic HF within 3 mo or LVEF ≤ 40%	Reversible AF, mitral stenosis, orther indication for anticoagulation, recent stroke, need for antiplatelet therapy (beyond low-dose aspirin), creat	Noninferiority: EFFICACY: stroke (ischemic or hemmorhagic) + systemic embolism; SAFETY: major bleeding	Superiority: EFFICACY: stroke (ischemic or hemmorhagic) + systemic embolism; all-cause mortality; SAFETY: major + clinical nonmajor bleeding	PRIMARY: ITT Efficacy: apixaban 1.27%/y vs warfarin 1.60%/y) Modified ITT Safety: apixaban 2.13% vs warfarin 3.09%; mortality apixaban 3.52% vs warfarin 3.94%. HF subgroup results not different (p for interaction 0.50) Efficacy: apixaban: HR: 0.79; 95% CI:

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						>2.5 mg/dL			0.66-0.9;, p<0.001 for noninferiority, p=0.01 for superiority; Mortality apixaban: HR: 0.89: 95% CI: 0.80-0.99; p=0.047. Safety: apixaban: HR: 0.69; 95% CI: 0.60-0.80; p<0.001 (apixaban RRR: 27%)
ROCKET AF Patel 2011 21830957 (196)	Compare rivaroxaban to warfarin in preventing ischemic strokes in pt with nonvalvular AF	Prospective multicenter double-blind double-dummy event-driven noninferiority RCT of rivaroxaban 20 mg/d (15 mg if Cr Cl 30-49 mL/min) vs. warfarin (INR 2-3)	N=14,264 randomized, median f/u=707 d	8909 (rivaroxaban 4467, warfarin 4441) (62.5%)	Nonvalvular AF, CHADS2 ≥2; HF (clinical dx or LVEF ≤ 35%)	Mitral stenosis, absolute non-AF indication for AC, high risk for anticoagulation	Primary efficacy: composite [ischemic or hemorragic stroke + systemic embolism]; Primary safety: composite [major + nonmajor clinically relevant bleeding]	Secondary efficacy: composite stroke + systemic embolism + CV mortality]; composite [stroke + systemic embolism + CV mortality + MI]; individual components of primary composite. Secondary safety	Active treatment analysis (by design): rivaroxaban (1.7% per year events) noninferior to warfarin (2.2% per year events) for primary outcome; no difference in safety endpoints; fewer CHN hemorrhage and fatal bleeding in rivaroxaban group. Findings consistent for all subgroups. Efficacy: Per protocol, rivaroxaban HR: 0.79; 95% CI: 0.66 - 0.96; p<0.001 for noninferiority; HF subgroup ITT p=0.419. Safety superiority of rivaroxaban p=0.02
Belch 1981 7291971 (197)	Effect of low-dose SQ H on lower extremity DVT in pts with HF and pts with chest infections	Prospective, randomized, open label, controlled study SQ H 5000 u q8h x 14 d or until discharge	Total N=100	HF subset n=38 (21 treatment, 17 control)	HF NYHA II-IV, clinical signs of volume overload	"Definite" risk of bleeding, DVT or PE on admission, >2 d bed rest prior to admission	DVT diagnosed by I-125 fribrinogen scanning every 2 d or until discharge	Clinical evidence of bleeding	H reduced demonstrable DVT Total group: DVT (Ctl 26% vs H 4% of treated, p<0.01); 20% had minor bleeding (bruising at injection site), no major bleeding
ARTEMIS Cohen 2006 16439370 (198)	Safety and efficacy of fondaparinux in reducing VTE in older, moderate-high risk medical inpt	Double-blind, placebo-controlled, block randomized, multicenter RCT of SQ fondaparinux 2.5 mg/d for 6-14 d started within 48 h of admission	N=849 medical inpt, mean f/u=1 mo	HF n=160 (fondaparinux 78, placebo 82)	CHF (NYHA III-IV) or acute respiratory illness; expected bed rest >4 d; age >60	High bleeding risk" or contraindicated to anticoagulation, Creat >2.0 mg/dL, contrast allergy, mechanical vent >24 h (total), indication for AC prophylaxis or therapy, life expectancy otherwise <1 mo	Efficacy: DVT diagnosed by contrast venogray (d 5-15), symptomatic VTE (inc PE by imaging or fatal) through d 15; Safety: major bleeding	Efficacy: composite [Total VTE + bleeding + death at 1 mo]; Safety: composite [death or minor bleeding]	ITT (efficacy): all pt with ≥1 dose of drug (safety); HF pts=predefined subgroup. Fishers Exact and log-rank HF subgroup: Primary: fondaparinux 7/78 (9%) vs placebo 10/82 (12.2%), p=NS; Primary safety: p=NS (1 bleed in each group)

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CERTIFY Tebbe 2011 21315215 (199)	Compare LMWH to heparin on VTE incidence in elderly HF pt	Prospective, double-blind, double dummy, active control, randomized noninferiority study of certoparin 3000 u/d vs H 5000 u TID SQ (HF predefined subgroup)	Total N=3239, mean hospitalization 12.2 +/-5.1 d, mean treatment period = 9 d	HF n=470; 238 pts (cert) vs 232 pts (H),	age ≥70, clinical diagnosis of HF on admission (no further details)	Contraindicated to anticoagulation, History of DVT, PE or HIT2, stroke <3 mo, >3 d immobilization before randomization, cast or fracture, surgery <3 wk, severe sepsis, mechanical ventilation, any heparin <5 d	Efficacy: composite [prox DVT (compression USG d 8-20) + nonfatal PE + VTE-related death]; Safety: composite [major bleeding + minor bleeding + HIT]	Prox DVT, nonfatal PE, fatal VTE, distal DVT, symptomatic DVT, all-cause mortality, documented symtpomatic VTE, composite [nonfatal PE + prox DVT + all-cause mortality]	Active treatment only. No difference in efficacy or safety endpoints in HF pt based on treatment arm. Primary: cert 3.78% vs heparin 4.74%, OR: 0.79; 95% CI 0.32-1.94; p=NS; multivariate: insufficient to confirm noninferiority in HF pt.
THE PRINCE Kleber 2003 12679756 (200)	Compare safety and efficacy of enoxaparin with UFH in preventing VTE in pts with HF or severe respiratory disease	Prospective, randomized, active control/parallel group open label, noninferiority comparison enoxaparin 40 mg/d vs heparin 5000 u TID for 10 +/- 2 d. 1-sided equivalence, upper limit = 9% or 4% difference in efficacy.	Total N=665	HF n=333 for safety endpoint, n=206 for efficacy	NYHA III-IV	Contraindicated to heparin or anticoagulation, contrast allergy, DVT or PE on admission, immobilized >24 h prior to admission, taking warfarin or >low dose aspirin on admission	Efficacy: Comfirmed TEE (DVT by venography or autopsy, PE by V/Q, CXR/Q scan [plus confirmatory venogram if +], angiogram or autopsy) within 1 d of completing treatment; Safety: Major bleeding	Efficacy: composite [TEE or death]	No differences in primary, secondary or safety endpoints 12.6% HF pt had events. Primary: enoxaparin (9.7%) vs heparin (16.1%) [CI -1.4 - +14.2], p=0.139. Secondary: mortality: enoxaparin 5.3% vs heparin 6.4% (no statistical comparison); Saftey: no difference (1 bleed in entire study population)
MEDENOX Samama 1999 10477777; Turpie 2000 11206019; Alikhan 2003 12945875 (201)	Compare safety and efficacy of 2 doses of enoxaparin vs placebo to prevent VTE in medical pt hospitalized ≤14 d	Prospective, randomized, double-blind, parallel arm of placebo vs enoxaparin 20 mg/d vs enoxaparin 40 mg/d	Total N=855; f/u = 110 d	HF n=290 (34%)	NYHA III-IV	Contraindicated to anticoagulation or heparin, contrast allergy, thrombophilic disease or coagulopathy, Creat >1.7, mechanical ventilation, any AC for >48 h prior to enrollment	VTE (DVT [contrast venograpy or compression USG day 6-14 or earlier with symptoms], PE [high prob V/Q, CTA or angio] or both) d 1-14	VTE d 1-110; Major or minor hemorrhage, mortality, thrombocytopenia, any adverse event, lab abnormalities (multiple)	Enoxaparin 20 mg = Placebo (excluded from final analysis); lower incidence of radiographic DVT in enoxaparin 40 mg vs placebo. No difference in mortality or AEs among treatment groups. Primary: All HF pts: enoxaparin 4.0% vs placebo 14.6%, (RR: 0.29; 95% CI: 0.10-0.84; p-0.02); Class III HF pts: enoxaparin 5.1% vs. placebo 12.3% (RR: 0.42; 95% CI: 0.13-1.29; p=0.20); Class IV HF pts: enoxaparin 0% vs. placebo 21.7%, (p=0.05); History of chronic HF as risk (regardless of admission diagnosis): enoxaparin 2.2% vs. placebo 12.1% (RR: 0.26; 95% CI: 0.08-0.92; p=0.04)

AC indicates anticoagulant; ACEI, angiotensin-converting-enzyme inhibitor; ACT, active control parallel; AE, adverse event; AP, apixaban; APT, antiplatelet therapy; AF, atrial fibrillation; ARB, angiotensin receptor blockers; AT, as treated; BID, twice a day; BNP, brain natriuretic peptide; CAD, coronary artery disease; CHF, congestive heart failure; CrCl, creatinine clearance; CTA, computed tomography angiography; CTR, cardiothoracic ratio; CV, cardiovascular; CXR, chest x-ray; Dab, dabigitran; DCM, dilated

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cardiomyopathy; DVT, deep venous thrombosis; EF, ejection fraction; f/u, follow-up; H, heparin; HD, heart disease; HF, heart failure; HIT2, heparin-induced thrombocytopenia; H/N, hydralazine and nitrates; HTN, hypertension; ICH, ischemia; INR, international normalized ratio; ITT, intent to treat; KM, kaplan-meier; LMWH, low moleducular weight heparin; LV, left ventricular; LVEDD, left ventricular end diastolic diameter; LVEF, left ventricular ejection fraction; MI, myocardial infarction; N/A, not applicable; NS, not significant; NYHA, New York Heart Association; OAT, oral anticoagulant therapy; PCI, percutaneous coronary intervention; PE, pulmonary embolism; PPM, pacemaker; pt, patient; QoL; quality of life; RCT, randomized control trial; SQ, subcutaneous; TEE, thromboembolic event; TIA, transient ischemic attack; TID, three times a day; UFH, unfractionated heparin; USG, ultrasonography; VO2, oxygen volume; V/Q, ventilation/perfusion scan; and VTE, venous thromboembolic disease.

Data Supplement 22. Statin Therapy (Section 7.3.2.8.2)

Study Name, Author, Year	Aim of Study	Study Type	Background Therapy	Study Size	Etiology	Patient Population		Severity	Endpoints		Mortality		Trial Duration	Absolute Benefit	Statistical Results	Study Limitations
			Pretrial standard treatment	*N (Total) n (Experimental) n (Control)*	*Ischemic/ Non-Ischemic*	*Inclusion Criteria*	*Exclusion Criteria*	*Severity of HF Symptoms*	*Primary Endpoint*	*Secondary Endpoint*	*Annualized Mortality*	*1st Year Mortality*				
Horwich et al, 2004 14975476 (202)	To investigate the impact of statin therapy in pts with advanced HF referred for transplant evaluation at UCLA.	Cohort study	ACEI/ARB, beta-blockers,spironolactone, diuretics	551; 248; 303	45%	Pts referred for transplant evaluation between 2000-2	LVEF >40%, baseline data incomplete	NYHA 3-4	Death or urgent transplant	N/A	N/A	75%	2 y	14%	HR 0.44; 95% CI 0.30-0.67; p<0.0001	Single-center, non-randomized, reason for drug use unclear, bias
Mozaffarian et al, 2004 15110204 (203)	To evaluate the relation of statin therapy with clinical outcomes in severe HF enrolled in the PRAISE study	Cohort study	ACEI/ARB, diuretics, digoxin	1,153; 1,019; 134	63%	Dyspnea or fatigue on exertion (NYHA 3b-4), LVEF ≥30%	N/A	NYHA 3b-4	All-cause mortality	Cause-specific mortality (SCD, pump failure death, fatal MI)	29 deaths/100 person-y	N/A	Mean 1.5 y	N/A	HR: 0.38; 95% CI: 0.23-0.65; Propensity-matched HR: 0.46. 95% CI: 0.26–0.75	Post-hoc analysis from clinical trial

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Ray et al, 2005 15642876 (204)	To determine whether statin use is associated with a lower risk of death and major CVD among adults newly diagnosed as having HF in Ontario registry	Cohort study	ACEI/ARB, beta-blockers,spironolactone, diuretics, nitrates	28,828; 1,146; 27,682	11.3% history of MI	Adults aged 66 to 85 y in Ontario Canada newly hospitalized with primary diagnosis of HF between April 1, 1995, and December 31, 2001 and survived at least 90 d after the index HF hospitalization	Pts hospitalized within 36 mo for HF or having diagnosis of cancer within past 365 d prior to index HF hospitalization discharge date; dispensed statin 365 d prior to hospital discharge, length of stay >60 d, direct transfer to chronic care hospital, cancer within 90 d following index HF hospitalization	N/A	Death from any cause, nonfatal acute MI, or nonfatal stroke	N/A	9.9% per 100 person-y vs 19.1% per 100 person-y	N/A	16.6 mo in the statin group and 24.4 mo in the nonstatin group	8.2% per 100 person-y	HR: 0.62; 95% CI: 0.53-0.69; aHR: 0.72; 95% CI: 0.63-0.83.	Retrospective cohort study, non-randomized, reason for drug use unclear, bias
Foody et al, 2006 16490817 (205)	To evaluate the association between statin use and survival among a national sample of elderly	Cohort study	ACEI/ARB, beta-blockers,spironolactone, diuretics, nitrates	54,960; 9,163; 45,797	30% history of MI	Sampling of Medicare fee-for-service beneficiaries hospitalized with a principal diagnosis of HF by ICD-9 code	<65 y of age, HF readmissions, transferred out of the hospital, left AMA, or had unknown discharge	NYHA 2-4	All-cause mortality	N/A	20%	N/A	3 y	N/A	HR: 0.62; 95%CI: 0.59–0.65; p<0.001 aHR: 0.80; 95%CI: 0.76–0.84; p<0.001	Retrospective cohort study, sampling, non-randomized, reason for drug use unclear, bias

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	Medicare beneficiaries hospitalized with HF from National Heart Care Project.					between 4/98-3/99 and 7/00-6/01.	disposition, died during hospitalization, had no date of death information available, hospitalized outside the US, discharged to hospice, contraindications to statin therapy, including statin allergy or liver dysfunction, or no medications recorded on discharge									
Anker et al, 2006 16846656 (206)	To assess the relationship between statin use and survival in ELITE-II as well as a 5-center registry	Cohort study	ACEI or ARB (as in ELITE-2), diuretics, digoxin	5,200; 1,103; 4,097	67%	ELITE-II: pts age ≥60 y; NYHA 2-4, LVEF ≥40%. European registry: diagnosis of HF followed by HF clinic	NR	NYHA 2-4	All-cause mortality	N/A	NR	12%	mean 1.5 y (ELITE-2); 2 y (European registry)	NR	ELITE-II: aHR 0.61; 95% CI: 0.44-0.84; p<0.0028 European registry: aHR 0.58; 95%CI adjusted 0.44-0.77; p<0.0001;	Retrospective cohort study and post-hoc analysis, sampling, non-randomized, reason for drug use unclear, bias

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Folkeringa et al, 2006 16520262 (207)	Investigate the effects of statins on survival in CHF pts using a matched case-controlled study in pts admitted to hospital because of severe CHF from the MARCH study	Case-control study	ACEI/ARB, diuretics, digoxin	524; 262; 262	50%	Pts admitted for HF with an uncomplicated survival for at least 1 mo after hospital discharge, group-wise matched between survivors and non-survivors on means of age, LVEF, renal function, and sex.	NR	NYHA 3-4	All-cause mortality	N/A	NR	NR	Mean 2.6 y	4%	OR: 0.42; 95% CI: 0.26–0.69	Retrospective cohort study, sampling, non-randomized, reason for drug use unclear, bias
Go et al, 2006 17077375 (208)	To evaluate the association between initiation of statin therapy and risks for death and hospitalization among adults with chronic HF in the Kaiser Permanente Chronic HF cohort	Cohort study	ACEI/ARB, diuretics, digoxin	24,598; 12,648; 11,950	54%	Adults (age ≥20 y) diagnosed with HF 1/96-12/04 with ≥1 hospitalizations with a principal diagnosis of HF; ≥2 hospitalizations with a secondary diagnosis of HF in which the principal diagnosis is cardiac-related; ≥3 hospitalizations with secondary	Pts who were receiving statin therapy at the study at entry date; who were not eligible for treatment based on national guidelines	NYHA 2-4	Death from any cause and hospitalization for HF	N/A	13.90%	NR	Median 2.4 y	NR	aHR: 0.76; 95%CI: 0.72-0.80	Retrospective cohort study, sampling, non-randomized, reason for drug use unclear, bias

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						diagnosis of HF; ≥2 outpatient diagnoses; ≥3 ED visit diagnoses; or ≥2 inpatient secondary diagnoses plus 1 outpatient diagnosis.										
Krum et al, 2007 16960445 (209)	To examine statin/beta blocker interactions within the context of a large-scale clinical trial of pts with systolic CHF in CIBIS-II	Cohort study	ACEIs/ARB, beta-blockers,spironolactone, diuretics	2,647; 220; 2,421	59%	Pts enrolled in CIBIS-II study	N/A	NYHA 2-4	Death	CV deaths included the following specific causes: sudden death, pump failure, MI and any other CV condition not listed above which led to the pt's death. Worsening HF only was counted as an outcome endpoint in CIBIS II when this (critical) event led to the hospitalizati	11.10%	NR	Mean 1.3 y	NR	HR 0.57; 95% CI: 0.37–0.94; aHR 0.60; 95% CI: 0.39–0.94	Retrospective cohort study, sampling, non-randomized, reason for drug use unclear, bias

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										on of the pt.						
Krum et al, 2007 17049646 (209)	To assess the outcome of pts enrolled in Val-HeFT according to statin use at the time of randomization to valsartan or placebo.	Cohort study	ACEI/ARB, beta-blockers,spironolactone, diuretics	5,010; 1,602; 3,408	57%	Pts enrolled in Val-HeFT study	N/A	NYHA 2-4	All-cause mortality	Mortality and morbidity (cardiac arrest with resuscitation, hospitalization for HF, or administration of IVinotropic or vasodilator drugs for 4 h or more without hospitalization)	7.90%	NR	Mean 1.9 y	7.20%	HR 0.81: 95%CI 0.70–0.94; p=0.005	Retrospective cohort study, sampling, non-randomized, reason for drug use unclear, bias
Dickinson et al, 2007 17383296 (210)	To examine the effects of statin in reducing mortality in SCD-HeFT	Cohort study	ACEI/ARB, beta-blockers,spironolactone, diuretics	2,521; 965; 1,556	52%	Ischemic and non-ischemic cardiomyopathy, NYHA 2-3 HF, LVEF 35% or less	N/A	NYHA 2-3	All-cause mortality	N/A	6.80%	NR	Mean 3.8 y	NR	aHR 0.7; 95% CI: 0.57-0.83	Retrospective cohort study, sampling, non-randomized, reason for drug use unclear, bias

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CORONA, Kjekshus et al, 2007 17984166 (211)	To investigate the beneficial effects of rosuvastatin on improving survival, reducing morbidity, and increasing well-being in pts with chronic, symptomatic, systolic, ischemic HF.	RCT	ACEI/ARB, beta-blockers,spironolactone, diuretics	5,011; 2,497; 2,514	100%	Age ≥18, symptomatic HF NYHA 2-4, IHD, LVEF <40%, does not need statin therapy, optimal medical therapy >2 wk	Myopathy or hypersensitivity to statin, ACS or revascularization <1 mo, reduced life expectancy, planned surgery <3 mo, Cr >2.5 mg/dL, ,CK >2x ULN, LFTs >1.5x ULN, uncorrected valve or HCM	NYHA 2-4	Composite of death from cardiovascular causes, nonfatal MI, and nonfatal stroke	Death from any cause, any coronary event (sudden death, fatal or nonfatal MI, PCI or CABG, ventricular defibrillation by an ICD, resuscitation after cardiac arrest, or hospitalization for UA), death from CV causes (with an additional analysis of cause-specific death from a CV cause), and the number of hospitalizations for CV causes, unstable angina, or worsening HF	11%	NR	Median 2.7 y	0.9% per 100 patient-y	HR: 0.92; 95% CI: 0.83-1.02; p=0.12	N/A
GISSI-HF, Tavazzi et al, 2008 18757089	To investigate the effi cacy and	RCT	ACEI/ARB, beta-blockers,spironolactone, diuretics	4,574; 2,285; 2,289	42% history of MI	≥18, symptomatic HF NYHA 2-4, if LVEF	Hypersensitivity to statin, investigatio	NYHA 2-4	Co-primary endpoint: time to	Death for a CV cause; first hospital	7.90%	NR	Median 3.9 y	-1%	HR: 1.02 99% CI: 0.923-1.130; p=0.594	N/A

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(212)	safety of the statin rosuvastatin in pts with HF.					>40% (10%) requires HF hospitalization within 12 mo	nal drug <1 month, MI <6 mo, ACS or revascularization <3 mo, reduced life expectancy, planned surgery/device <3 mo, Cr >2.5 mg/dL, LFTs >1.5x ULN, pregnant		death; time to death or admission for cardiovascular reasons	admission for any, CV, or HF cause; and the combined outcome measure of CV death or admission to hospital for any cause					aHR: 1.01; 99% CI 0.908-1.112, p=0.903;	

ACEI indicates angiotensin-converting-enzyme inhibitor; ACS, acute coronary syndrome; AMA, against medical advice; ARB, angiotensin receptor blocker; CABG, coronary artery bypass surgery; CHF, congestive heart failure; CIBIS-II, The Cardiac Insufficiency Bisoprolol Study II; CORONA, Controlled Rosuvastatin Multinational Trial in HF; CV, cardiovascular; ELITE-II, Losartan Heart Failure Survival Study; HF, heart failure; GISSI-HF, Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico; ICD, implantable cardioverter defibrillator; ICD-9, international classification of diseases 9th edition; IHD, ischemic heart disease; LVEF, left ventricular ejection fraction; MARCH, Maastricht Registry of Congestive HF; MI, myocardial infarction; N/A, not applicable, NR, not reported; NYHA, New York Heart Association; PCI, Percutaneous coronary intervention; PRAISE, Prospective Randomized Amlodipine Survival Evaluation; SCD, sudden cardiac death; SCD-HeFT , Sudden Cardiac Death in Heart Failure Trial;UA, unstable angina; UCLA, University of California Los Angelos; and Val-HeFT, Valsartan Heart Failure Trial.

Data Supplement 23. Omega 3 Fatty Acids (Section 7.3.2.8.3)

Study Name, Author, Year	Aim of Study	Study Type	Background Therapy	Study Size	Etiology	Patient Population		Severity		Endpoints		Mortality		Trial Duration	Statistical Anaylsis (Results)	Study Limitations	Complications/ Adverse Events
				N (Total) n (Experimental) n (Control)		*Inclusion Criteria*	*Exclusion Criteria*	*Severity of HF Symptoms*	*Study Entry Sverity Criteria*	*Primary Endpoint*	*Secondary Endpoint*	*Annualized Mortality*	*1st Year Mortality*				
GISSI-HF, Lancet 2008 18757090 (213)	To investigate whether omega-3 fatty acid supplementation could improve morbidity and mortality in a large	Randomised, double-blind, placebo-controlled trial (2x2, factorial design, rosuvastatin)	All treatments of proven efficacy for chronic HF (eg, ACEIs, beta blockers, diuretic drugs, italis, spironolactone) were positively recommende	7,046; 3494; 3,481 (placebo)	49.6% ischemic/50.4% non-ischemic-other	≥18 y, clinical evidence of HF of any cause classified as the ESC GL NYHA class II–IV, provided that LVEF was measured	Specific indication or contraindication to n-3 PUFA; known hypersensitivity to study treatments; presence of any non-cardiac comorbidity	Class II 63%, III 34%, IV 3%	NYHA Class II-IV HF	2 co-primary endpoints: time to death, and time to death or admission to hospital for	Cardiovascular mortality, cardiovascular mortality or admission for any reason, sudden cardiac death,	7%	7.0% (estimated from KM curves)	4.5 y, median f/u 3.9 y	1.8% absolute mortality reduction (95% CI 0·3–3·9%). Absolute benefit for mortality or admission for cardiovascular reasons was 2·3% (95% CI 0·0–4·6%). NNT for benefit is 56 pts need to be treated to avoid 1death and 44 pts treated to avoid 1event like death	By the end of the study, 1004 (29%) of pts in the omega 3 FA group and 1029 (30%) in the placebo group were no longer taking study	The rate of pts who had permanently discontinued taking the study drug because of adverse reactions was much the same in the omega 3 FA and in the placebo groups (102 [3%]

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	population of pts with symptomatic HF of any cause.		d. Background treatment rates of ACEI/ARB 93%, beta blockers 65%, aldosterone antagonists 40%, loop durietics 90%			within 3 mo before enrollment. When LVEF was >40%, the pt had to have been admitted at least 1 hospital for HF in the preceding y to meet the inclusion criteria.	(eg, cancer) incompatible with a long f/u; treatment with any other investigational agent within 1 mo before randomisation; ACS or revascularisation procedure within the preceding 1 mo; planned cardiac surgery, expected to be done within 3 mo after randomisation; significant liver disease; and pregnant or lactating women or women of childbearing potential who were not adequately protected against becoming pregnant.			cardiovascular reasons.	admission for any reason, admission for cardiovascular reasons, admission for HF, MI, and stroke.				or admission for cardiovascular reason for nearly 4 y. Mortality: aHR: 0·91; 95·5% CI 0·833–0·998; p=0·041. Mortality or were admitted to hospital for cardiovascular reasons (aHR: 0·92; 99% CI 0·849–0·999; p=0·009). Mortality: aHR 0.91 Mortality of CV Hospitalization aHR 0.92	drug for various reasons. Only evaluated a single dose. Study conducted in Italy where there is relatively high amount of dietary intake of omega 3 fatty acids. (p=0·45; table 5).	vs 104 [3%], p=0·87). Very well tolerated. No safety issues other than a slight excess of cerebrovascular events, which was a similar finding to that reported in the GISSI-Prevenzione trial. This excess was distributed fairly evenly between ischaemic and haemorrhagic cases. No drug interactions noted. with gastrointestinal disturbance being the most frequent cause in both groups (table 5).
GISSI-Prevention, Macchia A et al. EJHF 2005 (subgroup analysis) 16087142 (214)	To evaluate the effect of omega 3 fatty acid supplementation in post MI pts with LVD.	Randomized, multicenter, open-label, clinical trial with blinded validation of events.	Standard background therapy for pts who are post AMI	11323 pts ; 4324 (with LVEF ≤50%)	100% ischemic	Patient with AMI in prior 3 mo. Irrespective of LV function. No age limits.	Contraindications to the dietary supplements (ie, known allergy to omega-3 fatty acids). Unfavorable short-term outlook (eg,	No HF or NYHA Class I, subgroup analysis in pts with LVEF ≤50%		Time to death, and time to death or admission to hospital for cardiovascular	Sudden death	4% per y	4%	3.5 y	Treatment with n-3 PUFA reduced total mortality in pts with and without systolic dysfunction, 24% (40%-4%, p =0.02) and 19% (41% to +10%, p =0.17), respectively (heterogeneity test p=0.55). The effect on SD	Open label. Excluded pts with over HF.	Well tolerated.

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		Subgroup analysis of those pts with post MI LVD					overt CHF, cancers, etc).			reasons					reduction was asymmetrical, with a greater effect in pts with LVSD (RRR: 58%; 95% CI: 74%-33%; p =0.0003) as compared to pts with preserved systolic function (RRR: 11%; 95% CI: 54% - 69%; p =0.71), although the heterogeneity test was not statistically significant (p=0.07). LVD subgroup (0.60–0.96) p=0.02) RR 0.76 (subgroup with LVD)		
Omega 3 fatty acids in DCM, Nodari, JACC, 201 21215550 (215)	This study was designed to test the effects of 3 PUFAs on (LV) systolic function in chronic HF due to NICM	Randomized, single center double blind, clinical trial with blinded validation of events. Subgroup analysis of those pts with post MI LVD	Evidence based HF therapy ACE/ARB 100%, beta blockers 100%, aldosterone antagonists 60%, loop diuretics 100%	133; 67 experimental; 66 control	100% non-ischemic	Pts aged 18-75 y with a diagnosis of NICM, LVSD (defined as an EF <45%), and stable clinical conditions with minimal or no symptoms for at least 3 mo on evidence-based medical treatment at maximum tolerated target doses for at least 6 mo.	presence of symptoms or evidence of CAD diagnosed through noninvasive tests, PAD, presence of congenital or primary VHD, persistent AF, inability to perform bicycle ergometry for noncardiac causes, moderately severely reduced functional capacity, NYHA class IV, poor acoustic windows limiting the ability to assess echo	Mild, Class I, 15%, Class II 85%.	Mild severity on medical therapy	Change in LVEF	Peak V02, hospitalizations	0%	0%	12 mo	LVEF increased by 10.4% n-3 PUFA and decreased by 5.0% with placebo, p<.0001, peak VO2 (increased by 6.2% and decreased by 4.5%, respectively); exercise duration increased by 7.5% and decreased by 4.8%; and mean NYHA class decreased from 1.88 +/- 0.33 to 1.61 +/- 0.49 and increased from 1.83 +/- 0.38 to 2.14 +/- 0.65. The hospitalization rates for HF were 6% in the n-3 PUFAs and 30% in the placebo group (p = 0.0002).	Single center, small, no deaths.	None

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							measurements, chronic lung disease, advanced renal disease (eGFR <30 ml/min/1.73 m2), advanced liver disease; any disease limiting life expectancy to <1 y, contraindications to study drugs, and concomitant participation in other research studies.										

ACEI indicates angiotensin-converting-enzyme inhibitor; ACS, acute coronary syndrome; AMI, acute myocardial infarction; ARB, angiotensin receptor blocker; CAD, coronary artery disease; CV, cardiovascular; EF, ejection fraction; eGFR, estimated glomerular filtration rate; ESC GL, European Society for Cardiology guidelines; f/u, follow-up; GISSI-HF, Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico; HF, heart failure; KM, Kaplan-Meier; LVD, left ventricular dysfunction; LVEF, left ventricular ejection fraction; LVSD, left ventricular systolic dysfunction; MI, myocardial infarction; NICM, nonischemic cardiomyopathy; NNT, number needed to treat; NYHA, New York Heart Association; PAD, peripheral arterial disease; PUFA, polyunsaturated fatty acids; SD, sudden death

Data Supplement 24. Antiarrhythmic Agents to Avoid in HF (7.3.2.9.2)

Trials	Study				Study Drug Effect				Other Comments
	Design	Drug	Control	Patients	Mortality	CV events	Functional Capacity	QoL	
Class I Na Channel Blocker									
CAST 2473403 (216)	RCT	Encainide/ Flecainide/ Moricizine	P	Post-MI NSVT	↑ with encainide, flecainide RR 2.5	N/A	N/A	N/A	Study terminated early.
Class III K Channel Blockers									
SWORD 8691967 (217)	RCT	d-Sotalol	P	Post-MI LVEF≤40%	↑ RR 1.65	N/A	N/A	N/A	Study terminated early.

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Dronedarone Study Group 18565860 (218)	RCT	Dronedarone	P	NYHA II-IV LVEF≤35% hospitalized	↑ HR 2.13	↑ first CV hospitalizations	N/A	N/A	No difference in primary composite endpoint.

CAST indicates Cardiac Arrhythmia Suppression Trial; CV, cardiovascular; K, potassium; LVEF, left ventricular ejection fraction; MI, myocardial infarction; Na, sodium; NSVT, nonsustained ventricular tachycardia; N/A, not applicable; NYHA, New York Heart Association; P, placebo; QoL, quality of life; RCT, randomized control trial; and SWORD, Survival With Oral d-Sotalol.

Data Supplement 25. Calcium Channel Blockers to Avoid in HF (Section 7.3.2.9.3)

Trials	Study				Study Drug Effect				Other Comments
	Design	Drug	Control	Patients	Mortality	CV events	Functional Capacity	QoL	
Nondihydropyridine									
MDPIT 2899840 (219)	RCT	Diltiazem	P	Post-MI	NS	↑ In pts with LVEF<40% or pulm congestion on CXR HR 1.41	N/A	N/A	None
MDPIT 1984898 (220)	Retro	Diltiazem	P	Post-MI		↑ HF in pts with EF<40%, pulm congestion, or anterolateral Q wave MI	N/A	N/A	None
DiDi 8759075 (221)	RCT	Diltiazem	P	Idiopathic DCM NYHA II-III	NS	N/A	N/A	N/A	18% of pts did not finish study. No difference in transplant-free survival (85.2% vs. 80.4%, p=0.44).
DAVIT-II 2220572 (222)	RCT	Verapamil	P	Hospitalized for AMI	NS	N/A	N/A	N/A	HF pts had worse outcomes
Dihydropyridine									
Elkayam U *Circulation* 1990 2242521 (223)	RCT	Nifedipine	ISDN	NYHA II-III LVEF <40%	N/A	↑ HF hospitalization (nifedipine vs ISDN) ↑ worsening HF (nifedipine+ISDN vs either alone)	NS	N/A	None
Felodipine UK Study Group 7786657	RCT	Felodipine	P	NYHA II-III LVEF ≤40% 76% ICM	N/A	↑ worsening HF	NS	N/A	None

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(224)									
V-HeFT III 9264493 (225)	RCT	Felodipine	P	NYHA II-III LVEF ≤45% 55% ICM	NS	NS	NS	NS	More edema AE with felodipine. Not powered to study mortality.
PRAISE-2* 15921795 (226)	RCT	Amlodipine	P	NICM NYHA III-IV LVEF<30%	NS	NS	N/A	N/A	None
Amlodipine Exercise Trial 10689266 (227)	RCT	Amlodipine	P	NYHA II-IV LVEF ≤35% 53% ICM	N/A	N/A	NS	NS	None

AE indicates adverse event; AMI, acute myocardial infarction; CV, cardiovascular; CXR, chest x-ray; DAVIT-II, Danish Verapamil Infarction Trial II; DCM, dilated cardiomyopathy; DiDi, Diltiazem in Dilated Cardiomyopathy Trial; EF, ejection fraction; HF, heart failure; HR, hazard ratio; ICM, ischemic cardiomyopathy; ISDN, isosorbide dinitrate; LVEF, left ventricular ejection fraction; MDPIT, Multicenter Diltiazem Postinfarction Trial; MI, myocardial infarction; NICM, nonischemic cardiomyopathy; N/A, not applicable; NS, no statistically significant difference; NYHA, New York Heart Association; P, placebo; PRAISE-II, second Prospective Randomized Amlodipine Survival Evaluation; pts, patients; QoL, quality of life; RCT, randomized control trial; Retro, retrospective analysis; UK, United Kingdom; and V-HeFT, Vasodilator-Heart Failure Trial.

Data Supplement 26. NSAIDs Use in HF (Section 7.3.2.9.4)

Cohort Populations	Study				Results		Other Comments
	Design	Experimental (n)	Control (n)	Patients	Mortality	CV events	
Netherlands PHARMO 9605782 (228)	Obs	NSAID plus Diuretics	Diuretics alone	Age ≥55 y	N/A	↑ HF hospitalization aRR 1.8	Data presented in pt-y
New South Whales 10737277 (229)	Case-controlled cohort	HF admission (365)	Non-HF admission (658)	Mean age 76 y	N/A	↑ HF admission with non-ASA NSAID use OR 2.1 ↑1st HF admission in pts with h/o heart disease and NSAID use vs no h/o heart disease and NSAID use	None
Rotterdam Study 11822918 (230)	Cohort	No history of HF admission (7277)	None	Age ≥55 y FS>30%	N/A	↑ HF readmission during concurrent use of NSAID aRR 9.9	None
Ontario Drug Benefit Program 15172772 (231)	Retro Cohort	Rofecoxib (14,583) Celecoxib (18,908) Non-selective NSAID (5,391)	No NSAID (100,000)	Age ≥66 y 12% IHD	N/A	↑ HF hospitalization relative to non-NSAID users Rofecoxib aRR 1.8 NS NSAID aRR 1.4	No increased risk seen with celecoxib relative to non-NSAID users
Quebec 15947399 (232)	Retro Cohort	Rofecoxib (869) Non-selective NSAID (280)	Celecoxib (717)	Age ≥66 y Index HF admission	↑ NS NSAID HR 1.54 Rofecoxib HR 1.44	↑Recurrent HF ER visit or hospitalization NS NSAID HR 1.21 (0.92-1.6) Rofecoxib HR 1.17 (0.96-1.42)	Combined endpoint significant risk with NS NSAID and rofecoxib

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Danish National Patient Registry 19171810 (233)	Retro Cohort	Rofecoxib (6116) Celecoxib (5734) Ibuprofen (16875) Diclofenac (9377) Naproxen(2176) Other NSAID (11488)	No NSAID (70738)	Age ≥30 y Index HF admission 13% h/o MI	↑ Rofecoxib HR 1.7 Celecoxib HR 1.75 Ibuprofen HR 1.31 Diclofenac HR 2.08 Naproxen HR 1.22 Other HR 1.28	↑HF hospitalization Rofecoxib HR 1.4 Celecoxib HR 1.24 Ibuprofen HR 1.16 Diclofenac HR 1.35 Naproxen HR 1.18 Other NSAID HR 1.27	Increased risk with higher doses of NSAIDs for all types

aRR indicates adjusted relative risk; ASA, aspirin; ER, emergency room; FS, fractional shortening; HF, heart failure; h/o, history of; IHD, HR, hazard ratio; ischemic heart disease; MI, myocardial infarction; N/A, not applicable; NS, not statistically significant; NSAID, non-selective nonsteroidal anti-inflammatory drug; Obs, observational study; OR, odds ratio; pt-y, patient years; and Retro, retrospective analysis.

Data Supplement 27. Thiazolidinediones in HF (Section 7.3.2.9.5)

Cohort /Trial	Study				Results	
	Design	Experimental (n)	Control (n)	Patients	Mortality	CV events
Pharmetrics Integrated Outcomes Database 14578227 (234)	Retro Cohort	TZD (5441)	No TZD (28,103)	No HF Age >18 y DM II oral hypoglycemic agent	N/A	↑ incidence of HF TZD HR 1.7
PROactive 16214598 (235)	RCT	Pioglitazone (2065)	Placebo (2633)	NYHA I HF Age 35-75 y DM II Macrovascular disease	NS	↓ Composite all-cause mortality, non-fatal MI, and CVA HR 0.84 95% CI 0.72-0.98; p=0.27 ↑ HF events 11% Pioglitazone vs 8% placebo, P<0.0001
Dargie HJ *JACC* 2007 17448371 (236)	RCT	Rosiglitazone (110)	Placebo (114)	NYHA I-II HF LVEF ≤45% DM II oral hypoglycemic agent	NS	N.S.
Lipscombe LL *JAMA* 2007 18073359 (237)	Retro Cohort	TZD	Other oral hypoglycemic	Age ≥ 66 y DMII oral hypoglycemic agent	↑ RR 1.29 95% CI 1.02-1.62; p=0.03	↑ HF adjusted RR 1.60 95% CI 1.21-2.10; p<.001 ↑ AMI RR 1.40 95% CI, 1.05-1.86; p=.02
RECORD 19501900, 20118174 (238,239)	RCT	Rosiglitazone add-on (2220)	MET and SU (2227)	No HF DMII oral MET or SU	NS	↑ HF HR 2.1 95% CI 1.35-3.27, p=0.001 ↔ AMI HR 1.14 95% CI 0.8-1.63, p=0.47

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Giles TD *Congestive Heart Failure* 2010 20557330 (240)	RCT	Pioglitazone (151)	Glyburide (149)	NYHA I Mild cardiac disease DM II	NS	NS exercise capacity, HbA1c

AMI, acute myocardial infarction; CVA, cerebral vascular accident; DM II, type 2 diabetes mellitus; HbA1c, hemoglobin A1c; HF, heart failure; HR, hazard ratio; LVEF, left ventricular ejection fraction; MET, metformin; MI, myocardial infarction; N/A, not applicable; NS, no statistically significant difference; NYHA, New York Heart Association; PROactive, Prospective pioglitazone Clinical Trial In Macrovascular Events;RCT, randomized control trial; RECORD, Rosiglitazone evaluated for cardiovascular outcomes in oral agent combination therapy for type 2 diabetes; Retro, retrospective analysis; RR, relative risk; SU, sulfonylurea; and TZD, thiazolidinediones.

Data Supplement 28. Device-Based Management (Section 7.3.4)

Study Name, Author, Year	Aim of Study	Study Type	Study Size	Patient Population	Endpoints		Statistical Analysis (Results)	Study Limitations
					Primary Endpoint	*Secondary Endpoint*		
COMPASS, Bourge et al. 2008 JACC 18342224 (241)	Determine impact of clinician knowing continuous ambulatory right heart pressures	Single blind RCT	274	Class III-IV with hospitalization/6 mo, all EF	HF events	HF hospitalization (post hoc)	Failed primary, with 21% reduction (p=0.33). HF hospilization 36% reduction (HR: 0.64: p=0.03)	Both groups high clinical contact (0.95/wk). No protocol for response to information.
COMPASS –Diastolic HF, substudy. Zile, 2008 J Cardiac Fail 19041044 (242)	Determine impact of clinician knowing continuous ambulatory right heart pressures	RCT	70	Class III-IV, EF ≥50%	HF events	N/A	20% reduction (p=0.66). HF hopsitlization 29% reduction (p=0.43)	Both groups high clinical contact (0.95/wk). No protocol for response to information. Small subgroup.
REDUCE-HF Adamson,Congestive Heart Failure 2011 21906250 (243)	Determine impact of clinician knowing and acting on home pressures	Single blind RCT	400 of 1200 (target)	Class II/III	HF events	N/A	No trend for benefit	Trial stopped for anticipated lead problems
SENSE-HF Conraads 2011 Eur J Echo 21362703 (244)	Determine predictive value of impedance changes	Observational, Doubleblinded Phase I, unblinded Phase II	501	N/A	Predictive value of impendance changes	N/A	PPV for HF hosp increased from 4.7 to 38% during study	N/A
FAST Abraham 2011 Cong H Fail 21449992 (245)	Compare impedance Changes to daily weights for monitoring	RCT (Pts and study team blinded to impedance data)	156	Class III-IV With ICD or CRT, LVEF ≤35%	Number of threshold changes associated with HF event within 30 d	N/A	Greater sensitivity for impedance than daily weights: 76% vs 23% (p=0.001) Unexplained change rate 1.9 vs 4.3/pt-y. 1 in 7 impedance changes associated with	Weight changes defined as 3 lbs/1 d or 5 lbs in 3 d. Unknown relationship of weight changes to therapy change

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							event (p=0.0001)	
CHAMPION Abraham Lancet 2011 21315441 (246)	Determine impact of PAP information from wireless monitor	Single blind RCT	550	Class III HF and hospitalized in past y	HF hospitilizations	AUC 6 mo PAP, % admitted DAOH, MLHF	39% reduction in HF hospitalizations (HR: 0.7; p=0.0001), More reduction in PAP (p=0.008), Lower % pts with HF hospitalizations (HR: 0.7; p=0.02), DAOH, (p=0.02), Better MLHF (p=0.02)	7 procedure-related SAEs
CHAMPION EF ≥40% 21315441 (246)	Determine impact of PAP information from wireless monitor	Single blind RCT	119	Class III HF and hospitalized in past y	HF hospitilizations	N/A	HF hosp reduced from 0.33 to 0.16 (p=0.0001)	Subgroup small, same trend
HOMEOSTASIS Ritzema, Circulation 2011 20176990 (247)	Feasibility study of daily LAP monitoring to inform pt-directed therapy	Open-label Registry, uncontrolled	40	Class III-IV; hospitalized in past y all EF	N/A	N/A	LAP declined 17.6 to 14.8 (p=0.0003); % over 15 declined 67% (p=0.001) Beta blocker/ACE-I doses increased 40/37% (p=0.001) Loop doses decreased 27% (p=0.15)	Pilot observational, no controls. key concepts: physiology reduce diuretics. Pt responsibility
DOT-HF trial, 21931078 [5816 /id}	Determine impact of knowing impedance information	Single blind RCT	N/A	N/A	N/A	N/A	Monitoring increased hospilizations, clinic visits, No decrease in mortality	N/A

AUC, area under the curve; CHAMPION, CardioMEMS Heart Sensor Allows Monitoring of Pressure to Improve Outcomes in NYHA Class III Heart Failure Patients; COMPASS-HF, Chronicle Offers Management to Patients with Advanced Signs and Symptoms of Heart Failure; CRT, cardiac resynchronization therapy; DOT-HF, Diagnostic Outcome Trial in Heart Failure; EF, ejection fraction; FAST, Fluid Accumulation Status Trial; HF, heart failure; HOMEOSTASIS; Hemodynamically Guided Home Self-Therapy in Severe Heart Failure Patients; ICD; implantable cardioverter-defibrillator; LAP, left atrial pressure; lbs, pounds; LVEF, left ventricular ejection fraction; MLHF, Minnesota Living with Heart Failure Questionnaire; N/A, not applicable; PAP, pulmonary artery pressure; PPV, positive predictive value; pt, patient; pt-y, patient years; RCT, randomized control trial; REDUCE-HF, Reducing Decompensation Events Utilizing Intracardiac Pressures in Patients With Chronic Heart Failure; SAE, serious adverse event; SENSE-HF, Sensitivity of the InSync Sentry feature for the Prediction of Heart Failure.

Data Supplement 29. CRT (Section 7.3.4.2)

Study Name, Author, Year	Aim of Study	Study Type	Patient Population - N (total) n (experimental) n (control)	Follow-Up (mo)	Baseline Treatment	NYHA Class	EF (%)	QRS duration (ms)	Exclusion Criteria	QRS Subgroups by duration (ms)	Composite Endpoint (for QRS subgroups)	Results
COMPANION N Engl J Med 2004;350:2140-50. 15152059 (248)	Aim of trial was to compare optimal pharmacologic therapy plus CRT with a pacemaker, optimal pharmacologic therapy plus CRT	RCT	1520; 617; medical therapy*: 308; pacemaker-defibrillator: 595	16.2 (CRT), 11.9 (medical)	ACE-Is, beta blockers, and spironolactone	3 or 4	≤ 35	≥ 120	• non- randomized • no-CRT control group • enabled ICD implantation only in one study arm only • cross-over study design • did not report the clinical outcomes of	120-147 (n 324); 148-*168 (n 314); >168 (n 287)	All cause mortality or hospitalizations	CRT with a pacemaker decreased the risk of the primary end point (HR: 0.81; p=0.014), CRT with a pacemaker–defibrillator decreased the risk of the primary endpoint (HR: 0.80; p=0.01)

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	with a pacemaker–defibrillator, and optimal pharmacologic therapy alone in a population with advanced HF and intraventricular conduction delays.								interest • reported clinical outcomes without any relation to specific limited QRS ranges			Risk of the combined endpoint of death from or hospitalization for HFwas reduced by 34% in the pacemaker group (p<0.002) and by 40 % in the pacemaker–defibrillator group (p<0.001 for the comparison with the pharmacologic-therapy group). Pacemaker reduced the risk of the secondary endpoint of death from any cause by 24% (p=0.059), and a pacemaker–defibrillator reduced the risk by 36% (p=0.003).
CARE-HF N Engl J Med 2005;352:1539-49. 15753115 (249)	To analyze the effects of cardiac resynchronization on the risk of complications and death among pts who were receiving standard medical therapy for moderate or severe HF and cardiac dyssynchrony.	RCT	813; 409; medical therapy*: 404	29.4	ACE-Is, beta-blockers, and spironolactone	3 or 4	≤35	≥120	• not randomized • lacked non-CRT control group • enabled ICD implantation only in one study arm • had cross-over study design • did not report the clinical outcomes of interest such • reported clinical outcomes without any relation to specific limited QRS ranges.	120-159 (n 290); >159 (n 505)	All cause mortality or hospitalizations for major CV event including HF hospitalization	Primary endpoint was reached by 159 pts in the cardiac-resynchronization group, as compared with 224 pts in the medical-therapy group (39 % vs. 55%; HR: 0.63; 95 % CI: 0.51-0.77; p<0.001). There were 82 deaths in the cardiac-resynchronization group, as compared with 120 in the medical-therapy group (20% vs. 30%; HR: 0.64; 95 %CI: 0.48-0.85; p<0.002). As compared with medical therapy, cardiac resynchronization reduced the interventricular mechanical delay, the end-systolic volume index, and the area of the mitral regurgitant jet; increased the LVEF; and improved symptoms and the QoL (p<0.01 for all comparisons).

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REVERSE 19038680 (223)	To determine the effects of CRT in NYHA functional class II HF and NYHA functional class I (ACC/AHA stage C) pts with previous HF symptoms.	RCT	610; 419; CRT-off : 191	12	ACE-Is, beta blockers, and spironolactone	1 or 2	≤40	≥120	• not randomized • lacked non-CRT control group • enabled ICD implantation only in one study arm • had cross-over study design • did not report the clinical outcomes of interest such • reported clinical outcomes without any relation to specific limited QRS ranges.	120-151 (n 303); >151 (n 307)	All cause mortality or HF hospitalization or worsened HF resulting in cross-over or drop-out worsened NYHA class or moderately or markedly worsened HF symptoms	The HF clinical composite response endpoint, which compared only the percent worsened, indicated 16% worsened in CRT-ON compared with 21% in CRT-OFF (p =0.10). Pts assigned to CRT-ON experienced a greater improvement in LV end-systolic volume index (-18.4 + 29.5 ml/m2 vs. -1.3 +23.4 ml/m2, p < 0.0001) and other measures of LV remodeling. Time-to-first HF hospitalization was significantly delayed in CRT-ON (HR: 0.47; p=0.03).
MADIT-CRT 19723701 (250)	Aim of trial was to determine whether CRT with biventricular pacing would reduce the risk of death or HF events in pts with mild cardiac symptoms, a reduced EF, and a wide QRS complex.	RCT	1800 1089 medical therapy*: 731	28.8	ACE-Is, beta-blockers, and spironolactone	1 or 2	≤30	≥130	• not randomized • lacked non-CRT control group • enabled ICD implantation only in one study arm • had cross-over study design • did not report the clinical outcomes of interest such • reported clinical outcomes without any relation to specific limited QRS ranges.	130-149 (n 645); >149 (n 1175)	All cause mortality or HF event (HF hospitalization or outpatient intravenous diuretic therapy)	Primary end point occurred in 17.2% of the CRT–ICD group and in 25.3% of the ICD-only group. CRT–ICD group HR: 0.66; 95% CI: 0.52-0.84; p=0.001. The benefit did not differ significantly between pts with ischemic cardiomyopathy and those with nonischemic cardiomyopathy. CRT superiority was driven by a 41% reduction in the risk of HF events evident primarily in a prespecified subgroup of pts with a QRS duration ≥150 msec. CRT was associated with a significant reduction in LV volumes and improvement in the EF. There was no significant difference between the two groups in the overall risk of death, with a 3% annual mortality rate in each treatment group. SAEs were infrequent in the 2 groups.

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RAFT 21073365 (251)	Aim of trial was to evaluate whether adding CRT to an ICD and optimal medical therapy might reduce mortality and morbidity among such pts.	RCT	1800; 894; No CRT: 904	40	ACE, beta-blockers, and spironolactone	2 or 3	≤30	≥120	• not randomized • lacked non-CRT control group • enabled ICD implantation only in one study arm • had cross-over study design • did not report the clinical outcomes of interest such • reported clinical outcomes without any relation to specific limited QRS ranges.	120-149 (n 627); >149 (n 1036)	All casue mortality or HF hospitalization	Primary outcome occurred in 33.2% in the ICD–CRT group and 40.3% in the ICD group; ICD–CRT group HR: 0.75; 95% CI: 0.64-0.87; p<0.001. In the ICD–CRT group, 186 pts died, as compared with 236 in the ICD group (HR: 0.75; 95% CI: 0.62-0.91; p=0.003), and 174 pts were hospitalized for HF, as compared with 236 in the ICD group (HR: 0.68; 95% CI: 0.56-0.83; p<0.001). 30 d after device implantation, AEs had occurred in 124 pts in the ICD-CRT group, as compared with 58 in the ICD group (p<0.001).
PROSPECT Circulation. 2008;117: 2608-2616. 18458170 (252)	Aim of trial was to evaluate selected, predefined baseline echocardiographic parameters for their ability to predict clinical and echocardiographic response to CRT.	prospecti ve, multicent er, nonrand omized study (observat ional)	498-enrolled; 467-implanted; Not applicable	6	Medical therapy, unless contraindicated, was to include an ACE-I or ARB for at least 1 mo before enrollment and a beta blocker started at least 3 mo before and unchanged for at least 1 mo before enrollment	3 or 4	≤35	≥130	N/A	N/A	12 echocardiograp hic parameters of dyssynchrony, based on both conventional and tissue Doppler-based methods, were evaluated after site training in acquisition methods and blinded core laboratory analysis.	Clinical composite score was improved in 69% of 426 pts, whereas LV end-systolic volume decreased ≥15% in 56% of 286 pts with paired data. The ability of the 12 echo parameters to predict clinical composite score response varied widely, with sensitivity ranging from 6%- 74% and specificity ranging from 35%- 91%; for predicting LVESV response, sensitivity ranged from 9%-77% and specificity from 31%-93%. For all the parameters, the area under the ROC curve for positive clinical or volume response to CRT was ≤0.62. There was large variability in the analysis of the dyssynchrony parameters.
CONNECT J Am Coll Cardiol 2011;57:1181 –9	To determine if wireless remote monitoring with automatic clinician alerts reduces the	multicent er, prospecti ve, randomiz	1,997 REMOTE ARM: 1014 All automatic clinician alerts	15	N/A	Inclusion criteria: 1) being able and willing to replace	N/A	N/A	permanent AF chronic warfarin therapy previous ICD, CRT device, or pacemaker age <18 y	N/A	N/A	The median time from clinical event to clinical decision per pt was reduced from 22 d in the in-office arm to 4.6 d in the remote arm (p<0.001). The health care

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21255955 (252)	time from a clinical event to a clinical decision in response to arrhythmias, CV disease progression, and device issues compared to pts receiving standard in-office care. A secondary objective was to compare the rates of CV health care utilization between pts in the remote and in-office arms.	ed evaluation	were enabled for pts in the remote arm. Audible pt alerts were disabled with the exception of those related to lead and device integrity. IN-OFFICE ARM: 983 Only audible pt alerts associated with lead and device integrity were enabled for pts in the in-office arm because they are nominal settings and considered standard of care			regularly scheduled in-office follow-ups with remote followups; and 2) being able to attend all required follow-up visits. No HF as well as NYHA 1-4 were included in study			having a life expectancy <15 mo			utilization data revealed a decrease in mean length of stay per CV hospitalization visit from 4.0 d in the in-office arm to 3.3 d in the remote arm (p=0.002).
SMART AV Circulation. 2010;122:2660-2668 21098426 (253)	Aim of trial was to compare 3 alternative techniques and to assess the hypotheses that systematic AV delay optimization with echocardiography and/or the SD algorithm is superior to a fixed nominal AV delay as demonstrated by improved LV geometry after 6 mo and that programming according to SD is noninferior to using	randomized, multicenter, double-blinded, 3-armed trial	1014; 332 SD; 323-Echo; 325 Fixed nominal AV delay	6	Diuretics, beta blockers, and angiotensin-converting enzyme inhibitors or angiotensin receptor blockers,	3 or 4	≤35%,	≥120	• Complete heart block, or who otherwise are unable to tolerate pacing at VVI-40-RV for up to 14 d • Previously received CRT • Upgrade of a pacemaker or ICD and unable to tolerate pacing at VVI-40-RV for up to 14 d • Heart transplant during the course of the study • Cardiac surgeries or procedures planned during the study • Have or are likely to receive a tricuspid valve prosthesis (mechanical right valve)	N/A	The primary endpoint was LV end-systolic volume. Secondary endpoints included NYHA class, QoL score, 6-min walk distance, LV end-diastolic volume, and LVEF.	The medians (quartiles 1 and 3) for change in LV end-systolic volume at 6 mo for the SmartDelay, echocardiography, and fixed arms were 21 mL (45 and 6 mL), 19 mL (45 and 6 mL), and 15 mL (41 and 6 mL), respectively. No difference in improvement in left ventricular end-systolic volume at 6 months was observed between the SmartDelay and echocardiography arms (p=0.52) or the SmartDelay and fixed arms (p=0.66). Secondary end points, including structural (LV end-diastolic volume and LVEF) and functional (6-min walk, QoL, and NYHA classification) measures, were not significantly different between arms.

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	echocardiography-determined AV delay optimization.								• Neuromuscular, orthopedic, or other noncardiac condition that prevents normal, unsupported walking • Pregnant or planning to become pregnant • Enrolled in another investigational study or registry that would directly impact the current study			

*diuretics, ACEIs, beta-blockers, and spironolactone

ACEI indicates angiotensin-converting-enzyme inhibitor; ARB, angiotensin receptor blocker; AV, atrioventricular;CARE-HF, Cardiac resynchronization in heart failure; COMPANION, comparisons of medical therapy, pacing, and defibrillation in heart failure; CONNECT, Clinical Evaluation of Remote Notification to Reduce Time to Clinical Decision; CRT, cardiac resynchronization therapy; EF, Ejection Fraction; HCU; Health Care Utilization; HF, heart failure; HM, home monitoring; ICD, implantable cardioverter defibrillator; LVES left ventricular end-systolic; LVESV, left ventricular end-systolic volume; MADIT-CRT, multicenter automatic defibrillator implantation trial-cardiac resynchronization therapy; N/A, not applicable; NYHA, New York Heart Association; PROSPECT, Predictors of Response to CRT; Pt, patient; REVERSE, resynchronization reverses remodeling in systolic left ventricular dysfunction, RAFT, resynchronation-defibrillation for ambulatoryheart failure trial; ROC curve, receiver-operating characteristics curve; SMART-AV, SmartDelay Determined AV Optimization: A Comparison to Other AV Delay Methods Used in Cardiac Resynchronization Therapy; SD, SmartDelay™, TRUST, The Lumos-T Safely Reduces Routine Office Device Follow-Up;

Data Supplement 30. Therapies, Important Considerations (Section 7.4.2)

Study Name, Author, Yearl	Aim of Study	Study Type	Study Size	Patient Population		Results	P Values & 95% CI:	OR: HR: RR:	Study Limitations
				Inclusion Criteria	*Exclusion Criteria*				
Hemodynamic Assessment of Hospitalized Patient									
Binanay C, Califf RM, Hasselblad V et al. Evaluation study of congestive HF and pulmonary artery catheterization effectiveness: the ESCAPE trial. JAMA 2005 October 5;294(13):1625-33. 16204662 (254)	To determine whether PAC use is safe and improves clinical outcomes in pts hospitalized with severe symptomatic and recurrent HF	RCT	433	Pts with severe symptomatic HF despite recommended therapies. 1) hospitalization for HF within the past y; (2) urgent visit to the ED; or (3) treatment during the preceding mo with >160 mg of furosemide daily (or equivalent). LVEF ≤30%, SBP ≤125mmHg, and at least 1 sign and 1 symptom of congestion.	Exclusion criteria to minimize confounding comorbidities or urgent crossover included Crlevel >3.5 mg/dL (309.4 µmol/ L), or prior use of dobutamine or dopamine >3 µg/kg/min, or any prior use of milrinone during the current hospitalization.	PAC did not significantly affect the primary endpoint of d alive and out of the hospital during the first 6 mo (133 d vs 135 d; HR: 1.00; 95% CI: 0.82-1.21; p=.99), mortality (43 pts [10%] vs 38 pts [9%]; OR: 1.26; 95% CI: 0.78-2.03; p=.35), or the number of d hospitalized (8.7 vs 8.3; HR: 1.04; 95% CI: 0.86-1.27; p=.67). HR: 1.0 d alive outside hospital, HR: 1.26 for mortality (p=0.35), h 1.04 For d hospitalized.19 % mortality at 6 mo (dead at 180 d= 43 in PAC, 38 in CAG). Annualized mortality 36%. Inhospital AEs were more common among pts in the PAC group (47 [21.9%] vs 25 [11.5%]; p=.04). There were no deaths related to PAC use, and no difference for in-hospital plus 30-d mortality (10 [4.7%] vs 11 [5.0%]; OR: 0.97; 95% CI, 0.38-2.22; p=.97	p=0.35	1.26	Use of inotropes, variability between centers, generalizabiity of stringent hemodynamic targets ,individualized targets not applied

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Drazner MH, Hellkamp AS, Leier CV et al. Value of clinician assessment of hemodynamics in advanced HF: the ESCAPE trial. Circ Heart Fail 2008 September;1(3):170-7. 19675681 (31)	To determine whether estimated hemodynamics from history and physical examination reflect invasive measurements and predict outcomes in advanced HF	Retrospective analysis	194	Compared H&P estimates of filling pressures and cardiac index with invasive measurements in 194 pts in the ESCAPE trial. H&P estimates were compared with 6-mo outcomes in 388 pts enrolled in ESCAPE.	Crlevel >3.5 mg/dL (309.4 µmol/L), or prior use of dobutamine or dopamine >3 µg/kg/min, or any prior use of milrinone during the current hospitalization.	RAP was <8 mm Hg in 82% of pts with RAP estimated from jugular veins as <8 mm Hg, and was >12 mm Hg in 70% of pts when estimated as >12 mm Hg. From the H&P, only estimated RAP ≥12 mm Hg (OR: 4.6; p<0.001) and orthopnea ≥2 pillows (OR: 3.6; p<0.05) were associated with PCWP ≥30 mm Hg. Estimated cardiac index did not reliably reflect measured cardiac index (p=0.09), but "cold" versus "warm" profile was associated with lower median measured cardiac index (1.75 vs. 2.0 L/min/m(2); p=0.004). In Cox regression analysis, discharge "cold" or "wet" profile conveyed a 50% increased risk of death or rehospitalization. In advanced HF, the presence of orthopnea and elevated jugular venous pressure are useful to detect elevated PCWP, and a global assessment of inadequate perfusion ("cold" profile) is useful to detect reduced cardiac index. Hemodynamic profiles estimated from the discharge H&P identify pts at increased risk of early events.	p<0.05	Estimated RAP OR: 4.6, orthopnea OR: 3.6	posthoc, small sample
Shah MR, Hasselblad V, Stevenson LW et al. Impact of the pulmonary artery catheter in critically ill pts: meta-analysis of randomized clinical trials. *JAMA* 2005 October 5;294(13):1664-70 16204666 (255)	To estimate the impact of the PAC device in critically ill pts.	Meta-analysis	5051	MEDLINE (1985-2005), the Cochrane Controlled Trials Registry (1988-2005), the National Institutes of Health ClinicalTrials.gov database, and the US Food and Drug Administration Web site for RCTs in which pts were randomly assigned to PAC or no PAC were searched. Results from the ESCAPE trial of pts with severe HF were also included. Search terms included pulmonary artery catheter, right heart catheter, catheter, and Swan-Ganz.	N/A	HR for mortality 1.04. In critically ill pts, use of the PAC neither increased overall mortality or d in hospital nor conferred benefit. Despite almost 20 y of RCTs, a clear strategy leading to improved survival with the PAC has not been devised. The neutrality of the PAC for clinical outcomes may result from the absence of effective evidence-based treatments to use in combination with PAC information across the spectrum of critically ill pts.Use of the PAC was associated with a higher use of inotropes (OR: 1.58; 95% CI: 1.19-2.12; p= .002) and IV vasodilators (OR: 2.35; 95% CI: 1.75-3.15; p<.001).	p=0.53	The combined OR for mortality was 1.04 (95% CI: 0.90-1.20; p=.59). The difference in the mean number of d hospitalized for PAC minus the mean for no PAC was 0.11 (95% CI: -0.51-0.74; p=.73).	heterogenity of studies

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Allen LA, Rogers JG, Warnica JW et al. High mortality without ESCAPE: the registry of HF pts receiving pulmonary artery catheters without randomization. J Card Fail 2008 October;14(8):661-9 18926438 (256)	To characterize pts enrolled in ESCAPE Registry	Registry	439	ESCAPE sites enrolled 439 pts receiving PAC without randomization in a prospective registry. Baseline characteristics, pertinent trial exclusion criteria, reasons for PAC use, hemodynamics, and complications were collected. Survival was determined from the National Death Index and the Alberta Registry. Much sicker pts than ESCAPE	N/A	Registry pts had longer hospitalization (13 vs 6 d, p<.001) and higher 6-mo mortality (34% vs 20%, p<.001) than trial pts. On average, registry pts had lower blood pressure, worse renal function, less neurohormonal antagonist therapy, and higher use of IV inotropes compared with trial pts. Although clinical assessment anticipated less volume overload and greater hypoperfusion among the registry population, measured filling pressures were similarly elevated in the registry and trial pts, whereas measured perfusion was slightly higher among registry pts. 6 mo mortality 34%	p<0.05	N/A	N/A
Positive Pressure Ventilation Studies									
Gray A, Goodacre S, Newby DE, Masson M, Sampson F, Nicholl J. Noninvasive ventilation in acute cardiogenic pulmonary edema. *N Engl J Med* 2008 July 10;359(2):142-51. 18614781 (257)	Noninvasive ventilation CPAP or NIPPV appears to be of benefit in the immediate treatment of pts with acute cardiogenic pulmonary edema and may reduce mortality. To determine whether noninvasive ventilation reduces mortality and whether there are important differences in outcome associated with the method of treatment (CPAP or NIPPV).	RCT	1069 (trandomized to standard oxygen therapy, (n-367) versus CPAP (5 to 15 cm of water) (n=346) OR NIPPV (inspiratory pressure, 8 to 20 cm of water; expiratory pressure, 4 to 10 cm of water) (n=356).	Age > 16 y, clinical diagnosis of acute cardiogenic PE, PE on chest radiograph, respiratory rate >20 breaths/min, and arterial hydrogen ion concentration >45 nmol/L (pH <7.35).	N/A	There was no significant difference in 7-d mortality between pts receiving standard oxygen therapy (9.8%) and those undergoing noninvasive ventilation (9.5%, P=0.87). There was no significant difference in the combined endpoint of death or intubation within 7 d between the two groups of pts undergoing noninvasive ventilation (11.7% for CPAP and 11.1% for NIPPV, p=0.81). In pts with acute cardiogenic PE, noninvasive ventilation induces a more rapid improvement in respiratory distress and metabolic disturbance than does standard oxygen therapy but has no effect on short-term mortality. CPAP or NIPPV MAY be considered as adjunctive therapy in pts with severe acute cardiogenic pulmonary oedema in the presence of severe respiratory distress or when there is a failure to improve with pharmacological therapy.As compared with standard oxygen therapy, noninvasive ventilation was associated with greater mean improvements at 1 h after the beginning of treatment in pt-reported dyspnea (treatment difference, 0.7 on a visual-analogue scale ranging from 1 to 10; 95% CI: 0.2-1.3; p=0.008), heart rate (treatment difference, 4 beats/min; 95% CI; 1-6; p=0.004), acidosis (treatment difference, pH 0.03; 95% CI: 0.02-0.04; p<0.001), and hypercapnia (treatment difference, 0.7 kPa [5.2 mm Hg]; 95% CI: 0.4-0.9; p<0.001).	p=0.87	N/A	N/A

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Masip J, Roque M, Sanchez B, Fernandez R, Subirana M, Exposito JA. Noninvasive ventilation in acute cardiogenic pulmonary edema: systematic review and meta-analysis. *JAMA* 2005 December 28;294(24):3124-30 16380593 (258)	To systematically review and quantitatively synthesize the short-term effect of noninvasive ventilation on major clinical outcomes.	Meta-analysis	15 trials comparing noninvasive ventilation to to convention al oxygen	Acute PE, relevant randomized controlled trials and systematic reviews published from 1988-2005. Included trials were all parallel studies comparing noninvasive ventilation to conventional oxygen therapy in pts with acute PE. Comparisons of different techniques, either CPAP or bilevel NIPSV, were also included	N/A	Overall, noninvasive ventilation significantly reduced the mortality rate by nearly 45% compared with conventional therapy (RR: 0.55; 95% CI; 0.40-0.78; p=.72 for heterogeneity). The results were significant for CPAP (RR: 0.53; 95% CI: 0.35-0.81; p= .44 for heterogeneity) but not for NIPSV (RR: 0.60; 95% CI, 0.34-1.05; p=.76 for heterogeneity), although there were fewer studies in the latter. Both modalities showed a significant decrease in the "need to intubate" rate compared with conventional therapy: CPAP (RR: 0.40; 95% CI: 0.27-0.58; p=.21 for heterogeneity), NIPSV (RR, 0.48; 95% CI: 0.30-0.76; p=.24 for heterogeneity), and together (RR: 0.43; 95% CI: 0.32-0.57; p=.20 for heterogeneity). There were no differences in intubation or mortality rates in the analysis of studies comparing CPAP and NIPSV.Noninvasive ventilation reduces the need for intubation and mortality in pts with acute cardiogenic pulmonary edema. Although the level of evidence is higher for CPAP, there are no significant differences in clinical outcomes when comparing CPAP vs. NIPSV.	p<0.05 for mortality reduction with noninvasive ventilation	RR: 0.55	N/A
Severe Cardiogenic Shock Patient, Role of PVADs to Bridge to Recovery or Bridge/Transplant									
Kar B, Gregoric ID, Basra SS, Idelchik GM, Loyalka P. The percutaneous ventricular assist device in severe refractory cardiogenic shock. *J Am Coll Cardiol* 2011 February 8;57(6):688-696. 20950980 (259)	To determine the efficacy and safety of the pVAD in pts in SRCS despite intra-aortic balloon pump and/or high-dose vasopressor support.	Prospective Cohort	117	Cardiogenic shock pts with a SBP of 90 mm Hg, a cardiac index of 2.0 l/(min·m2) and evidence of end-organ failure despite IABP/pressor support.A total of 117 pts with SRCS implanted with TandemHeart pVAD were studied, of whom 56 pts (47.9%) underwent active cardiopulmonary resuscitation immediately before or at the time of implantation	N/A	56 (47.9%) of the 117 pts (41 of 80 [51.2%] with ICM; 15 of 37 [40.5%] with NICM) were undergoing CPR during pVAD placement.The average time from CPR onset to TandemHeart implantation was 65.6+/-41.3 min. 80 pts had ischemic and 37 pts had nonischemic cardiomyopathy. The average duration of support was 5.8 d. After implantation, the cardiac index improved from median 0.52 (interquartile range [IQR]: 0.8) l/(min·m2) to 3.0 (IQR: 0.9) l/(min·m2) (p=0.001). The SBP and mixed venous oxygen saturation increased from 75 (IQR: 15) mm Hg to 100 (IQR: 15)mm Hg (p 0.001) and 49 (IQR: 11.5) to 69.3 (IQR: 10) (p 0.001), respectively. The PCWP, lactic acid level, and Crlevel decreased, respectively, from 31.53 to 10.2 mm Hg to 17.29 10.82 mm Hg (p 0.001), 24.5 (IQR: 74.25) mg/dl to 11 (IQR: 92) mg/dl (p=0.001), and 1.5 (IQR: 0.95) mg/dl to 1.2 (IQR: 0.9) mg/dl (p 0.009). The mortality rates at 30 d and 6 mo were 40.2% and 45.3%, respectively.	N/A	N/A	N/A

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Thiele H, Lauer B, Hambrecht R, Boudriot E, Cohen HA, Schuler G. Reversal of cardiogenic shock by percutaneous left atrial-to-femoral arterial bypass assistance. *Circulation* 2001 December 11;104(24):2917-2922. 11739306 (260)	To characterize whether PVAD may offer effective treatment for cardiogenic shock	Case Series	18	VADs were implanted in 18 consecutive pts who had cardiogenic shock after MI.	N/A	Mean duration of cardiac assistance was 4+/-3 d. Mean flow of the VAD was 3.2+/-0.6 L/min. Before support, cardiac index was 1.7+/-0.3 L/min per m(2) and improved to 2.4+/-0.6 L/min per m(2) (p<0.001). Mean blood pressure increased from 63+/-8 mm Hg to 80+/-9 mm Hg (p<0.001). PCWP, central venous pressure, and pulmonary artery pressure were reduced from 21+/-4, 13+/-4, and 31+/-8 mm Hg to 14+/-4, 9+/-3, and 23+/-6 mm Hg (all p<0.001), respectively. Overall 30-d mortality rate was 44%.	N/A	N/A	N/A
Idelchik GM, Simpson L, Civitello AB, Loyalka P, Gregoric ID, Delgado R, III, Kar B. Use of the percutaneous left ventricular assist device in pts with severe refractory cardiogenic shock as a bridge to long-term left ventricular assist device implantation. *J Heart Lung Transplant* 2008 January;27(1):106-111. 18187095 (261)	To evaluate the efficacy of a PVAD as a bridge to LVAD implantation in pts in cardiogenic shock refractory to IABP and pressor support.	Case Series	18	18 pts in SRCS received a PVAD as a bridge to LVAD placement or orthotopic heart transplantation. 6 pts had ischemic cardiomyopathy, and 12 had nonischemic cardiomyopathy. At the time of PVAD placement, 17 were receiving IABP support, and 10 were undergoing cardiopulmonary resuscitation	N/A	The mean duration of PVAD support was 4.2 +/- 2.5 d. During this time, the cardiac index improved from 0.86 +/- 0.66 to 2.50 +/- 0.93 liters/min/m2 (p < 0.001), SBP improved from 72 +/- 11 to 98 +/- 15 mm Hg (p=0.001), and systemic mixed venous oxygenation improved from 37 +/- 7 to 62 +/- 6 mm Hg (p < 0.001). We terminated life support in 4 of the 18 pts before LVAD placement; 14 were successfully bridged to LVAD or heart transplantation. The mortality rate was 27% at 30 d and 33% at 6 mo. There were no PVAD-associated deaths. CONCLUSION: In pts with terminal hemodynamic collapse, PVAD support is an effective bridging therapy to LVAD and appears to be a viable alternative to other invasive methods of support	N/A	N/A	N/A
Cheng JM, den Uil CA, Hoeks SE, van der EM, Jewbali LS, van Domburg RT, Serruys PW. Percutaneous left ventricular assist devices vs. intra-aortic balloon pump counterpulsation for treatment of cardiogenic shock: a meta-analysis of controlled trials. *Eur Heart J* 2009 September;30(17):2102-2108 19617601 (262)	A meta-analysis of controlled trials of PVADs vs. intra-aortic balloon pump counterpulsation for treatment of cardiogenic shock for 30 d mortality	Meta-Analysis		2 trials evaluated the TandemHeart and a recent trial used the Impella device	N/A	After device implantation, percutaneous LVAD pts had higher CI (MD 0.35 L/min/m(2), 95% CI: 0.09-0.61), higher MAP (MD 12.8 mmHg, 95% CI: 3.6-22.0), and lower PCWP (MD -5.3 mm Hg, 95% CI: -9.4 to -1.2) compared with IABP pts. Similar 30-day mortality (RR: 1.06; 95% CI: 0.68-1.66) was observed using percutaneous LVAD compared with IABP. No significant difference was observed in incidence of leg ischaemia (RR: 2.59, 95% CI: 0.75-8.97) in percutaneous LVAD pts compared with IABP pts. Bleeding (RR: 2.35, 95% CI: 1.40-3.93) was significantly more observed in TandemHeart pts compared with pts treated with IABP.Although percutaneous LVAD provides superior haemodynamic support in pts with cardiogenic shock compared with IABP, the use of these more powerful devices did not improve early survival. These results do not yet support percutaneous LVAD as first-choice approach in	N/A	N/A	N/A

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						the mechanical management of cardiogenic shock.			
Seyfarth M, Sibbing D, Bauer I, Frohlich G, Bott-Flugel L, Byrne R, Dirschinger J, Kastrati A, Schomig A. A randomized clinical trial to evaluate the safety and efficacy of a percutaneous left ventricular assist device versus intra-aortic balloon pumping for treatment of cardiogenic shock caused by myocardial infarction. *J Am Coll Cardiol* 2008 November 4;52(19):1584-1588 19007597 (263)	To test whether the LVAD Impella LP2.5 provides superior hemodynamic support compared with the IABP.	RCT (ISAR-SHOCK Trial)	26	Cardiogenic shock post AMI	N/A	In 25 pts the allocated device (n=13 IABP, n=12 Impella LP2.5) could be safely placed. 1 pt died before implantation. The CI after 30 min of support was significantly increased in pts with the Impella LP2.5 compared with pts with IABP (Impella: DeltaCI = 0.49 +/- 0.46 l/min/m(2); IABP: DeltaCI = 0.11 +/- 0.31 l/min/m(2); p = 0.02). Overall 30-d mortality was 46% in both groups.percutaneously placed LVAD (Impella LP 2.5) is feasible and safe, and provides superior hemodynamic support compared with standard treatment using an IABP.	mortality p= ns	N/A	N/A
Burkhoff D, Cohen H, Brunckhorst C, O'Neill WW. A randomized multicenter clinical study to evaluate the safety and efficacy of the TandemHeart percutaneous ventricular assist device versus conventional therapy with intraaortic balloon pumping for treatment of cardiogenic shock. *Am Heart J* 2006	To test the hypothesis that the TandemHeart (PVAD) provides superior hemodynamic support compared with IABP.	RCT (Tandem vs IABP)	42	Pts from 12 centers presenting within 24 h of developing cardiogenic shock.randomized to treatment with IABP (n=14) or TandemHeart PVAD (n=19). Thirty pts (71%) had persistent shock despite having an IABP in place at the time of study enrollment.	N/A	Cardiogenic shock was due to MI in 70% of the pts and decompensated HF in most of the remaining pts. The mean duration of support was 2.5 d. Compared with IABP, the TandemHeart PVAD achieved significantly greater increases in cardiac index and mean arterial blood pressure and significantly greater decreases in PCWP. Overall 30-dsurvival and SAEs were not significantly different between the 2 groups	Mortality =ns	N/A	N/A

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September;152(3):469-8 16923414 (264)									

AMI indicates, acute myocardial infarction; CPAP, continuous positive airway pressure; IABP, intra-aortic balloon pump; LVAD, left ventricular assist device; N/A, not applicable; NIPPV, noninvasive intermittent positive-pressure ventilation; NIPSV noninvasive pressure support ventilation; PAC, pulmonary artery catheter; PCWP, pulmonary capillary wedge pressure; PE, pulmonary edema; PVAD; percutaneous ventricular assist device; RAP, right atrial pressure; SBP, systolic blood pressure; SRCS, severe refractory cardiogenic shock;

Data Supplement 31. Sildenafil (Section Section 7.4.2)

Study Name, Author, Year	Aim of study	Study Type	Study Size	Etiology	Patient Population		Severity	Endpoints	Trial Duration (Years)	Absolute Benefit	P Values & 95% CI:
				Ischemic/Non-Ischemic	*Inclusion Criteria*	*Exclusion Criteria*	*Severity of HF Symptoms*	*Primary Endpoint*			
PDE5 Inhibition With Sildenafil Improves LVDF, Cardiac Geometry, and Clinical Status in Pts With Stable Systolic HF, Guazzi M, 2011 21036891 (265)	To test the effects of PDE5 inhibition (sildenafil) on LVEF, LVDF, cardiac geometry, and clinical status	RCT	45	50% ICM	NYHA II-III HF with clinical stable conditions defined as no changes in HF regimens or hospitalization since 6 mo before study entry; Negative exercise stress test before study; FEV1/FVC >70%; LVEF <40% Presence of LV diastolic dysfunction determined by Doppler analysis with documen- tation of a mitral inflow early (E) velocity to mitral annulus early velocity (E') >10.	Unable to complete a maximal exercise test; Resting SBP <110 mm Hg; therapy with nitrate preparations; LVADs; History of sildenafil intolerance; significant lung or valvular diseases, neuromuscular disorders, or peripheral vascular disease; Diabetic pt	100% NYHA II-III (42% NYHA II/58% NYHA III) peak VO2 12.8 ml/min/kg VE/VCO2 slope 35.3	LV diastolic function, chamber dimensions, and mass	1 y	D Mitral E/A @ 1yr placebo 0 vs SIL -0.19 D IVRT @ 1y placebo +1.4 vs SIL -6.0 D E/E', lat @ 1yr placebo -0.8 vs. SIL +3.7 D LVEDD (mm)@ 1y placebo +0.9 vs SIL -4.2d D LVMI @ 1yr placebo no change, SIL decrease (value not provided) D peak VO2 @ 1y placebo +0.3 vs SIL +2.7 D VE/VCO2 Slope at 1y placebo +0.4 vs SIL -6.0; D QOL (breathlessness, fatige, emotional function)	p<0.01 for all parameters

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PDE5A inhibitor treatment of persistent pulmonary hypertension after mechanical circulatory support, Tedford RJ, 2008 19808294 (266)	To test the hypothesis that when PH persists after adequate LV unloading via recent LVAD therapy, phosphodiesterase type 5A inhibition would decrease PH in this population.	Open label clinical trial	58	56% ICM	Advanced LV dysfunction, treatment with LVAD implantation, and persistent PH (defined by a PVR >3 Wood Units 7 to 14 d after LVAD implantation) despite normalization of their PCWP to a value <15 mmHg were consented for and received treatment with sildenafil in an attempt to reduce PVR before cardiac transplantation	Combined LVAD and RVAD; Pts receiving chronic inotrope therapy	N/A	The primary endpoint of the 12 to 15 wk change in PVR andcontractility index (dP/dtmax/IP)	Enrollment 1999-2007; 12-15 wk of sildenafil treatment/follow-up;	Lowering of PVR from 5.87±1.93 to 2.96±0.92 Wood Units (mm Hg/ L/min;) after 2- 4 wk of sildenafil therapy; vs. no change in PVR in LVAD only group. Also, marked improvement in RV systolic and diastolic function, as measured by RV contractility index (dP/dtmax/IP; 8.69±1.78 to 13.1±3.3) in LVAD + sildenafil group	Change in PVR, p<0.001 for LVAD +sildenafil group Change in RV contractility index for LVAD+sildefanil group, p<0.0001
Sildenafil Improves Exercise Capacity and Quality of Life in Pts With Systolic HF and Secondary Pulmonary Hypertension, Lewis GD, 2007 17785618 (267)	To test the hypothesis that sildenafil, an effective therapy for pulmonary arterial hypertension, would lower pulmonary vascular resistance and improve exercise capacity in pts with HF complicated by PH	RCT	34	50% ICM	≥18 y of age, LVEF<40%,NYHA II-IV chronic HF despite standard HF therapies Pts were required to have secondary PH as defined by a mean pulmonary arterial pressure >25 mm Hg	Pts with a noncardiac limitation to exercise, provocable ischemia, hemodynamic instability, or ongoing nitrate therapy were excluded. Additional exclusion criteria included concentric LV hypertrophy, critical aortic stenosis, or long-term use of medications that inhibit cytochrome P450 3A4.	100% NYHA II-IV (53% NYHA II / 38% NYHA III/ 9% NYHA IV) peak VO2 11.1 ml/kg/min	No predefinied primary endpoints; measured exercise capacity, invasive hemodyanamic parameters, QoL, and biomarkers	12 wk trial	Peak VO2 increased from 12.2±0.7 to 13.9±1.0 mL/ kg/min in the sildenafil group (p=0.02) and did not change in the placebo group. Change in peak VO2 from baseline among pts treated with sildenafil (1.8±0.7 mL/· kg/min) was greater than the change in the placebo group (-0.27 mL/kg/min; p=0.02). Sildenafil treated pts had improvement in RVEF at rest and with exercise; control group had no improvement in RVEF. Mean MLHFQ score decreased (reflecting improvement) by 13±5 and 16±5 at wk 6 and 12, respectively, among pts receiving sildenafil (p=0.007) and did not change in pts receiving placebo.	

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Long-term use of sildenafil in the therapeutic management of HF, Guazzi M, 2007 18036451 (268)	To test the functional exercise capacity and endothelial function in a cohort of CHF pts treated with chronic type 5 phosphodiesterase (PDE5) inhibitor	RCT	46	ICM 46%	Stable NHYA II-III CHF ; negative exercise stress test prior to study; FEV1/FVC >70%; LVEF <45%, determined by echocardiography.	Unable to complete a maximal exercise test; SBP >140 or <110 mm Hg; DM; Therapy with nitrate; History of sildenafil intolerance; Significant lung or valvular diseases, neuromuscular disorders, AF, claudication, or peripheral vascular disease	NYHA II-III peak VO2 15 ml/min/kg	No predefined primary endpoint; assessments (at 3 and 6 mo) of endothelial function by brachial artery FMD, cardiopulmonary exercise testing, ergoreflex response, and QOL questionnaire (CHF) were performed	6 mo f/u	In the sildenafil group only, at 3 and 6 mo, systolic PAP decreased from 33.7 to 25.2 mm Hg and then 23.9 mm Hg, ergoreflex effect on ventilation decreased from 6.9 to 2.3/min and 1.9L/min, VE/VCO2 decreased from 35.5 to 32.1 and 29.8, and breathlessness (score) from 23.6 to 16.6 and 17.2, FMD increased from 8.5% to 13.4% and 14.2%, peak VO2 from 14.8 to 18.5 ml/min/kg and 18.7 ml/min/kg, and ratio of VO2 to work rate changes from 7.7 to 9.3 and 10.	p<0.01 for all changes
Sildenafil Effects on Exercise, Neurohormonal Activation, and Erectile Dysfunction in Congestive HF, Bocci EA, 2002 12196335 (94)	To investigate the acute effects of sildenafil on exercise, neurohormonal activation, and clinical status of CHF pts with (ED). To evaluate the efficacy and safety of sildenafil for ED treatment in a 1-mo follow-up	RCT	23	ICM 22%	CHF outpatients who were referred for ED treatment (ED was defined as the inability to achieve or maintain an erection sufficient to permit satisfactory sexual intercourse); History of ED x ≥ 4 mo, present interest in sex and in a stable relationship; Concomitant new symptoms of CHF, worsening of HF clinical status, or a change in specific medication for CHF; All pts were in stable clinical condition without required changes in treatment within the last 3 mo.	ED considered secondary to causes other than CHF; Previous therapy for ED, Recent use of PDE inhibitors; Severe systemic disease, visual disturbances, psychiatric or psychological disorder; UA or MI within the previous 3 mo;, Syncope, Angina, HR <55 bpm, high-risk arrhythmias, new atrial tachycardia/fibrillation/flutter or uncontrolled high ventricular response, new or high degree of AV block HCM Valvular disease, Symptomatic hypotension or SBP <85 mm Hg Unstable CHF, low systemic	NYHA II-IV	First phase: 6MWT, exercise test Second phase: efficacy of sildenafil in ED was evaluated by the 15 questions of the IIEF; adverse side effects	1 mo	Peak VO2 (ml/kg/min) placebo 16.6±3.4 vs sildenafil 17.7±3.4 Ve/VCO2 slope placebo 33+8 sildenafil 31±5	p=0.025 p=0.027

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						perfusion, or venous or pulmonary congestion.					

6MWT indicates 6 minute walk test; AF, atrial fibrillation; AV, atrioventricular; CHF, congestive heart failure; D, Doppler; DM, diabetes mellitus; ED, erectile dysfunction; EF, ejection fraction; FEV, forced expiratory volume; FMD, flow-mediated dilatation; FVC, forced vital capacity; HCM, hypertrophic cardiomyopathy; HF, heart failure; HR, heart rate; ICM, ischemic cardiomyopathy; IIEF, International Index of Erectile Function; LVAD, left ventricular assist device; LVDF, left ventricular diastolic function; LVEDD, left ventricular end diastolic diameter; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; Mitral E/A, Mitral early-to-late velocity; MLHFQ, Minnesota Living with Heart Failure Questionaire; MI, myocardial infarction; NYHA, New York Heart Association; PAP, pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; PDE5A, phosphodiesterase type 5A; PH, pulmonary hypertension; pts, patients; PVR; pulmonary vascular resistance; QoL, quality of life; RCT, randomized control trial; RVAD, right ventricular assist device; RVEF, right ventricular ejection fraction; SBP, systolic blood pressure; SIL, sildenafil; UA, unstable angina; VE/VCO2, ventilation efficiency ventilation to CO_2 production slope; VO2, oxygen volume.

Data Supplement 32. Inotropes (Section 7.4.4)

Study Name, Author, Year	Aim of study	Study Type	Background Therapy	Study Size	Etiology	Patient Population		Severity		Endpoints		Mortality		Trial Duration (Years)	Absolute Benefit or Major Finding	Statistical Analysis (Results)	Study Limitations	Complications/Adverse Events
			Pretrial standard treatment	*N (Total) n (Experiment) n (Control)*	*Ischemic/ Non-Ischemic*	*Inclusion Criteria*	*Exclusion Criteria*	*Severity of HF Symptoms*	*Study Entry Sverity Criteria*	*Primary Endpoint*	*Secondary Endpoint*	*Annualized Mortality*	*1st Year Mortality*					

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Intermittent 6-mo low-dose dobutamine infusion in severe HF: DICE Multicenter Trial, Oliva F, 1999 10426835 (269)	To reduce hospitalizations for worsening of CHF by administering intermittent low-dose dobutamine (2.5-5mg/kg/min for 48-72hrs/wk)	RCT	ACEI 82% Digoxin 95% Furosemide 95% Nitrates 63% Amiodarone 39%	38; 19 (dobutamine); 19 (control)	47% ICM	Age >18 y; NYHA III-IV CHF ; Hospitalized for CHF and administration of IV inotropes in the 6 mo before the evaluation; ≥ 48 h of clinical stability on oral therapy. CI ≤2.2 L/min/m2 6. LVEF ≤ 30%.	History of documented malignant arrhythmias without an automatic defibrillator in place; Neoplastic or systemic disease affecting short-term prognosis UA, angiographically documented effective coronary stenosis Surgically curable valvular heart disease	100% NYHA III-IV 6MWTD 298m	NYHA III-IV symptoms, CI ≤2.2L/min/m2	Reduction of hospitalizations for worsening of CHF	Changes in NYHA functional class, 6-min walking test, and mortality rates.	N/A	N/A	Enrollment 18 mo (7/94-12/95); 6 mo f/u	No benefit in hospitalization, functional status, or mortality rate.	Time to first CV death or hospitalization for any cause, p=0.91	Small sample size	N/A
Levosimendan Infusion versus Dobutamine Study (LIDO), Follath F, 2002 12133653 (270)	To compared the effects of levosimendan and dobutamine on haemodynamic performance and clinical outcome in pts with low-output HF	RCT	Digoxin 75%, Diuretics 53%, ACEI 89%, bblockers 38%, oral nitrates 41%, anticoagulants 43%, Class III antiarrhthmic agents 15%, CCB 4%, antiplatelet agents 1%	203; 103 levosimendan; 100 dobutamine	48% Ischemic	Hospitalized with low-output HF, requiring haemodynamic monitor-ing and treatment with IV inotropic agent. a) deterioration of severe chronic HF despite optimum oral therapy with vasodilators and diuretics, including those awaiting cardiac transplantation; b) severe	Age <21 y Childbearing potential HF due to restrictive or hypertrophic cardiomyopathy or to uncorrected stenotic valvular disease; Chest pain at the time of randomisation; Sustained VT/VF within prior 2 wk; AVB of 2nd or 3rd degree; HR >120 bpm at rest; SBP< 85 mm Hg; Severe renal	Severity determined by invasive hemodynamic monitoring, not symptomatology	CI < 2.5 L/min/m2 Mean PCWP > 15 mm Hg	Proportion of pts with haemodynamic improvement (defined as an increase of 30% or more in CO and a decrease of 25% or more in PCWP) at 24 h.	Changes from baseline in haemo-dynamic variables other than CO and PCWP (eg, CI, stroke volume, PADP, mean RAP, BP, HR and total peri-pheral resistance) at 24 h; Changes from baseline to 24 h in HF symptoms (dyspnoea and fatigue) on a 4-grade scale (much better, slightly better, no change, worse); Proportion of pts needing IV rescue therapy with positive inotropic	N/A	N/A	Enrollment 1/97-11/98 (23mo); study drug infusion up to 24 hrs, follow up out to 180 d	The primary haemodynamic endpoint was achieved in 28% levosimendan-group pts and 15% in the dobutamine group. Secondary end point: At 180 d, 26% levosimendan group pts had died, compared with 38% in the dobutamine group	Primary endpoint: HR; 1.9; 95% CI 1.1-3.3; p=0.022; Secondary endpoint: HR 0.57; p=0.029	No placebo control Small study size No information on the duration of infusion of levosimendan needed for optimum benefit or on how often it may be repeated in pts who do not respond initially or who relapse after an initial response. Exclusion of pts with cardiogenic shock. Short-term	Angina, chest pain, or myocardia ischaemia (7% dobutamine vs 0% levosimendan, p=0.013); Arrhythmias (13% dobutamine vs 4% levosimendan, p=0.023

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						HF after cardiac surgery; or c) acute HF related to a cardiac or non-cardiac disorder of recent onset. LVEF<35% (by echo or radio-nuclide ventriculography w/in 1 mo of study enrolment) CI < 2.5 L/min/m2 Mean PCWP >15 mm Hg.	failure (SCr >450 mol/L); Hepatic failure Cardiac tamponade; ARDS; Septic shock.				drugs, vasodilators, or diuretics during the infusion of study drug; No. of d alive and out of hospital and not receiving IV drugs during the 1st mo; Time to development of worsening HF or death. Safety endpoints: a) AEs, b) laboratory safety tests (blood and urine), and c) all-cause mortality at 31 d and 180 d after randomization.						hemodynamic assessment Not powered to assess mortality	
OPTIME-CHF, Cuffe MS, 2002 11911756\ (271)	To prospectively test whether a strategy that includes short-term use of milrinone in addition to standard therapy can improve clinical outcomes of pts hospitalized with an exacerbation of chronic HF	RCT	ACEI 70%, ARB 12%, bblocker 22%, Diuretic 90%, Digoxin 73%, CCB 11% placebo v 16% milrinone ASA 46% Amiodarone 15%	949; 477 (milrinone); 472 (placebo)	ICM 51%	Age ≥18 y LVEF <40% within the past y. Known systolic chronic HF Hospitalized for exacerbation of chronic HF ≤48 h earlier.	If treating physician judged that IV inotrope was essential (eg, for shock, metabolic acidosis, or severe hypotension). Active myocardial ischemia within the past 3 mo Atrial fibrillation with poor ventricular rate control (>110/min) Sustained ventricular tachycardia or	100% NYHA II-IV 7% NYHA II 46% NYHA III 47% NYHA IV	NYHA II-IV symptoms	Total number of d hospitalized for CV causes (or d deceased) within the 60 d after randomization. Hospital d were defined as inpt d and ED visit d.	Main secondary outcome included the proportion of cases failing therapy because of AE or worsening HF 48 h after initiation of therapy. Other secondary outcomes included the proportion of pts achieving target doses of ACEI therapy and time to achieve target dose, symptoms, improvement in HF score, length of initial hospitalization, d of hospitalization	N/A	N/A	Recruitment 7/97-11/99 (29 mo); Study drug treatment for up to 72 h with 60 day follow-up period from time of randomization	No difference in primary efficacy end point Milrinone was associated with higher rate of treatment failure at 48 h due to AE (12.6% vs 2.1%)	p=0.71, d of hospitalization for CV causes within 60 d p=0.92, death or readmission within 60 d p<0.001 for treatment failure due to AE	Did not directly address pts with ADHF for whom inotropic therapy was felt to be essential (eg, low cardiac output state with tissue hypoperfusion), Not structured to assess pts for NSVT, a known adverse effect of milrinone. Inadequately powered to evaluate mortality.	Sustained hypotension, (SBP< 80 mm Hg for more than 30 min, requiring intervention); 10.7% with milrinone, 3.2% with placebo, p<0.001 Significant atrial arrhythmias during index hospitalization; 4.6% milrinone, 1.5% placebo, p=0.004

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							ventricular fibrillation. Baseline SBP< 80 mm Hg SCr level > 3.0mg/dL				for CV events from initial hospital discharge to 60 d, d of hospitalization for CV events within 30 d after randomization, all-cause hospitaliz-ation, and mortality.							
HF Etiology and Response to Milrinone in Decompensated HF (subanalysis of OPTIME-CHF), Felker GM, 2003 12651048 (272)	To assess the interaction between HF etiology and response to milrinone in decompensated HF	Post-hoc analysis	ACEI 70%, bblocker 23%, Amiodarone 15%, Digoxin 73%,	949 (total); 477 (randomized to milrinone); 242 (ICM, milrinone) ; 235 (NICM, milrinone); 243 (ICM, placebo); 229 (NICM, placebo)	485 ICM (51% of total) 464 NICM (49% of total)	Age >18 y LVEF < 40% within the past year. Known systolic chronic HF Hospitalized for exacerbation of chronic HF < 48 h earlier.	If treating physician judged that IV inotrope was essential (eg, for shock, metabolic acidosis, or severe hypotension). Active myocardial ischemia within the past 3 mo Atrial fibrillation with poor ventricular rate control (>110/min) Sustained ventricular tachycardia or ventricular fibrillation. Baseline SBP< 80 mm Hg SCr level > 3.0mg/dL	100% NYHA II-IV 7% NYHA II 46% NYHA III 47% NYHA IV	NYHA II-IV symptoms	D hospitalized for CV causes or death within 60 d after randomization	Main secondary outcome included the proportion of cases failing therapy because of adverse events or worsening HF 48 hr after initiation of therapy. Other secondary outcomes included the proportion of pts achieving target doses of ACEI therapy and time to achieve target dose, symptoms, improvement in HF score, length of initial hospitalization, d of hospitalization for CV events from initial hospital discharge to 60 d, d of hospitalization for CV events within 30 d after randomization, all-cause hospitaliz-ation, and mortality.	N/A	N/A	Recruitment 7/97-11/99 (29mo); Study drug treatment for up to 72 h with 60 d f/u period from time of randomization	D hospitalized for CV causes or death w/in 60d after randomization was 13.0±14.2d for ischemic HF pts, 11.7±13.9d for nonischemic HF pts 60 d mortality was greater for ischemic (11.6%) than for non-ischemic pts (7.5%). Combined end point of death or rehospitalization at 60 d was 38.7% in ischemic pts and 31.5% in the nonischemic pts. More pts with nonischemic HF were able to reach target dosing of ACEI at hospital discharge (49%) compared w/ischemic HF pts (36%). Treatment failure while on the study drug was similar btwn the 2 groups (14.2% for ischemic vs. 15.2% for nonischemic pts).	Primary endpoint, p=0.2 60d mortality, P=0.03 Combined endpoint, p=0,02 Able to reach target ACEI dose, p=0.001 Treatment failure on study drug, p=0.7	Retrospective study; No data collected on the level of care that pts received (i.e., ICU vs. monitored bed), which potentially could have affected the results of study; Imbalanced follow up btwn etiologic groups (4 pts in ischemic group vs. 8 pts in nonischemic group lost to follow-up)	In pts with ischemic HF, milrinone tended to be associated with prolonged hospitalization and higher mortality. Composite of death or rehospitalization at 60 d was 42% for ischemic pts treated with milrinone and 36% for those treated w/placebo (p=0.01 for etiology-treatment interaction). In-hospital mortality for milrinone-treated pts with ischemic HF was 5.0% vs. 1.6% for placebo (p =0.04 for etiology-treatment interaction), and 60 d mortality was 13.3% for milrinone vs 10% for placebo (p= 0.21 for etiology-treatment interaction).

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															Baseline QoL data did not differ between the 2groups.			
Inhospital mortality in pts with acute decompensated HF requiring intravenous vasoactive medications: an analysis from the Acute Decompensated HF National Registry (ADHERE), Abraham WR, JACC 2005 15992636 (273)	To compare in hospital mortality in pts with acute decompensated HF receiving treatment with 1 of 4 vasoactive meds (NTG, nesiritide, milrinone, dobutamine)	Registry	Beta blocker 50% ACEI 43% ARB 12% Spironolactone 15% (varied amongst subgroups 7-24%)	65180; 6549 (NTG); 5220 ; (nesiritide) ; 2021 (milrinone) ; 4226 (dobutamine) ; 49950 (all others)	56% ICM	admitted to a participating acute care hospital and given a discharge diagnosis of HF	HF is not the principal focus of diagnosis or treatment during the admission or if their medical record cannot be accessed for administrative reasons	NYHA IV 45% (dyspneic at rest)	N/A	Inhospital mortality	Total LOS, ICU LOS	N/A	Inpatient mortality Milrinone: 12.3% Dobutamine: 13.9% NTG: 4.7% Nesiritide: 7.1% All others: 3.1%	10/01-7/03	Worse inpatient mortality and longer LOS with IV inotropes compared to IV vasodilators or neither.	Inhospital Mortality Dob vs Milrinone: OR: 1.24; 95% CI: 1.03-1.55: p=0.027 NTG vs Dobutamine: OR: 0.46; 95% CI:.37-0.57, p<0.005 NTG vs Milrinone: OR: 0.69; 95% CI:0.53-0.89; p<0.005	Observational analysis Retrospective analysis Clinician judgement for medical management /choice of IV med Non-randomized Differences in clinical severity between subgroups	N/A
Survival of Pts with Acute HF in Need of Intravenous Inotropic Support (SURVIVE), Mebazaa A, 2007 17473298 (274)	To assess the effect of a short-term IV infusion of levosimendan or dobutamine on long-term survival	RCT	Beta blocker 51% ACEI/ARB 69% Aldosterone antagonist 53% IV diuretics 79% IV nitrates 37% IV dopamine 6%	1327; 664 (levosimendan); 663 (dobutamine)	76%	Age ≥18 y Hospitalized with ADHF. LVEF ≤30% within prior 12 mo Required IV inotropic support, as evidenced by an insufficient response to IV diuretics and/or vasodilators, and ≥1 of the following at screening: (a) dyspnea at rest or mechanical ventilation for ADHF; (b) oliguria	Severe ventricular outflow obstruction; SBP persistently <85 mm Hg HR persistently ≥ 130 bpm; IV inotrope use during the index hospitalization (except dopamine 2 µg/kg/min or digitalis); History of torsade de pointes; SCr> 5.1 mg/dL (450 µmol/L) or on dialysis.	86% NYHA IV	Low-output ADHF	All-cause mortality during the 180 d following randomization.	All-cause mortality during 31 d, change in BNP level from baseline to 24 h; No. of d alive and out of the hospital during the 180 d; change in pt assessed dyspnea at 24 h; Pt assessed global assessment at 24 h; CV mortality through 180 d.	N/A	N/A	Enrollment 3/03-12/04 (22mo), study drug infusion for minimum of 24 h and total duration of unknown period, follow up at 180 d,	During the 180 d after study drug infusion, there were 173 deaths (26%) in the levosimendan group and 185 deaths in the dobutamine group (28%). No difference in secondary endpoints, except in mean change in BNP at 24 h from baseline (-631 levosimendan vs -397 dobutamine)	Primary endpoint: HR 0.91; 95% CI 0.74-1.13; p=0.40 Secondary endpoint (DBNP): p<0.001	Short duration of treatment. Detail of duration of infusion and dose of study drug used is not provided. No information regarding clinical symptomatology at baseline.	Hypokalemia (9.4% levosimedan vs 5.9% dobutamine, p=0.02) AF (9.1% levosimedan vs 6.1% dobutamine, p=0.05), Headache (8.3% levosimedan vs 4.7% dobutamine, p=0.01) PVCs (6.1% levosimedan vs 3.6% dobutamine, p=0.05) Agitation (1.1% levosimedan vs 0% dobutamine, p=0.02)

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						not as a result of hypovolemia ; or (c) PCWP ≥18 mm Hg and/or CI < 2.2 L/min/m2.												
Enoximone in Intravenous Inotrope-Dependent Subjects Study (EMOTE), Feldman AM, 2007 17967591 (275)	To determine whether low-dose oral enoximone could wean pts with ultra-advanced HF (UA-HF) from intravenous (IV) inotropic support	RCT	Diuretic 88%, ACEI 62%, ARB 18%, bblocker 40%, digoxin 70%, antiarrhythmic 37%, ICD 42%, Milrinone 62%, dobutamine 36%, both dobutamine and milrinone 3% Continuous IV inotrope 74%	201; 101 (enoximone); 100 (placebo)	61% ICM	Age > 18 y NYHA III or IV CHF Ongoing need for ≥ 5 d of continuous IV inotropic therapy or the need for intermittent IV inotropic therapy with either dobutamine (≥2 µg/kg/min) or milrinone (≥0.125 µg/kg/min) for ≥6 h at a frequency of ≥1x/ wk, and for ≥4 wk. LVEF of ≤25% by radionuclide ventriculography or ≤30% by 2-dimensional echocardiography Cardiac dilatation (LVEDD ≥2.7 cm/m2 or ≥5.4 cm as measured by 2-dimensional echocardiography within 26 wk	Received a positive inotropic agent other than digoxin, dobutamine, or milrinone within 12 h of randomization Trough digoxin levels were >1.0 ng/mL. ICD firing within 90 d.	100% NYHA III-IV (56% NYHA IV)	Low-output ADHF	Ability to wean subjects from IV inotropic support. Assessed using the prespecified CMH test, adjusted for cardiomyopathy etiology. The primary efficacy variable was also assessed as a protocol and statistical analysis plan–prespecified secondary end point using time-to-event (Kaplan-Meier) curves and the log-rank statistic, over the entire 182 d study period.	Time to reinitiation of IV inotrope Total number of d on IV inotrope Total number of hospitalization d for all cause, CV, and CV/vascular events; Measurements of symptoms (SAS scale, NYHA) and pt well-being (Visual Analog Scale, global assessments) at 4 and 26 wk.	N/A	N/A	Enrollment 7/00-2/04 (44mo); 26 wk trial	30 d after weaning, 51% of placebo pts and 61.4% enoximone pts were alive and free of IV inotropic therapy At 60 d, the wean rate was 30% in placebo group and 46.5% in enoximone group Kaplan-Meier curves demonstrated a trend toward a decrease in the time to death or reinitiation of IV inotropic therapy over the 182-day study period and a reduction at 60 d and 90 d after weaning in the enoximone group.	Unadjusted primary end point p=0.14, adjusted for etiology p= 0.17 60d wean rate unadjusted p=0.016 Time to death/ reinitiation of IV inotrope: 95% CI 0.55-1.04 Reduction at 60d, 95% CI 0.43-0.89, p = 0.009 Reduction @ 90d, 95% CI 0.49-0.97, P = .031 Time to death/ reinitiation of IV inotrope: HR 0.76 Reduction @60d HR 0.62 Reduction @90d HR 0.69	Small sample size. Not designed or powered as mortality study	Exacerbation of CHF in 54% enoximone vs 52% placebo, NS Dyspnea, 5% enoximone vs 0% placebo, P<0.05

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						of the baseline visit). Ongoing and stable (>30 d) therapy with optimal and stable doses of conventional medications												
Use and impact of inotropes and vasodilator therapy in hospitalized pts with severe HF (ESCAPE), Elkayam U, Am Heart J 2007 17174645 (276)	To determine 6-mo risks of all-cause mortality and all-cause mortality plus rehospitalization associated with the use of vasodilators, inotropes, and their combination	Post-hoc analysis of RCT	ACEI 79% Diuretics 98% bBlocker 62% IV inotrope 42% IV vasodilator 28%	433; 75 (vasodilator); 133 (IV inotrope); 47 (both); 178 (neither inotrope/vasodilator)	50% ICM	Hospitalized for severe ADHF Age>18 y; Hx of HF for ≥3 mo; On ACEI and diuretics for z3 mo;. LVEF<30% in the 12 mo before randomization; SBP ≤125 mm Hg; elevated LV filling pressure as indicated by at least 1 physical sign and 1 symptom; At least 1 prior admission for ADHF during the previous 12 mo or aggressive outpatient therapy for at least the previous mo.	N/A	Mean peak VO2 10.0 mean 6MWTD 414 ft	N/A	All- cause mortality	Combined end point of all-cause mortality plus rehospitalization	N/A	6 mo mortality	N/A	Worse 6 mo outcomes (mortality and either mortality/rehospitalization) with inotropes (whether alone or with vasodilator)	6 mo mortality (adjusted), p, 95% CI Inotrope 1.10-4.15, p=0.024 Both ino & vasodilator 2.34-9.90, p<0.001 6mo mortality or rehosp (adjusted) Inotrope 1.37-2.82, p<0.001 Both ino & vasodilator 1.88-4.48, p<0.001 6 mo mortality HR adjusted Inotrope 2.14 Both inotrope and vasodilator 4.81 6 mo mortality or rehosp HR (adjusted) Inotrope 1.96 Both ino & vasodilator 2.90	Severe ADHF Conducted by HF specialists at academic medical centers Small study size Non-randomized Retrospective analysis	N/A
Prospective Randomized Milrinone Survival Evaluation (PROMISE), Packer	To determine the effect of oral milrinone on the mortality of	RCT	Nitrates 58% Antiarrhythmics 25% Digoxin level 1.5nmol/l	1088; 561 (milrinone); 527 (placebo)	54% ICM	NYHA III-IV CHF x ≥3mo LVEF ≤ 35% Medical regimen of digoxin, diuretics,	Obstructive valvular disease Active myocarditis HCM or cardiac	100% NYHA III-IV 58% NYHA III /42% NYHA IV	NYHA III-IV	All cause mortality	CV mortality, No. of hospitalizations, Addition of vasodilators for treatment of worsening hf,	N/A	N/A	Enrollment 22mo (1/89-10/90); stopped early because	Increased mortality with milrinone (30% milrinone vs 24% placebo); Log-rank test, milrinone	All-cause mortality: nominal P=0.038, 95% CI 0.01-0.61; adjusted P=0.06, CV mortality: 95% CI 0.06-0.69, nominal P=0.016; adjusted	Background medical management is outdated and suboptimal	Stopped study drug due to worsening HF, 1.8% milrinone v 0.9% placebo

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M, 1991 1944425 (277)	pts with severe chronic HF who remained symptomatic despite conventional therapy					and ACEI for ≥ 4wk	amyloid Uncorrected thyroid disease Malfunctioning artificial heart valve				Symptoms, Adverse reactions			of adverse effect of milrinone; median duration of follow-up, 6.1mo	associated with 28% increase in mortality; Log-rank test, milrinone associated with 34% increase in CV mortality	P=0.037		
Continuous intravenous dobutamine is associated with an increased risk of death in pts with advanced HF: Insights from the Flolan International Randomized Survival Trial (FIRST), O'Connor CM, 1999 10385768 (278)	To evaluate clinical characteristics and outcomes of pts with advanced HF receiving intravenous continuous dobutamine in the FIRST Trial (Flolan International Randomized Survival Trial).	Post-hoc analysis	N/A	471; 80 (dobutamine); 391 (no dobutamine)	67% Ischemic	NYHA IIIB or IV HF for ≥1 mo while receiving a regimen including a loop diuretic, digitalis glycoside, and an ACEI, unless contraindicated. LVEF <25% by a multigated angiocardiogram within 3 mo of enrollment, unless the pt was being treated with an IV inotropic agent, in which case LVEF <30% was accepted. Pts receiving IV vasoactive medications were required to have not responded to an attempt to wean from the medicines	SBP<80 mm Hg; Significant valvular stenosis; Anticipated revascularization or valvular surgery; MI within 3 mo; Uncontrolled tachyarrhythmias; Unstable or symptom-limiting angina; Requirement for a mechanical assist device to maintain life; Major change in IV vasoactive medicat-ions within 12 hr of randomization; CHF caused by uncontrolled thyroid disease, myocarditis, high output failure, or infiltrative cardio-myopathy; Significant	No dobutamine: 47% NYHA III 53% NYHA IV Dobutamine: 11% NYHA III 89% NYHA IV	NYHA IIIB-IV	Occurrence of clinical events from the FIRST trial, including worsening HF, need for mechanical assist device, resuscitation from sudden cardiac death, MI, and death	QoL meaures	N/A	N/A	N/A	The dobutamine group had a higher occurrence of first event (85.3% vs 64.5%) and a higher mortality rate (70.5% vs 37.1%) compared with the no dobutamine group. No difference in QOL between groups.	Primary endpt 1st event p=0.0006 mortality p=0.0001	Observational analysis No details provided regarding duration and dose of dobutamine	At 6 mo First event 85.3% dobutamine vs 64.5% no dobutamine , p=0.0006 Death 70.5% dobutamine vs 37.1% no dobutamine, p=0.0001

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						within 1 wk of enrollment. Ineligibility for cardiac transplant-ation and eligibility for long-term oral anticoagulation therapy were also required.	congenital heart disease with shunts, valvular or vascular obstruction; Substance or alcohol abuse w/in 1year; Moderate or severe lung disease; Other comorbid conditions likely to shorten survival; Current use of another investigational drug or device.											
Care processes and clinical outcomes of continuous outpatient support with inotropes (COSI) in pts with refractory endstage HF, Hershberger RE, J Cardiac Failure 2003 12815567 (279)	To assess the outcomes of chronic home inotropic support in Stage D HF pts	Cohort Study	ACEI/ARB 72% Dobutamine 100% Dopamine 22% Milrinone 11%	36	47% ICM	Hospitalized advanced end-stage HF pts Declined cardiac transplantation or ineligible for cardiac transplantation	N/A	N/A presumably NYHA IIIb-IV	N/A	Survival after hospital discharge	Total hospitalizations, causes for rehospitalization, cause of death	N/A	1 y mortality 94% 6 mo mortality 74%	N/A	≥2 rehospitalizations: 36% 0-1 rehospitalization: 64% 30% of rehospitalizations 2/2 worse HF Cause of death Worsening HF 80% SCD 14% Unknown 6%	N/A	Lack of QOL assessment Lack of cost evaluation Small study size Retrospective	Line infection/sepsis (15% of rehospitalizations)

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Prognosis on chronic dobutamine or milrinone infusions for stage D HF, Gorodeski EZ, Circ HF 2009 19808355 (280)	To investigate the relationship between choice of dobutamine or milrinone and mortality in inotrope-dependent stage D HF pts	Case-controlled	ASA 39% beta blocker 5% (dob) v 34% (mil) ACEI 43% ARB 5% Aldosterone blocker 52% Amiodarone 50% Furosemide 78% Other diuretic 17%	112; 56 (dobutamine); 56 (milrinone)	41% ICM	Stage D HF pts deemed inotrope dependent	N/A	N/A presumably NYHA IIIb-IV	Inotrope dependent	Survival	N/A	N/A	6 mo mortality (propensity matched) Dobutamine 60% Milrinone 54% 1yr mortality Dobutamine 69% Milrinone 63%	N/A	No difference in mortality between inotrope type (multivariate analysis)	Propensity matched mortality, log-rank p= 0.74	Retrospective analysis Single center study Small study size Lack of QOL assessment	N/A
The Studies of Oral Enoximone Therapy in Advanced HF (ESSENTIAL), Metra M, 2009 19700774 (281)	To investigate the effects of low doses of the positive inotrope enoximone on symptoms, exercise capacity, and major clinical outcomes in pts with advanced HF who were also treated with beta blockers and other guideline-recommended background therapy	RCT	ESSENTIAL-I beta blockers 83%, ACEI/ARBs 94%, Aldosterone antagonist 62% Diuretics 95%, DIgitalis glycosides 69% Warfarin 31% Amiodarone 22% ICD 21% ESSENTIAL-II bblocker 90% ACEI/ARBs 99% Aldosterone antagonist 54% Digitalis glycosides 46% Warfarin 8% Amiodarone 14% ICD 5%	ESSENTIAL-I: 904 ESSENTIAL-II: 950 enoximone ESSENTIAL-I 454 ESSENTIAL-II 472 placebo ESSENTIAL-I 450 ESSENTIAL-II 478	ESSENTIAL-I 52% ICM ESSENTIAL-II 59% ICM	Age >18 y HF caused by ischaemic or nonischaemic cardiomyopathy LVEF ≤ 30%, LVEDD > 3.2 cm/m2 or 6.0 cm; NYHA III–IV for >2 mo ≥1 hospitalization or 2 outpatient visits requiring IV diuretic or vasodilator therapy w/in 12 mo before screening; Optimal medical therapy including diuretics, beta-blockers, and ACEIs or ARBs unless intolerant or contraindicat	Acute MI in previous 90 d, CV surgery in prior 60 d, Symptomatic ventricular arrhythmias or ICD firing in prior 90 d Serum potassium <4.0 or >5.5 mEq/L, Digoxin levels >1.2 ng/mL Magnesium levels <1.0 mEq/L SCr≥ 2.0 mg/dL Serum bilirubin > 3.0 mg/dL.	91% NYHA III 8% NYHA IV 6MWT 274m (ESSENTIAL-I) 6MWT 293m (ESSENTIAL-II)	NYHA III-IV x > 2 mo	First co-primary endpoint (time to all-cause mortality or CV hospitalizations) and for safety (all-cause mortality) (ESSENTIAL-I and II, combined) Co-primary endpoint 6MWTD (ESSENTIAL-I,-II separately) Co-primary endpoint Patient Global Assessment, (ESSENTIAL-I and -II, separately)	N/A	N/A	N/A	Enrollment 2/02-5/04 (28mo); Median follow-up duration 16.6 mo	No difference in first co-primary endpoint: all-cause mortality, all-cause mortality and CV hospitalizations No difference in change in 6MWTD No difference in PGA changes	All-cause mortality, p=0.73, 95% CI: 0.80-1.17 All-cause mortality and CV hospitalizations, p=0.71, 95% CI 0.86-1.11 Change in 6MWTD, p=0.16 (ESSENTIAL-I), p=0.57 (ESSENTIAL-II) Change in PGA, p=0.79 (ESSENTIAL-I), p=0,11 (ESSENTIAL-II) All cause mortality, HR 0.97 All-cause mortality and CV hospitalizations, HR 0.98	Crude global assessment for QOL; 6MWT may not be sensitive enough to detect improvements in exercise capacity/functional status	1Worsening HF, 39% enoximone vs 39% placebo, p=0.88 Diarrhea, 12% enoximone vs 7% placebo, p=0.0001, Palpitations 8% enoximone vs 5% placebo, p=0.01

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A Prospective Sutdy of Continuous Intravenous Milrinone Therapy for Status IB Pts Awaiting Heart Transplant at Home, Brozena SC, 2003 15454175 (282)	To determine the feasibility and safety of continuous IV milrinone therapy administered at home in pts listed as Status IB for heart transplant	Cohort study	Digoxin 96.6% Loop diuretic 88.3% Warfarin 83.3% Beta-blocker 73.3% ACE-I 66.6% Statin therapy 63.3% Aspirin 63.3% Spironolactone 41.6% Amiodarone 28.3% ARB 25.0% Hydralazine/ nitrate 13.3%	60; 60 (milrinone); none	66.6% ICM	Milrinone dose ≤0.5 mg/kg/min; Stable dose of diuretic to maintain dry weight; Long-term venous access; AICD; Adequate social support system as assessed by a transplant social worker; Functional class <NYHA IV on therapy	Uncontrolled arrhythmia; SBP<80 mm Hg; Recurrent electrolyte abnormality; Infection requiring IV antibiotic; Requirement for >1 inotropic agent; Acute renal failure; Hepatic transaminases >2x normal	NYHA II-III Peak VO2 11.4 ml/kg/min	NYHA II-III	Survival to transplant	Hospitalizations, QoL measures cost	N/A	N/A	43 mo f/u	88.3% of pts underwent OHT 3.2% died before transplant 1.6% LVAD 3.2% BIVAD QoL improved (MLHFQ score decreased by -13.3±3.4 points)	QOL/MLHFQ score change from baseline, p=0.0061	Not randomized; No control; Limited cost data; Small study size	8% hospitalized for IV line infection 65% rehospitalized for ADHF during study period
Comparison of dobutamine versus milrinone therapy in hospitalized pts awaiting cardiac trnsplantation, Aranda JM, 2003 12595851 (283)	To compare clinical outcomes and costs associated with the use of dobutamine or milrinone in hospitalized pts awaiting cardiac transplanta	RCT	N/A	36; 19 (dobutamine); 17 (milrinone)	56% ICM	Age >18 y; Prior approval for cardiac transplant; Exacerbation of HF not only necessitating hospitalization but demonstrating inotropic dependency.	Any history of intolerance to either dobutamine or milrinone, Hemodynamic instability at time of random assignment requiring mechanical cardiac support (IABP or	Not presented (presumably NYHA IIIb-IV)	not presented	Hemodynamic decompensation (assessed by periodic right heart catheterization), occurrence of ventricular arrhythmias requiring increased antiarrhythmic therapy,	death, need for mechanical cardiac support, heart transplantation, and need to add or cross over to the alternative inotropic agent	N/A	N/A	Enrollment 17mo (1/99-5/00);	No difference between milrinone and dobutamine with respect to clinical outcomes or hemodynamic measures	N/A	Background medical management not included in manuscript. Data not presented for beta-blocked use in milrinone arm. Small study size No report of SAE/complic	N/A

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	tion						LVAD), Normal LV filling pressures (mean PCWP < 15 mm Hg), Development of noncardiac medical illness sufficient to remove pts from the cardiac transplant waiting list			and need for additional vasodilator or inotropic therapy (nitroprusside or dopamine).							ations from continuous inotrope (e.g. line infections, etc)	
LVAD as Destination for pts undergoing intravenous inotropic therapy: a subset analysis from REMATCH, Stevenson LW, 2004 15313942 (284)	To analyze outcomes in pts undergoing inotropic infusions at randomization for LVAD destination therapy	Post-hoc analysis	Diuretic 95% >1 Diuretic 52% bblocker 20% ACE-I 55%	91 (on inotrope at randomization); 45 (LVAD); 46 (OMM)	N/A	LVEF ≤25% NYHA IV symptoms for 60 of 90 d despite attempted therapy with ACEIs, diuretics, and digoxin. Peak VO2 ≤12-14 mL/kg/min with evidence of anaerobic metabolism, Dependence on IV inotropic agents supported by completion of a weaning failure form.	Advanced age, diabetes with end-organ damage, SCr>2.5 mg/dL for ≥90 d,	NYHA IV	Peak VO2 <14 mL/kg/min	All-cause mortality during the 180 d following randomization.	QoL at 1 y	N/A	N/A	Enrollment 5/98-7/01;	In pts undergoing inotropic therapy at randomization, 1 y survival with LVAD was 49% vs. 24% for OMM and by 2 y, 28% were alive with LVAD group compared with 11% in OMM group	p=0.0014	Did not capture inotropic dependency status in all pts. Post-hoc, subgroup analysis. Outdated LVAD model.	N/A

ACEI indicates angiotensin-converting-enzyme inhibitor; ADHF, acute decompensated heart failure; AE, adverse event; AICD, automated implantable cardioverter defibrillator; ARDS, acute respiratory distress syndrome; ASA, aspirin; AVB, atrioventricular block; BIVAD, biventricular assist device; BNP, B-type natriuretic peptide; BP, blood pressure; CCB, calcium channel blockers; CHF, congestive heart failure; CMH, Cochran-Mantel-Haenszel; CO, cardiac output; CrCl, creatinine clearance; CV, cardiovascular; ED, emergency department; F/U, follow-up; HCM, hypertrophic cardiomyopathy; HF, heart failure; HR, heart rate; IABP, intra-aortic balloon pump; ICD, implantable cardioverter defibrillator; ICM, ischemic cardiomyopathy; ICU, intensive care unit; IV, intravenous; LOS, length of stay; LVAD, left ventricular assist device; LVEDD, left ventricular end diastolic diameter; LVEF, left ventricular ejection fraction; MLHFQ, Minnesota Living with Heart Failure Questionaire; MWTD, minute walk test distance; N/A, not applicable; NSVT, non-sustained ventricular tachycardia; NTG, nitroglycerin; NYHA, New York Heart Association; OHT, orthotopic heart transplantation; OMM, optimal medical management; OPTIME_CHF, the Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure study; PADP, pulmonary artery diastolic pressure; PCWP, pulmonary capillary wedge pressure; PGA, polyglycolide; pts, patients; PVC, premature ventricular contraction; QoL, quality of life; RAP, right atrial pressure; RCT, randomized control trial; SAE, serious adverse event; SAS, specific activity scale; SBP, systolic blood pressure; SCD, sudden cardiac death; SCr, serum creatinine; UA, unstable angina; UAHF, ultra-advanced; VF, ventricular fibrillation; VT, ventricular tachycardia.

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Data Supplement 33. Inotropic Agents in HF (Section 7.4.4)

Study	Study				Results				
	Design	Drug	Support Duration	Patients	Hemo-dynamics	Functional Capacity	QoL	Hospitalization	Survival
PROMISE 1944425 (277)	RCT	M vs. P	Chronic	NYHA III-IV LVEF <35%	N/A	N/A	N/A	N/A	↓
Aranda JM 2003* 12595851 (283)	RCT	M, D	Chronic	Txplt-C	M ≅ D	N/A	N/A	N/A	M ≅ D
FIRST 10385768 (278)	RCT (post-hoc)	D vs. none	Chronic	NYHA III-IV LVEF <25-30% Txplt-IE	N/A	N/A	N/A	N/A	↓
COSI 12815567 (279)	Cohort	M, D	Chronic	Hospitalized Txplt-IE	N/A	N/A	NS	N/A	6% @ 1 y 26% @ 6 mo
Brozena SC 2004* 15454175 (282)	Cohort	M	Chronic	Txplt-C (1B)	N/A	N/A	↑	N/A	N/A
Gorodeski EZ 2009 19808355 (280)	Case Control	M vs. D	Chronic	stage D ino-dpdt	N/A	N/A	N/A	65%	M ≅ D 31%-37% @ 1 y
OPTIME-CHF 11911756 (271)	RCT	M vs. P	Short-term (<72 h)	Hospitalized for HF, NYHA II-IV, LVEF <40%	N/A	N/A	NS	NS	NS
ESCAPE 17174645 (276)	RCT (post-hoc)	M,D	Short-term	Hospitalized for HF, LVEF <30%	N/A	N/A	N/A	↑	↓
ADHERE 15992636 (273)	Retro Obs	M, D	Short-term	Hospitalized for HF	N/A	N/A	N/A	↑ LOS	↓ in-hosp

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DICE 10426835 (269)	RCT	D	Intermittent (48-72 h/wk x 6 mo)	Hospitalized NYHA III-IV LVEF <30%, prior h/o ino	N/A	NS	N/A	NS	NS

*Study limited to patients awaiting cardiac transplantation.
1B indicates UNOS Status 1B; ADHERE, Acute Decompensated HF National Registry; ADHF, acute decompensated heart failure; COSI, continuous outpatient support with inotropes; D, dobutamine; DICE, Dobutamina nell'Insufficienza Cardiaca Estrema; ESCAPE, Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness; FIRST, Flolan International Randomized Survival Trial; in-hosp, in-hospital mortality; ino-dpdt, inotrope-dependent; LOS, length of stay; LVEF, left ventricular ejection fraction; M, milrinone; N/A, not applicable; NS, no significant benefit; NYHA, New York Heart Association; OPTIME-CHF, the Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure study; P, placebo; Post-hoc (RCT), post-hoc analysis of an RCT; PROMISE, PROspective Imaging Study for Evaluation of Chest Pain; RCT, randomized, controlled clinical trial; RetroObs, retrospective observational study; QoL, quality of life; Txplt-C, cardiac transplantation candidate; and Txplt-IE, transplantation ineligible.

Data Supplement 34. Mechanical Circulatory Support (Section 7.4.5)

Study	Study					Evidence of Benefit				Adverse Events	Comments
	Design	Device (n)	Control (n)	Patients	DOS	Survival	HD Support	Function	QoL		
REMATCH 11794191, 15313942 (284,285)	RCT	HM XVE (68)	OMM (61)	Txplt-IE 74% ICM 71% ino	P	+	N/A	N/A	+	Bleeding Neuro SVT Sepsis	1 y Mortality RR 0.52 No benefit at 2 y
INTrEPID 17707178 (286)	pNRCT	NovaCor (37)	OMM (18)	Txplt-IE 38% ICM 100% ino	P	+	N/A	N/A	N/A	Neuro Infxn	1 y Survival 27% (NovaCor) vs. 11% (OMM)
HMII-DT 19920051 (287)	RCT	HMII (134)	HM XVE (66)	Txplt-IE 67% ICM	P	+	N/A	+ +[21]	+ +[21]	PumpRplt Sepsis RespFail RenalFail RV Fail Rehosp	2 y Survival 58% (HMII) vs. 24% (HM XVE) Lower AE rate with HMII
HMII-BTT 17761592, 19608028 (288,289)	Cohort	HMII (281)	*None*	Txplt-C 43% ICM	T	+	N/A	+[8, 21]	+[8, 21]	Bleeding RespFail Infxn (NV) VT Sepsis RV Fail	Mortality 12mo: 27%; 18mo: 28%
EuroHMII 19616963 (290)	Registry	HMII (411)	*None*	21% Txplt-IE 73% Txplt-C 70% ICM 100% ino	21% P 79% T	+	N/A	N/A	N/A	MOF Infxn RV Fail Bleeding VT Neuro	1 y mortality 28.5%
INTERMACS 21545946 (291,292)	pNRCT	HMII (169)	HM XVE (135) Th-IVAD (34)	Txplt-C 80-89% ino	T	+	N/A	N/A	N/A	Infxn Bleeding	1 y Survival 85% (HMII) vs 70% (comp)

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											Lower rate of infxns with HMII
Grady K, *Ann Thorac Surg* 2004 15063260 (293)	pNRCT	HM XVE (78)	*None*	Txplt-C	T		N/A	+/-	+/-	n/a	N/A
ADVANCE	pNRCT	Heart Ware (137)	INTER MACS (499)	Txplt-C 41% ICM 82% ino	T	+	N/A	+	+	Infxn Bleeding Neuro	HeartWare is NON-INFERIOR to control Lower AE rate for bleeding, infxn
Elhenawy A, *J Card Surg* 2011 21883463 (294)	ObsRS	BTC (22) NovaCor 6, HMXVE 11, HMII 5	BTT (15) NovaCor 1, HMXVE 7, HMII 7,	41% Txplt-C 59% Txplt-IE 27% ICM	T	+	N/A	N/A	N/A	Infxn/ Sepsis RVAD MOF	No difference in BTC vs. BTT Post-OHT survival 1 y: 67% vs. 100% 2 y: 67% vs. 90% and 3 y: 64% vs. 87%
Alba A, *JHLT* 2010 20620083 (295)	Obs	Fixed pHTN (22) NovaCor 2, HMXVE 14, HMII 6	No pHTN (32) NovaCor 4, HMXVE 19, HMII 9	Txplt-C 22% ICM	T	+/-	N/A	N/A	N/A	n/a	Comparable post-OHT survival 1 y: 93% vs. 96% 5 y: 77% vs. 86% Higher peri-OHT mortality in fixed pHTN: 18% vs. 0%
Nair P, *JHLT* 2010 20113910 (296)	Obs	pHTN (14) NovaCor, Th-LVAD, Th-IVAD, HM XVE	No pHTN (44) NovaCor, Th-LVAD, Th-IVAD, HM XVE	Txplt-C 100% ino 40% ICM	T	+	+	N/A	N/A	Infxn	Comparable post-VAD and post-OHT survival Early ↓TPG with VAD, sustained ↓mPAP with ongoing MCS
MOMENTUM 18765394 (297)	RCT	Orqis Cancion (109)	OMM (59)	ADHF 100% ino or vasodilator 47% ICM	T	N.S	NS	N/A	NS	Bleeding Infxn	65d mortality 33.9% (pVAD) vs. 32.2% (OMM)
Seyfarth M, *JACC* 2008 19007597 (263)	RCT	Impella (12)	IABP (13)	Post-MI CS	T	N/A	+	N/A	N/A	n/a	No difference in MOF or sepsis
Burkhoff D, *AHJ* 2006 16923414 (264)	RCT	TandemHeart (19)	IABP (14)	CS	T	N/A	+	N/A	N/A	Arrhythmia Bleeding Neuro (NS)	Not powered to fully assess hemodynamic effects or clinical outcomes
Thiele H, *EHJ* 2005 15734771 (298)	RCT	Tandem Heart (21)	IABP (20)	Post-MI CS	T	NS	+	N/A	N/A	Infxn/Sepsis DIC (VAD)	Not powered to detect mortality benefit

+ indicates survival benefit; ADHF, hospitalized for acute decompensated heart failure; AE, adverse event; BTC, bridge to candidacy; BTT, bridge to transplantation; DOS, duration of support; Expt, Experimental group; HMII, HeartMate II; HIMI-BTT, HeartMate II bridge to transplant; HIMI-DT, HeartMate II destination therapy; HM XVE, HeartMate XVE; IABP, intra-aortic balloon pump; ICM, ischemic cardiomyopathy; ino, inotrope-dependent at time of randomization/implantation; Infx, infection; Infxn (NV), non-VAD related infection; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; INTREPID, Investigation of Nontransplant-Eligible Patients Who Are Inotrope Dependent; MCS, mechanical circulatory support; MOF, multi-organ failure; MOMENTUM, Multicenter Trial of the Orqis Medical Cancion System for the Enhanced Treatment of Heart Failure Unresponsive to Medical Therapy; mPAP, mean pulmonary artery pressure; N/A, not applicable; Neuro, neurological complication (e.g. stroke); NS, no significant difference; Obs, Observational study; OHT, orthotopic heart transplantation; OMM, optimal medical management; P, permanent; pNRCT, prospective non-randomized clinical trial; post-MI CS, post-myocardial infarction cardiogenic shock; PumpRplt, pump replacement; RCT, randomized clinical trial; Rehosp, rehospitalization; REMATCH, Randomized Evaluation of

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Mechanical Assistance in Treatment of Chronic Heart Failure; RenalFail, renal failure; RespFail, respiratory failure; RV Fail, right ventricular failure requiring inotropic support; RVAD, need for right ventricular assist device; RR, relative risk; SVT, supraventricular tachycardia; T, temporary; Th-IVAD, Thoratec implantable ventricular assist device; Th-LVAD, extracorporeal VAD; TPG, transpulmonary gradient; Txplt-C, transplant candidate; Txplt-IE, transplant ineligible; and VT, ventricular tachycardia.

Data Supplement 35. LVADs (Section 7.4.5)

Study Name, Author, Year	Aim of Study	Study Type	Study Size	Patient Population		Endpoints		Mortality	Trial Duration (Years)	Absolute Benefit or Major Study Findings	Complications/ Adverse Events
			N (Total Study Size)	*Inclusion Criteria*	*Exclusion Criteria*	*Primary Endpoint*	*Secondary Endpoint*	*1st Year Mortality*			
SELECTION OF VAD CANDIDATES											
Clinical outcomes for continuous-flow LVAD pts stratified by pre-operative INTERMACS classification, Boyle AJ, JHLT 2011 21168346 (299)	To compare post-implant outcomes across different INTERMACS classification levels.	Case-controlled	101	Pts implanted with an LVAD prior to 8/27/07 at University of Minnesota, University of Pittsburgh, and Columbia University with either a VentraAssist or HM II, classified by INTERMACS level at time of implant (Goup 1: INTERMACS profile 1; Group 2: INTERMACS profiles 2-3; Group 3: INTERMACS profiles 4-7)	N/A	Survival to discharge, LOS after VAD implantation, actuarial survival while on MCS	N/A	N/A	~2 y	Actuarial survival Group 3: 95.8%, Group 2: 68.8%, p=0.065 vs Group 3 Group 1: 51.1%, p=0.011 vs Group 3 survival to discharge Group 3: 95.8%, p=0.02 vs Group 1 Group 2: 93.8%, p=0.009 vs Group 1 Group 1: 70.4%	N/A
VAD AS DT											
Randomized Evaluation of Mechanical Assistance for the Treatment of CHF REMATCH, Rose E, 2001 11794191 (285)	To evaluate the suitability of implantable LVAD for their ultimate intended use as a long-term myocardial-replacement therapy for pts who are ineligible for cardiac transplantation	RCT	129	Adults with chronic end-stage HF and contraindications to transplantation. NYHA IV HF for ≥60 of 90 d despite attempted therapy with ACEI, diuretics, and digoxin; LVEF ≤ 25% Peak VO2 ≤12-14ml/kg/min or a continued need for IV inotropic therapy owing to symptomatic hypotension, decreasing renal function, or worsening pulmonary	HF due to thyroid disease, obstructive cardiomyopathy,pericardial disease, amyloidosis, or active myocarditis Technical obstacles that pose an inordinately high surgical risk INR >1.3 or PT >15 sec BSA ≤1.5 m^2 BMI >40 kg/m^2 Severe COPD (FEV≤1.5 L/min) Positive serum pregnancy test Fixed pHTN with PVR≥ 8	The primary end point was death from any cause and was compared between groups with the use of the log-rank statistic.	Secondary endpoints included the incidence of SAEs, the no. of d of hospitalization, the QoL, symptoms of depression, and functional status.	1 y Mortality: LVAD 48% OMM 75% p=0.002 2yr Mortality: LVAD 77% OMM 92% p=0.09	Enrollment 5/98-7/01 (39mo);	Reduction of 48 % in the risk of death from any cause — the primary endpoint — in LVAD group, as compared with medical-therapy group (OMM) QoL suggested greater improvement in LVAD group, though not all measures reached statistical significance. (RR 0.52; 95% CI: 0.34-0.78; p=0.001)	Sepsis (Rate Ratio 2.03) Non-neurologic bleeding (Rate Ratio 9.47) Neurologic dysfunction (Rate Ratio 4.35) SVT (Rate Ratio 3.92) Suspected malfunction of LVAD (0.75 rate/pt-y)

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				congestion. NYHA III-IV for ≥ 28 d and who had received at least 14 d of support with IABP or with a dependence on IV inotropic agents, with 2 failed weaning attempts.	Wood units Candidate for CABG, valvular repair, LV reduction, or cardiomyoplasty Hx of cardiac transplantation, LV reduction or cardiomyoplasty Mechanical AV that will not be converted to bioprosthesis AST, ALT, TBili > 5x normal or biopsy-proved liver cirrhosis Stroke w/in 90d or cerebrovascular dz with > 80% extracranial stenosis Impaired cognitive function, Alzheimer's disease and/or other irreversible dementia, Untreated AAA ≥5 cm Suspected or active systemic infection Platelet count <50x10^3/mm^3 SCr ≥3.5 mg/dL or dialysis Peripheral vascular disease with rest claudication or leg ulceration CCB (except amlodipine) or type I or type III antiarrhythmic agent. Abdominal operation planned Psychiatric disease /Substance abuse Participating in another clinical study Other condition with survival < 3 y						

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LVAD as Destination for pts undergoing intravenous inotropic therapy: a subset analysis from REMATCH, Stevenson LW, 2004 15313942 (284)	To analyze outcomes in pts undergoing inotropic infusions at randomization for LVAD destination therapy	Post-hoc analysis	91 (on inotrope at randomization)	LVEF ≤25% NYHA IV symptoms for 60 of 90 d despite attempted therapy with ACEI, diuretics, and digoxin. Peak VO2 ≤12-14 mL/kg/min with evidence of anaerobic metabolism, Dependence on IV inotropic agents supported by completion of a weaning failure form.	Advanced age, Diabetes with end-organ damage, SCr >2.5 mg/dL for ≥90 d	All-cause mortality during the 180 d following randomization.	QoL at 1 y	1 y Mortality: LVAD 51% OMM 76% p=0.0014 2yr Mortality: LVAD 72% OMM 89%	Enrollment 5/98-7/01;	In pts undergoing inotropic therapy at randomization, 1 y survival with LVAD was 49% vs 24% for OMM and by 2 y, 28% were alive with LVAD group compared with 11% in OMM group (p=0.0014).	N/A
Investigation of Nontransplant-Eligible Pts Who Are Inotrope Dependent (INTrEPID Trial), Rogers JG, 2007 17707178 (286)	To evaluate the impact of LVAD support on survival and QoL in inotrope-dependent HF pts ineligible for cardiac transplantation	Prospectivenonrandomized clinical trial	55	Adults with inotrope-dependent stage D HF; LVEF < 25%, NYHA IV symptoms for ≥ 3 mo before enrollment and were not candidates for cardiac transplantation Treated with maximally tolerated doses of ACEI, beta-blockers, digoxin, diuretics, and/or other vasodilators.	BSA <1.5 m2 Contraindication to chronic anticoagulation Presence of a mechanical aortic valve constituted an exclusion criterion for LVAD support CVA or TIA within 6 mo before enrollment, a 70% carotid stenosis, or an ulcerated carotid plaque. Unresolved drug or alcohol dependency Active systemic infection SCr >5.0 mg/dL, Tbilli >5.0 mg/dL Mechanical ventilatory support for >48 h at the time of enrollment Comorbid medical condition limiting life expectancy < 2 y	All-cause mortality at 6 mo	AEs, functional capacity HRQoL	1st y mortality 73% (LVAD) vs 89% (OMT) 6mo mortality: 54% (LVAD) vs 78% (OMT)	Enrollment 39 mo (3/00-5/03); 12 mo follow-up	6 mo survival 46% (LVAD) vs 22% (OMT) (HR 0.47; 95% CI 0.23-0.93; p=0.03) 1 y survival 27% (LVAD) vs 11% (OMT) Absolute reduction of 1 y mortality by 16% with LVAD (HR: 0.48; 95% CI: 0.25-0.85; p=0.02)	CVA 34.5% Infection 24%
Advanced HF treated with continuous-flow LVAD, (HeartMateII DT), Slaughter MS, 2009 19920051 (287)	To compare the outcomes of pts ineligible for cardiac transplantation with pulsatile versus continuous flow	RCT	200	Age >18 y BSA > 1.5m2 for a pt to be randomized HM XVE - HM II. If BSA < 1.5 m2and > 1.2 m2, the pt must meet the remaining criteria and can be enrolled in the Small Size	HF is due to uncorrected thyroid disease, obstructive cardiomyopathy, pericardial disease, amyloidosis, active myocarditis or RCM. Technical obstacles, which pose an inordinately high surgical risk, in the	The primary composite endpoint was, at 2 y, survival free from disabling stroke and reoperation to	Secondary endpoints included survival, frequency of AE, the QoL, and functional capacity.	1st y mortality: 32% (continuous flow LVAD) vs 42% (pulsatile flow LVAD)	Enrollment 5/05-5/07 (2 y) Follow-up ≥2 y or until death, cardiac transplant, or	The primary composite endpoint was achieved in more pts assigned to receive a continuous-flow LVAD than in those assigned to receive a pulsatile-flow LVAD (46% vs. 11%)	Higher complication rate with pulsatile LVAD (p<0.001) Pump replacement Sepsis Respiratory failure Renal failure RV failure requiring extended inotrope Rehospitalization

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	LVAD destination therapy			Cohort. NYHA IIIB or IV HF and 1 of following: i. On OMM, including dietary salt restriction, diuretics, digitalis, beta blockers, spironolactone and ACE-I, for ≥ 45 out of the last 60 d and failing to respond; ii. NYHA III-IV HF for ≥14 d and dependent on IABP for 7 d and/or inotropes for ≥14 d iii. Treated with ACE-I or beta blockers for ≥ 30 d and found to be intolerant. Female pts of childbearing potential must agree to use adequate contraception Ineligible for cardiac transplant. VO2max ≤ 14 mL/kg/min or <50% of predicted VO2max with attainment of anaerobic threshold, if not contraindicated due to IV inotropes, angina or physical disability. LVEF is ≤ 25%.	judgment of the investigator. Ongoing mechanical circulatory support other than IABP. BMI >40 kg/m2. Positive pregnancy test Presence of mechanical AV that will not be converted to a bioprosthesis History of cardiac transplant or cardiomyoplasty. Platelet count < 50,000 Untreated aortic aneurysm > 5cm. Psychiatric disease, irreversible cognitive dysfunction, psychosocial issues that are likely to impair compliance Active, uncontrolled infection. Intolerance to anticoagulant or antiplatelet therapies or any other peri/post operative therapy that may be required INR > 2.5, not due to anti-coagulant therapy, or Plavix within 5 days AST, ALT, or total bilirubin > 5x normal or biopsy proven liver cirrhosis Severe COPD or restrictive lung disease. Fixed pHTN with a PVR >8 Wood units Stroke w/in 90 d, or cerebral vascular disease with >80% extra cranial stenosis. SCr >3.5 mg/dl or on dialysis Significant peripheral vascular disease with rest	repair or replace the device.			explant of LVAD	On the basis of the as-treated analysis, the Kaplan–Meier estimate of actuarial survival was significantly better for pts who had a continuous- flow LVAD as compared with those with a pulsatile-flow LVAD Improvements in functional status by NYHA Class and 6MWT did not differ between the two groups. Primary composite endpoint: HR 0.38; 95%CI: 0.27 to 0.54; p<0.001 Actuarial survival, RR: 0.54 95% CI, 0.34 to 0.86; p=0.008	

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					pain or ulceration. Moderate to severe AIy without plans for correction Participation in any other clinical investigation CCB (except amlodipine), or Type I /III antiarrhythmic (except amiodarone) within 28 d prior to enrollment. Any condition that could limit survival to <3 y.						
BTT											
Use of a continuous-flow device in pts awaiting heart transplantation (HMII BTT), Miller LW, 2007 17761592 (289)	To assess the efficacy of continuous-flow LVAD for providing hemodynamic support of at least 6 mo to pts awaiting heart transplantation	Cohort	133	Transplant listed. BSA > 1.2 m2. NYHA IV HF symptoms. Female pts of childbearing potential must agree to use adequate contraception On inotropic support, if tolerated. Despite medical therapy, the pt must meet one of the following criteria: a. No contraindication for Status 1A listing b. No contraindication for Status 1B listing PCWP or PAD > 20 mmHg, CI < 2.2 L/min/m2 or SBP < 90 mmHg	HF due to uncorrected thyroid disease, obstructive/restrictive cardiomyopathy, pericardial disease, or amyloidosis. Technical obstacles, which pose an inordinately high surgical risk. Ongoing mechanical circulatory support other than IABP BMI > 40 kg/m2. Positive pregnancy test Mechanical aortic valve that will not be converted to a bioprosthesis Hx of cardiac transplant. Platelet count <50,000/mL. Untreated aortic aneurysm > 5cm. Psychiatric dz irreversible cognitive dysfunction, psychosocial issue Active uncontrolled infection. Intolerance to anticoagulant or antiplatelet therapies or any other peri/post operative therapy that may be required Any one of the following	The principal outcomes were the proportions of pts who, at 180 d, had undergone transplantation, had undergone explantation of the device because of recovery of ventricular function, or had ongoing mechanical support and remained eligible for transplantation (i.e., were not removed from the waiting list owing to irreversible complications or clinical	Secondary outcomes included overall survival, survival while receiving device support, survival after transplantation, frequency of AEs, assessment of functional class by a 6-min walk test, independent evaluation of NYHA functional class by a physician, and QoL.	1 y mortality 32%	Enrollment 3/05-5/06 (15mo); follow-up through 180d	75% reached principal outcomes 18.8% died before 180d of support	Bleeding requiring pRBCs Local infection, non-LVAD Ventricular arrhythmias Sepsis Right HF

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					risk factors for and indicators of severe end-organ dysfunction or failure: a) INR >2.5 not due to anticoagulant therapy or Plavix within 5 d. b) Total bilirubin > 5mg/dl, or shock liver (AST, ALT >2,000), or biopsy proven liver cirrhosis. c) Severe COPD or severe restrictive lung disease. d) Fixed pulmonary hypertension, with a recent PVR >6 Wood units, e) Unresolved stroke or uncorrectable cerebrovascular disease. f) SCr >3.5 mg/dL or the need for chronic dialysis. g) Significant peripheral vascular disease with rest pain or ulceration Moderate to severe aortic insufficiency without plans for AVR Participation in any other clinical investigation	deterioration)					
Extended Mechanical Circulatory Support with a Continuous-Flow Rotary LVAD (HMII BTT), Pagani FD, 2009 19608028 (288)	To evaluate the use of a continuous-flow rotary LVAD as a bridge to heart transplantation over an extended period, up to 18 mo	Cohort Study	281	Same as above (HMII Study)	Same as above (HMII Study)	Survival and transplantation rates were assessed at 18 mo.	Pts were assessed for AEs throughout the study and for QoL, functional status, and organ function for 6 mo.	6 mo Mortality 18% (95% CI: 77-87%) 1 y Mortality 27% (95% CI: 66-80%) 18 Mo Mortality 28% (95% CI: 65-79%)	Enrollment 3/05-4/08 (38 mo); 18 mo follow-up	79% of LVAD pts reached primary outcome measure, either received a transplant, recovered cardiac function and underwent device explantation, or remained alive with ongoing LVAD support at 18-mo follow-up	Bleeding requiring pRBCs Respiratory failure Local infection, non-LVAD Ventricular arrhythmias Sepsis Right HF requiring extended inotropic support

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Evaluate the Safety and Efficacy of a Percutaneous LVAD vs. IABP for Treatment of Cardiogenic Shock Caused by Myocardial Infarction, Seyfarth M, 2008 19007597 (263)	To test whether the percutaneous LVAD Impella LP2.5 provides superior hemodynamic support compared with IABP	RCT	26	Pts with acute MI within 48 h and cardiogenic shock within 24 h CI ≤ 2.2 l/min/m2 and PCWP >15 mm Hg *or* an angiographically measured LVEF <30% and LVEDP >20 mm Hg	Age <18 y; Prolonged resuscitation (>30 min) HCM; LV thrombus; Treatment with intra-aortic balloon pump; Severe valvular disease or mechanical heart valve; Cardiogenic shock caused by mechanical complications of AMI such as ventricular septal defect, acute mitral regurgitation greater than second degree, or rupture of the ventricle; Predominant RV failure or the need for a RVAD; Sepsis; Known cerebral disease; bleeding with a need for surgical intervention; Allergy to heparin or any known coagulopathy; Moderate to severe AI; Pregnancy; Inclusion in another study or trial	The hemodynamic improvement at 30 min after implantation defined as the change in CI from baseline.	Hemodynamic and metabolic parameters; All-cause mortality at 30 d; Device-related complications including hemolysis, major bleeding, cerebrovasc-ular events, limb ischemia, and multiple-organ dysfunction scores at 30 d using MODS and SOFA criteria.	n/a	N/A; follow-up of 30d	The CI after 30 min of support was significantly increased in pts with the Impella LP2.5 compared with pts with IABP (Impella:DCI=0.49±0.46 l/min/m2; IABP: DCI=0.11± 0.31 l/min/m2). p= 0.02	No difference in adverse effects between pLVAD and IABP
Impact of Center Volume on Outcomes of LVAD Implantation as DT: Analysis of the Thoratec HeartMate Registry, 1998 to 2005, Lietz K, 2009 19808309 (300)	To examine the impact of LVAD center volume on the outcomes of DT	Registry ; Retrospective analysis	351	NYHA IV symptoms for ≥ 60 d despite maximized oral therapy or requirement of inotropic support LVEF ≤ 25% Peak VO2 <12 mL/kg/min or documented failure to wean IV inotropic therapy; Contraindication to HT attributable to age >65 y, insulin-dependent DM with end organ damage, chronic renal failure, or	Not specifically outlined; similar to REMATCH	1 y survival with DT		1 y Mortality low volume: 52.2% medium volume:42.8% high volume: 32.6%	Enrollment: 5/98-12/05 (92 mo); total duration of observation: 102 mo; median follow-up period 9.5mo	High volume center compared with low volume center has an absolute benefit of 19.6% reduction in mortality at 1 y (1y mortality of 32.6% vs 52.2%) OR 0.4; 95% CI 0.2-0.7; p=0.006;	Sepsis Multiorgan failure Stroke Right HF LVAD failure/complications

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				other comorbidities.							
Predictors of death and transplant in pts with a mechanical circulatory support device: a multi-institutional study (INTERMACS), Holman WL, 2009 19134530 (301)	To identify predictors for death and transplantation based on initial results from INTERMACS	Registry	420	Pt underwent implantation of mechanical circulatory support device (INTERMACS registry)	Not specifically stated	1 y survival post LVAD implantation	AEs	1 y Mortality DT: 37% BTT: 24%	19 mo, 12 mo follow-up	Risk factors for death 1. INTERMACS level 1 (p=0.02) 2. Older age (≥ 60yr) (p<0.01) 3. Presence of ascites (p=0.003) 4. Elevated total bilirubin (p=0.05) 5. BiVAD (p=0.002) 6. Total artificial heart (p=0.03)	CNS events Infection
European results with a continuous-flow VAD for advanced HF pts, Lahpor J, 2010 19616963 (290)	To report on the European experience with the Heart Mate II LVAD	Registry	411	NYHA IIIB-IV CHF on maximum medical treatment including IV inotropic support At least LVAD implantation took place at least 6 mo prior to closing date of study	Not specifically stated	6 mo and 1 y survival	AEs	6 mo mortality: 26% 1st y mortality: 8.5%	52mo (3/04-8/08)	Overall survival to transplantation, recovery of natural heart function with evice removal, or ongoing device support at end of study: 69%	Multiorgan failure Infections (sepsis, local non-VAD related, drive line) Right heart failure Bleeding Ventricular arrhythmias Neurologic complications

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Post–cardiac transplant survival after support with a continuous-flow LVAD: Impact of duration of LVAD support and other variables, John R, 2010 20447659 (302)	To determine factors related to posttransplant survival in pts supported with continuous-flow LVADs	Registry	468	Adult pts with end-stage HF and listed for heart transplantation (SAME AS HMII BTT STUDIES)	Severe renal, pulmonary, or hepatic dysfunction, Active uncontrolled infection Mechanical aortic valve or aortic insufficiency, Aortic aneurysm, Other MCS (other than IABP) Technical obstacles thought to pose an increased surgical risk	1 mo and 1 y survival; survival after transplantation		Overall 1 y mortality: 13%	Enrollment 38 mo (3/05-4/08); follow-up for 1 y post-transplant and for 18 mo post-LVAD if not transplanted	Post-transplant survival at 1y: <30 d LVAD support: 94% 30-89 d LVAD support: 93% 90-179 d LVAD support: 84% >180 d LVAD support: 81% (p=0.18)	Bleeding requiring pRBCs
Results of the Post-U.S. FDA-Approval Study With a Continuous Flow LVAD as a Bridge to Heart Transplantation (INTERMACS), Starling RC, JACC 2011 21545946 (291)	To determine whether results with the HMII LVAD in a commercial setting are comparable to other available devices for the same indication	Registry	338	INTERMACS registry, LVAD for BTT		Survival (transplant or death)	30 d mortality, inhospital mortality, LOS, QOL, AE	12 mo mortality 13% HMII vs. 22%COMP	Enrollment 9/07-2/09; at least 12 mo follow-up post VAD	12 mo survival: 85% HMII vs 70% COMP no difference between INTERMACS profiles within each group 12 mo survival: log rank p<0.001	Bleeding event rate/pt-y 1.44 HMII v 1.79 COMP, p=0.19 Infection event rate/pt-y 1.0 HMII v 2.12 COMP, p<0.0001
BIVAD											
Survival after biventricular assist device implantation: An analysis of INTERMACS database, Cleveland JC, 2011 21621423 (303)	To identify the underlying pre-implant characteristics of the population requiring BiVAD support that contribute to reduced survival, and to identify differences in postoperative outcomes with respect to AEs compared with pts supported with LVAD alone.	Registry	1852	INTERMACS registry, LVAD or BiVAD implantation	N/A	Survival	AEs	6 mo mortality BiVAD: 44% LVAD: 14% p<0.0001	15 mo (6/06-9/09)	Risk factors for death with BiVAD Older age Higher BSA Presence of Ascites Elevated creatinine Elevated total bilirubin Elevated INR History of valve surgery Failure to wean from bypass	Bleeding Infection

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PERCUTANEOUS VAD											
Multicenter Trial of the Orqis Medical Cancion System for the Enhanced Treatment of HF Unresponsive to Medical Therapy (MOMENTUM), Greenberg B, 2008 18765394 (297)	To compare percutaneous continuous aortic flow augmentation (flow≤.5 L/min for up to 96 h) plus medical therapy vs. medical therapy alone	RCT	168	LVEF≤35% Persistent clinical, hemodynamic, and renal derangement despite standard oral medication and treatment for ≥ 24 h with ≥1 of the following drugs at minimum dosage (stable for ≥6 h): a) dobutamine 2.5 mg/kg/min b) milrinone 0.3mg/kg/min c) dopamine 5 mg/kg/min , d) nesiritide 0.01mg/kg/min e) nitroprusside 0.25mg/kg/min , or f) nitroglycerine 0.25mg/kg/min PCWP ≥18 mm Hg continuously for 12 h and >20 mm Hg at time of randomization; CI < 2.4 L/min/m 2; SCr >1.2 mg/dL or IV furosemide dose ≥120 mg/d or equivalent.	Recent Q-wave MI or cardaic revascularization; Severe lung disease; Primary liver disease; SCr >4.0 mg/dL or on dialysis; CRT device implanted within 14 d; SBP <80 mm Hg; Need for cardiac mechanical support; Platelet count <50 000/ L; INR > 1.5 in the absence of anticoagulation; Systemic infection; CVA or TIA within 3 mo; Active status on the cardiac transplantation list unless transplant was considered unlikely within 65 d; Peripheral vascular disease with absent pedal pulse or evidence of limb ischemia; Significant uncorrected primary valvular disease.	Overall success composite based on technical (device group only), hemodynamic, and clinical success defined as follows: technical success (device group only), insertion and attainment of flow ≥1 L/min for ≥24 h; hemodynamic success, mean PCWP decrease from baseline of 5 mmHg calculated as the average of values at 72-96 h; and clinical success, from d 1-35 after randomization, any of the following: ≥10 consecutive d alive out of hospital, no alternative mechanical support, absence of death, and absence of readmission for HF	Change in SCr at d 3 Change in body weight at d 4 Change in CI (72- 96 h average), Change in NT-proBNP at d 3; Change in KCCQ Overall Summary score at 2 wk and 35 d.	65 d mortality pVAD 33.9% control 32.2% (HR:1.05; p=0.87)	Enrollment 9/04-8/07 (3y), out to 64 d since randomization	Primary efficacy endpoint success (hemodynamic and clinical success for both groups plus technical success in the device group) was seen in 13.6% of the control group and 17.4% of the device group pts (p=0.45) No significant difference was found in SCr, NT-proBNP, or body weight. KCCQ Overall Summary and Clinical Summary scores increased more in the device group (p=0.10) than in the control group (p=0.095), but treatment differences were not significant	Any bleed (40.4% device vs 13.6% control, p=0.0004)
QOL											

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Longitudinal Change in QoL and Impact on Survival After LVAD Implantation, Grady KL, 2004 15063260 (293)	To describe change with time (from 1mo to 1 y) in pts who received a Heart Mate vented elecric LVAD as BTT and to identify QOL (predictors of survival after LVAD implantation)	Cohort Study	78	Received either HeartMate VE LVAD or Heart Mate implantatble pneumatic LVAD between 8/1/94 and 8/31/99 at 1 of 9 medical centers in US and one medical center in Australia as BTT Age ≥ 18 y Able to read and write English Physically able to participate	N/A	QOL questionnaires: QOL Index, Rating Question Form, HF Symptom Checklist, and Sickness Impact Profile	N/A	N/A	N/A	QoL outcomes were fairly good and stable from 1 mo to 1 y after LVAD implantation. Overall QoL was unchanged, however both positive and negative changes in subareas of QoL were noted. Pt satisfaction with life improved in area of health/functioning but worsened in satisfaction with significant others. Cardiopulmonary, neurologic, psychological, and physical symptom distress improved. Functional disability with respect to work, sleep/rest, self-care, and physical disability improved over time. However, functional disability with respect to home management and social interaction worsened.	N/A
Continuous Flow LVAD Improves Functional Capacity and QoL of Advanced HF Pts, Rogers JG, 2010 20413033 (304)	To assess the impact of continuous flow LVADs on functional capacity and HF-related QoL	Cohort Study	655	Pts enrolled in either HM II BTT or DT clinical trials	N/A	NYHA Functional Class assess by clinician Pt reported activity levels (METS) and 6MWT Heart failure-related QOL by MLWHF and KCCQ	N/A	N/A	N/A	LVAD pts demonstrated early and sustained improvements in functional status and QOL. NYHA functional class improved from class IV to class I or II in majority of pts (about 80%). Improved 6MWT distance as well as MLWHF and KCCQ scores.	N/A

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QOL and functional status in pts surviving 12 mo after LVAD implantation, Allen JG, 2010 19837607 (305)	To review QoL in pt on LVAD support for ≥1 y	Retrospective analysis	30	Pts who underwent HMII or HMI LVAD implantation between 2000-2008 at Johns Hopkins Hospital	Pt transplanted or died before 365 d of MCS	6MWT distance, MET tolerance, MLHFQ, NYHA functional class	Hospital readmissions, infectious complications	N/A		LVAD pts spend the majority of time outside the hospital enjoying a good QoL	90% of pts experienced hospital readmissions, with mean no. of readmissions per year of 2.9 with mean length of stay of 13.8 d. 43% of readmissions were for infectious complications. 77% of LVAD pts required additional operations for various indications.

AAA indicates abdominal aortic aneurysm; ACEI, angiotensin-converting-enzyme inhibitor; AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; AV, atrioventricular; AVR, aortic valve replacement; BMI, body mass index; BSA, body surface area; BTT, bridge to transplantation; CABG, coronary artery bypass surgery; CCB, calcium channel blocker; CHF, congestive heart failure; Cl, clearance; COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accident; DM, diabetes mellitus; DT, destination therapy; dz, disease; FEV, forced expiratory volume; HCM, hypertrophic cardiomyopathy; HF, heart failure; HM II, HeartMate II; HM XVE, HeartMate XVE; HT, heart transplantation; hx, history; IABP, intra-aortic balloon pump; INR, international normalized ratio; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; IV, intravenous; KCCQ, Kansas City Cardiomyopathy Questionnaire; LOS, length of stay; LV, left ventricle; LVAD, left ventricular assist device; LVEF, left ventricular ejection fraction; MCS, mechanical circulatory support; METS, metabolic equivalents; MLWHF, Minnesota Living with Heart Failure; MWT, minute walk test; MODS, multiple organ dysfunction scores; N/A, not applicable; NT-proBNP, N-terminal pro-B-Type natriuretic peptide; NYHA, New York Heart Association; OMM, optimal medical management; PAD, peripheral arterial disease; pRBC, packed red blood cells; PCWP, pulmonary capillary wedge pressure; pHTN, pulmonary hypertension; pts, patients; PVR, peripheral vascular resistance; QoL, quality of life; RCM, Restrictive cardiomyopathy; RCT, randomized control trial; RV, right ventricule; SAE, serious adverse event; SBP, systolic blood pressure; SCr, serum creatinine; SOFA, sequential organ failure assessment; SVT, supraventricular tachycardia; Tbilli, total bilirubin; TIA, transient ischaemic attack; VAD, ventricular assist device; and VO2, oxygen volume.

Data Supplement 36. Transplantation (Section 7.4.6)

Study Name, Author, Year	Aim of study	Study Type	Background Therapy	Study Size	Patient Population		Severity	Endpoints	Mortality	Trial Duration (Years)	Absolute Benefit or Major Finding	P Values & 95% CI:
			Pretrial standard treatment.	*N (Total Study Size)*	*Inclusion Criteria*	*Exclusion Criteria*	*Severity of HF Symptoms*	*Primary Endpoint*	*1st Year Mortality*			
PATIENT SELECTION												
Value of peak exercise oxygen consumption for optimal timing of cardiac transplantation in ambulatory pts with HF, Mancini DM, Circulation, 1991 1999029 (27)	To determine whether measurement of peak VO2 during maximal exercise testing can be used to identify pts in whom transplantation can be safely deferred	Case-control	ACEI 95% Diuretics 100% Digoxin 100% Vasodilators 98% PDE3 inhibitors 13% Antiarrhythmics 10% ICD 1%	122	Ambulatory HF pt referred for cardiac transplantation evaluation	Dependent on inotrope or mechanical support; Unable to achieve anaerobic threshold on CPX	NYHA II 13% NYHA III 70% NYHA IV 17%	Death	1 y mortality peak VO2 ≤14, accepted for transplant: 30% peak VO2 >14: 6% peak VO2 ≤14, rejected for transplant: 53%	3	Pts with preserved exercise capacity despite severe resting hemodynamic impairment have survival and functional capacity equal to those afforded by cardiac transplantation	N/A

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Predicting Survival in Ambulatory Pts With Severe HF on Beta Blocker Therapy, Lund LH, Am J Cardiol 2003 14636921 (306)	To examine the predictive value of peak VO2 and the HFSS in pts referred for cardiac transplantation in the beta blocker era	Case-control	Beta blockers 65%	221	Ambulatory HF pts referred for heart transplant evaluation	N/A	N/A	Outcome events: death before transplant, LVAD implantation, inotrope-dependent transplantation	1 y event-free survival: beta blocker 75% no beta blocker 56%	6	No difference in 1 y event-free survival amongst beta blocker users by peak VO2 statum; however, significant difference by HFSS statum	Survival by HFSS, p<0.0002 (total cohort), p<0.02 (beta blocker pts) Survival by VO2, p=0.3 (total cohort), p=0.29 (beta blocker pts)
Selection of Pts for Heart Transplantation in the Current Era of HF Therapy, Butler J, JACC 2004 14998618 (307)	To assess the relationship between survival, peak exercise oxygen consumption (VO2), and HF survival score (HFSS) in the current era of HF (HF) therapy	Case-control	ACEI 92% Diuretic 96% Digoxin 94% beta blocker 10% (past) vs. 72% (current) Spironolactone 2% (past) vs. 41% (current) Antiarrhythmic 13% AICD 11% (past) v 19% (current)	507	HF pts with LVEF <40%; Underwent CPX in 1994-1997 (past era) or 1999-2001; (current era) Underwent OHT in 1993-2000	On inotrope; Angina or orthopedic issue restricting exercise capacity; Significant valvular stenosis; Exertional oxygen desaturation	NYHA III-IV 84%	1 y event-free survival (without need for LVAD or urgent- Status 1A-transplantation) for HF pts; Overall 1-y survival for transplanted pts	Overal 1-y survival Transplanted: 88% Current era HF: 88% Past era HF: 78%	N/A	No difference in 1 y event-free survival in current era by initial peak VO2; trend towards difference in survival when stratified by HFSS	N/A
Peak VO2 and VE/VCO2 slope in pts with HF: a prognostic comparison, Arena R, Am Heart J, 2004 14760336 (308)	To examine the ability of peak VO2 and VE/VCO2 slope to predict cardiac-related mortality and hospitalization	Retrospective analysis	ACEI 70% Digitalis 57% Diuretic 63% Oral nitrate 29% beta blocker 42% CCB 15% anticoagulant 35% Antiarrhythmic 15%	213	HF diagnosis; Evidence of LV systolic dysfunction by echocardiogram or cardiac catheterization		N/A	Cardiac-related mortality and hospitalization 1-y after exercise testing via medical chart review and the Social Security Death Index	1 year mortality VE/VCO2 < 34: 0.8% VE/VCO2 ≥34: 16.9%	8 y, 7 mo (CPX from 4/93-10/01), plus 1 y f/u	Peak VO2 (≤14 ml/kg/min) was revealed by multivariate Cox regression analysis to add significantly to the VE/VCO2 slope (≥34) in predicting 1-y cardiac-related hospitalization (residual X^2 =6.5; p=0.01). The addition of peak VO2 did not provide additional value to the VE/VCO2 slope in predicting overall cardiac-related mortality (residual	1 y cardiac mortality VE/VCO2 slope ≥34, p <0.0001

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											X2 = 0.2; p=0.89) or 1-year cardiac-related mortality (residual X2= 1.5; p=0.29).	
Prognostic usefulness of the functional aerobic reserve in pts with HF, Chase P, Am H J, 2010 21095281 (309)	To develop a prognostic model using FAR as a continuous variable that incorporates pts with an undetectable VT. Secondarily, to determine the prognostic power of the FAR with that of VO2pk and the VE/VCO2 slope in pts with HF	Case-control	Beta blocker 86% (no VT) vs 75% (VT) ACEI 76% CCB 7% Diuretic 90% (no VT) vs 70% (VT)	874	Chronic HF with stable HF symptoms and medications for at least 1 mo before exercise testing, LVEF≤45%	N/A	NYHA III-IV 89% (no VT) vs. 45% (VT)	Major cardiac-related events (heart transplantation, LVAD implantation, and cardiac-related death) for 2 y after CPX testing	2 y event-free survival based upon CPX responses--- favorable responses defined as VE/VCO2 <36, VO2pk > 10 mL O2/kg/min, FAR > 3ml O2/kg/ min) All favorable responses: 95% 1 unfavorable: 83.1% 2 unfavorable: 76.0% All unfavorable: 58.3%	11 y (CPX between 5/97-5/08); 2 yfollow-up	Pts without a detectable VT had worse prognosis. VE/VCO2 slope (≥36) is the strongest overall univariate and multivariate predictor; FAR (≤3 ml O2/kg/min) and peak VO2 (≤10ml O2/kg/min) are additive to the VE/VCO2 slope	No VT vs VT: p<0.001, 95% CI 2.3-4.8 Prognostic classification p<0.001
Ventilatory Efficiency and the Selection of Pts for Heart Transplantation, Ferreira AM, Circulation HF, 2010 20176714 (310)	To assess whether Ve/VCO2 slope would identify individuals likely to benefit from heart transplant more accurately than current exercise criteria for listing	Case-control	N/A	663	HF pts who underwent cardiopulmonary testing at 4 laboratories; NYHA II-IV; LVEF ≤40%	Primary valve disease; Congenital heart disease; Planned coronary; revascularization; Planned cardiac surgery; Age <18 y; Primary pulmonary disease; Previous cardiac transplantation; Submaximal CPX (peak RER	NYHA II-IV	Death or heart transplant	During follow-up period, 15.2% underwent transplant 13,7% died	Median f/u 26 mo	Ve/VCO2 slope <43, 1y survival 97% 3y survival 89.4% Ve/VCO2 slope ≥43 1y survival 77.8% 3y survival 55.1%	Ve/VCO2 slope <43, 1y survival: 95% CI: 95.4-98.6, y survival: 95% CI: 85.8-93.0 p<0.001 Ve/VCO2 slope ≥43 1 y survival: 95% CI: 71.3-84.3%, 3 y survival: 95% CI: 45.2-65.0

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						ratio <1.05).						
The HF Survival Score outperforms the peak oxygen consumption for heart transplantation selection in the era of device therapy, Goda A, JHLT 2011 21093299 (311)	To evaluate peak VO2 and HFSS as prognostic tools in pts with and without CRT-D referred for heart transplant evaluation	Case-control	ACEI/ARB 80% b-blocker 64% (no device) v 76% (any device)	715	Systolic HF pt referred for heart transplant evaluation	Excluded pts unable to exercise for any reason	mean NYHA class 2.82 (total), 2.7 (no device) vs 2.9 (any device)	Outcome events were defined as death, urgent transplantation (UNOS Status 1), or implantation of LVAD. Pts who underwent transplant as non-urgent (UNOS status 2) were censored alive on the date of the transplant.	1 y event-free survival with peak VO2 10.1-14 Total cohort: 77% CRT+/-ICD: 84% ICD +/- CRT: 80% Any device: 80% 1 year event-free survival with peak VO2 ≤ 10 Total cohort: 65% CRT+/-ICD: 52% ICD +/- CRT: 59% Any device: 58%	N/A	HFSS significantly discriminates between the 3 risk strata across all device groups, whereas peak VO2 <10 only discriminates high risk from low/medium risk.	1y event-free survival, amongst CRT+/-ICD pts low risk HFSS 90%, medium risk HFSS 72%, high risk HFSS 56%
FUNCTIONAL/QOL OUTCOME												
Improvement in QoL in Pts with HF who Undergo Transplantation, Grady KL, 1996 8878757 (312)	To compare QoL of pts with HF at time of loisting for a heart transplant with that 1 y after transplantation	Cohort	Post-transplant maintanence immunosuppression included cyclosporine, prednisone and azathioprine. Some received induction anti-T-cell therapy.	148	Underwent cardiac transplantation at Loyola University of Chicago Medical Center or University of Alabama at Birmingham	N/A	N/A	Symptoms, health perception, functional status, stress, coping, life satisfaction, and overall QoL as measured by 6 point-completed instruments. Demographic and clinical data from chart review.	N/A	N/A	Total symptom distress decreased after heart transplantation. Overall level of functional disability improved after heart transplantation, though remained low.	N/A

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A Controlled Trial of Exercise Rehabilitation After Heart Transplantation, Kobashigawa JA, 1999 9920951 (313)	To assess the effects of structured 6 mo training (cardiopulmonary rehabilitation) on the capacity for exercise early after cardiac transplantation	RCT	All pts were treated with triple-drug immunosuppression--cyclosporine, azathioprine, and prednisone.	27	Underwent cardiac transplantation	Multiple medical issues limiting ability to participate in exercise training	N/A	Differences in results of cardiopulmonary exercise stress testing at 1- and 6- mo after transplantation	N/A	Enrollment 11 mo; 6 mo followup (total 17mo)	6 mo D peak VO2: +4.4 L/min/kg (exercise) +1.9 L/min/kg (control)	p=0.01
Predictors of QoL in Pts at 1 y After Heart Transplantation, Grady KL, 1999 10328145 (314)	To describe QoL, examine relationships between quality of life and demographic, physical, and psychosocial variables, and identify predictors of Q0L in pts 1 y post-transplant	Cohort study	Some pt receieved induction anti-T celll therapy with HATG or OKT3, some did not. All pts were on maintenance immmunosuppression consisting of cyclosporine, prednisone, and azathioprine. Prednisone was rapidly tapered to 0.1mg/kg/d by 1 y post-OH.	232	Pts who survived to 1 y post-cardiac transplant and completed the study booklet	N/A	N/A	QoL domains and multiple subscales within these domains: somatic sensation, psychological state, physical and occupational function, social interaction	N/A	Recruited pts listed for OHT from 3/88-8/96	Predictors of better QoL at 1 y post-OHT were: less total stress, more helpfulness of information, better health perception, better compliance with transplant regimen, more effective coping, more functional ability, less symptom distress, older age, fewer complications Predictors of POOR outcome were primarily psychological	p<0.00001 for all
Lifestyle and QoL in Long- Term Cardiac Transplant Recipients, Salyer J, 2003 12633699 (315)	To describe long-term (>1 y) cardiac transplant recipients' perceptions of barriers to health-promoting behaviors; ability to manage their health, health-promoting lifestyle, health status and QoL; and determine predictors of QoL.	Cross-sectional study	N/A	93	Cardiac transplant recipients who were: (1) >18 y of age at the time of transplant; (2) could read and write English; and (3) had the visual acuity to read and respond to written questionnaires.	N/A	N/A	Self-report questionnaire incorporating: (1) pt characteristics; (2) barriers to health promotion, perceived health competence and health-promoting lifestyle; (3) perceived health status; and (4) QoL.	N/A	Mean time since transplant was 101.4 mo (SD 49.44 mo, range 12-188 mo)	Despite having multiple co-morbidities, heart transplant recipients evaluate their health as good. QoL in recipients who are, on average, 8.5 y post-transplant and demonstrate that, overall, they are moderately satisfied with their lives Predictors of better perceptions of QoL included less education, longer time since transplant,	N/A

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											ischemic etiology of HF, fewer barriers, higher perceived health competence and a health-promoting lifestyle (R^2 =0.51; F=14.77; p=0.001).	
Changes in exercise capacity, ventilation, and body weight following heart transplantation, Habedank D, 2007 17023206 (316)	To prospectively examine changes in peak VO2 and ventilatory efficiency (VE/VCO2 slope) over 24 mo following heart transplantation and evaluate the potentially confounding effects of weight gain	Case control	In txplt pts Immunosuppression: cyclosporine/tacrolimus 100% prenisolone 100% azathioprine/MMF 100% ACE-I/ARB 99% CCB 93% Diuretics 92% alpha blocker 17% beta blocker 12%	125	Underwent cardiac transplantation between 9/97 and 1/02 at German Heart Institute, Berlin; Healthy volunteers	N/A	N/A	Peak VO2, Ve/VCO2 slope	N/A	N/A	Ve/VCO2 slope improved (decreased) at 6 mo and remained improved at 12, 24 mo post-txplt compared with pre-txplt value and no different than matched normal at 6 mo. Peak VO2 improved at 6 mo and remained improved at 12, 24 mo post-txplt compared to pre-txplt baseline but remained lower than normal matched controls.	Ve/VCO2, p<0.001 vs. baseline, p=0.12 vs matched normals Peak VO2, p<0.01 vs baseline, p<0.0001 vs matched normals
Patterns and Predictors of QoL at 5 to 10 Y After Heart Transplantation, Grady KL, 2007 18022086 (317)	To describe QoL over time and identify predictors of QoL longitudinally from 5-10 y after heart transplantation	Cohort	N/A	555	Transplanted between 7/1990 and 6/1999; Survived 5-10 y post-transplant Completed pt survey pamphlet; Age ≥21y; Literate in English	N/A	N/A	N/A	N/A	N/A	QoL is positive and stable at 5 to 10 y after heart transplantation. Bio-psychosocial variables predicted satisfaction with overall QoL and HRQoL.	N/A
SURVIVAL OUTCOMES												
Long-term Results of Cardiac Transplantation in Pts Older than 60 Y, Bull DA, 1996	To examine the long-term results of cardiac transplantation in pts >60 y	Case-control	N/A	527	NYHA IV HF unremedial to surgical treatment other than cardiac replacement,	Severe pHTN (PVR >6 Wood units, irreversible) Severe irreversible	NYHA IV	Survival after transplant	6 y mortality >60y/o: 46% <60y/o: 28%	9 y	18% worse survival/higher mortality at 6 y post-transplant for pts transplanted at age > 60 y.	6-y mortality: p<0.05 Death from infection: p<0.003

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8583816 (318)					Limited life expectancy, 1-y mortality >50% Age <65 y; No systemic illness other than abnormalities related to HF, Emotional stability, Strong family support system.	hepatic, renal or pulmonary disease, Active systemic or pulmonary infection, Recent pulmonary infarction, Uncontrollable HTN, Uncorrectable peripheral vascular disease, Active peptic ulcer disease, History of substance abuse (including alcohol) or behavior problem that would interfere with medical compliance					Older transplant recipient (>60y/o) more likely to die of an infectious complication after transplantation. Older transplant recipient (>60y/o) more likely to die of malignant disease after transplantation. Older pts (>60y/o) had significantly fewer rejection episodes per pt than those < 60 years at transplantation (1.9±1.3 vs 2.6 ±1.8)	Death from cancer: p=0.015 Rejection episodes: p=0.009
Comparative Outcome and Clinical Profiles in Transplantation (COCPIT) Study, Deng MC, 2000 10968814 (319)	To determine whether there is a survival benefit associated with cardiac transplantation in Germany.	Prospective observational cohort	N/A	889	Age ≥16 y, listed for cardiac transplantation	N/A	NYHA IV	Mortality, stratified by HF severity.	1 y mortality after listing: high risk: 51% medium risk: 32% low risk: 29% p <0.0001 1y mortality while waiting on transplant list: high risk: 32% medium risk: 20% low risk: 19% p <0.0003 for high risk compared with low/medium	N/A	For the total cohort there was no survival benefit from transplantation. However, for high risk pts, a mortality risk reduction was observed within 2 wk of transplantation (RR <1.0). This benefit disappeared after eight months.	p=0.04 (mortality risk reduction for high risk pts)

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									1y mortality s/p transplant high risk: 64% medium risk: 76% low risk: 75% p=0.2			
Reversible pulmonary HTN in heart transplant candidates—pretransplant evaluation and outcome after OHT, Klotz S, 2003 14607204 (320)	To assess the value of prostaglandin E1 (PG-E1) for reduction of PHT and to predict the postoperative outcome, compared to pts without PHT	Case-control	ACEI 81% Digitalis 74% Diuretics 75% beta blockers 38%	151	Referred for heart transplant evaluation at Munster University between 3/98-4/01	Pts with implanted MADs; clinical decompensation or inotropic-support at initial evaluation	NYHA IIIB-IV	1 y post-transplant Mortality	1y post-txplt mortality Non-pHTN: 14.8% Reversible pHTN: 22% Wait list mortality Non-pHTN: 17% Reversible pHTN: 17% Non-wait list Mortality Non-pHTN: 7% Reversible pHTN: 13%, p= 0.39 Irreversible pHTN: 50%, p<0.05	>3 y	Non-wait list, wait list, and 1y post-txplt mortality rates are similar for pts with reversible pHTN as those without pHTN.	N/A
Evolving trends in risk profiles and causes of death after heart transplantation: A 10 y multi-institutional study, Kirklin JK, 2003 12698152 (321)	To examine differences in risk-adjusted expected versus observed actuarial outcomes of cardiac transplantation over time at a single institution	Cohort, Registry	N/A	7290	7290 pts undergoing cardiac trans-plantation at 42 institutions over a 10-y period (1990-2000)	N/A	N/A	The primary end point of this study was death from all causes.	1y post-txplt mortality 1990-1992: 16% 1993-1995: 15% 1996-1999: 15% 3 y post-txplt mortality 1990-1992: 24% 1993-1995: 21% 1996-1999: 21%	10 y registry + 3 y follow-up, 13 y observation period	Later transplantation date reduced late post-transplant mortality, particularly that due to rejection and graft vasculopathy, refelcting increasing institutional expertise, changing immunosuppression regimens.	N/A

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Retransplantation in 7,290 Primary Transplant Pts: A 10-Y Multi-Institutional Study (Cardiac Transplant Research Database Group), Radovancevic B, 2003 12909465 (322)	To determine subsets of pts for whom cardiac retransplantation is appropriate therapy	Cohort, Registry	N/A	7290	Pts in CTRD that underwent a second cardiac transplantation between January 1990 and December 1999		NYHA IIIB-IV	Freedom from events (retransplantation and subsequent death, rejection, and infection)	1 y retransplantation rate: 0.8% 10 y retransplantation rate: 3.2% 1y mortality 15% after first transplant 46% after 2nd transplant 1y mortality post-2nd txplt by indication for re-txplt 68% acute rejection 50% early graft failure	10 y	Major indications for cardiac retransplantation: 1. Acute rejection 2. Early graft failure 3. Allograft vasculopathy Improved survival post re-txplt if primary reason is allograft vasculopathy, not acute rejection or early graft failure; survival similar to that of pts undergoing primary OHT	Improved survival post-retxplt if done for CAV, p=0.02 Post-retxplt survival for CAV no different than that for primary txplt of any cause, p=0.67
Outcome in Cardiac Recipients of Donor Hearts With Increased LV WT, Kuppahally SS, 2007 17845572 (323)	To evaluate the outcome in recipients of donor hearts with increased LVWT ≥1.2	Case-control	Cyclosporine 58% Tacrolimus 41% Sirolimus 31% Mycophenolate 69%	157	Pts transplanted between 1/01 and 12/04 at Stanford University Medical Center and the affiliated Northern California Kaiser Permanente heart transplant programs	Pediatric pts, multiple organ recipients, recipients who died within 3 d after transplantation	N/A	Incidence of cardiac recipient death or cardiac retransplantation	Overall mortality (mean 3 y f/u) donor LVH (≥1.2): 21.3% donor normal LVWT: 20% donor LVH (>1.4): 50% total: 20.4%	N/A	Donor heart LVWT>1.4cm increases post-transplant mortality and risk of allograft vasculopathy	Increased mortality with donor LVWT>1.4, p=0.003, 95% CI 1.8-21.5 VAD BTT, p=0.04, 95% CI 1.02-6.85
Long-term outcomes of cardiac transplantation for PPCM: a multiinstitutional analysis (CTRDG), Rasmusson KD, 2007 18022074 (324)	To assess outcomes in a relatively large group of PPCM allograft recipients with long-term follow-up	Registry	Induction cytolytic rx 31% Steroids (at 1y): 88%	671	1. Age ≤40 y at time of cardiac transplant 2. Etiology of HF: PPCM or IDCM	N/A	N/A	Rejection, infection, cardiac allograft vasculopathy, and survival	N/A	15 y registry	PPCM recipients had similar long-term survival as male IDCM recipients; PPCM recipients trended towards better survival compared with female IDCM, +h/o pregnancy recipients; PPCM recipients appeared to have better survival than	Overall survival PPM vs male IDCM, p=0.9 PPM vs +P, P=0.05 PPM vs -P, p=0.07

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											femail idiopathic DCM, never pregnancy recipients but not statistically significant.	
Clinical outcomes after cardiac transplantation in muscular dystrophy pts (CTRDG), Wu RS, 2010 19864165 (325)	To investigate the clinical out-comes of cardiac transplantation in muscular dystrophy pts with an extended follow-up period and to assess the outcomes in comparison with an age-matched control cohort	Case-controlled	Calcineurin inhibitors Cyclosporine 87% Tacrolimus 9% Unknown 4% Azathioprine 61% Mycophenolate 33% Uknown 6% Steroids (@1yr) 25%	304	Muscular dystrophy pts who underwent cardiac transplantation and matched-control cohort of IDCM pts (matched by age, BMI, gender, and race)	N/A	N/A	Survival after transplant	1y post-txplt mortality: Muscular dystrophy 11% Matched-control 9% 5 y post-txplt mortality: Muscular dystrophy 17% Matched-control 21% p=0.5	15 y registry	N/A	p=0.5 (post-txplt mortality)
The effect of transplant center volume on survival after heart transplantation: A multicenter study, Shuhaiber JH, 2010 20138635 (326)	To elucidate the effect of transplant center volume on 1-y mortality	Case-control	N/A	147 transplant centers/ 13230 heart transplants	Data from the Scientific Registry of Transplant Recipients of heart transplantations between 1/1/99 and 5/31/05	N/A	N/A	1 y mortality	1st y post-transplant mortality significantly higher at very low-volume transplant centers compared with low to high volume transplant centers.	5.5 y registry	Low-, medium, and high-volume transplant centers have lower 1y post-transplant mortality than very-low volume transplant centers.	p<0.001 for each group compared with very-low volume center group, 95% CI: Low volume 0.62-0.82 Med volume 0.56-0.74 High volume 0.48-0.65

ACEI indicates angiotensin-converting-enzyme inhibitor; AICD, automatic internal cardiac defibrillator; BMI, body mass index; BTT, bridge to transplant; CAV, cardiac allograft vasculopathy; CCB, calcium channel blocker; COCPIT, Comparative Outcome and Clinical Profiles in Transplantation; CPX, cardiopulmonary stress testing; CRT, cardiac resynchronization therapy; CRT-D, cardiac resynchronization therapy defibrillator; CTRD, Cardiac Transplant Research Database; DCM, dilated cardiomyopathy; FAR, functional aerobic reserve; f/u, follow-up; HATG, anti-T cell therapy; HF, heart failure; HFSS, heart failure survival score; h/o, history of; HTN, hypertension; ICD, implantable cardioverter defibrillator; IDCM, idiopathic dilated cardiomyopathy; LVEF, left ventricular ejection fraction; LVSD, left ventricular systolic dysfunction; LVWT, left ventricular wall thickness; MAD, mechanical assist device; N/A, not applicable; NYHA, New York Heart Association; OH, organ harvest; OHT, orthotopic heart transplantation; OKT3, Othoclone; PG-E1, prostaglandin E1; PDE3, phosphodiesterase enzyme; pHTN, pulmonary hypertension; PPCM, peripartum cardiomyopathy; PVR, pulmonary vascular resistance; QoL, quality of life; RCT, randomized controlled trial; RER, espiratory exchange ratio; SD, standard deviation; txplt, transplant; UNOS, United Network for Organ Sharing; VAD, ventricular assist device; VE/VCO2, carbon dioxide production; VO2, oxygen consumption; and VT, ventricular tachychardia.

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Data Supplement 37. Comorbidities in the Hospitalized Patient (Section 8.1)

Study Name, Author, Year	Aim of Study	Study Type	Background Therapy	Study Size	Etiology	Patient Population		Endpoints	Absolute Benefit	P Values & 95% CI:	OR: HR: RR:
			Pretrial standard treatment.	*N (Total Study Size)*	*Ischemic/Non-Ischemic*	*Inclusion Criteria*	*Exclusion Criteria*	*Primary Endpoint*			
Diabetes and Hyperglycemia											
Intensive vs. Conventional Glucose Control in Critically Ill Pts: The NICE-SUGAR Investigators. NEJM 2009; 360: 1283-97 (327) 19318384	Randomization of ICU pts to intensive vs. conventional glucose control	RCT	Tight glucose control recommended by some	6104	N/A	Hospitalized pts	N/A	Death	-2.60%	95% CI: 1.02 - 1.28 (p=0.02)	OR:1.02 death at 90 d
Elevated Admission Glucose and Mortality in Elderly Pts Hospitalized with HF. Kosiborod M, Inzucchi SE, Spertus JA, Wang Y, Masoudi FA, Havranek EP, Krumholz HM. Circulation 2009; 119: 1899-1907. (328) 19332465	To investigate the association between admission glucose and mortality in elderly pts hospitalized with HF	Cohort	Tight glucose control recommended by some	50,532	59.7% ischemic	Hospitalized pts	N/A	Death	N/A	p=0.64	0.998 fully adjusted model per 10 mg/dL increase in admission glucose
Seven-Year mortality in HF pts with undiagnosed DM: an observational study. Flores-LeRoux JA et al. Cardiovasc Diabetol 2011; 10:39 (329) 21569580	To assess the prognosis of hyperglycemia (previously undiagnosed DM) in pts admitted to the hospital with HF	Cohort	N/A	400	43% ischemic	Acute HF admission	Lost to follow-up	Total mortality	N/A	95% CI: 1.17 - 2.46 (p=0.006); 95% CI: 1.10 - 1.99 (p=0.009)	aHR unknown DM 1.69 (ACM); HR clinical DM 1.48 (ACM)
Berry C, Brett M, Stevenson K, McMurray JJV, Norrie J. Nature and prognostic importance of abnormal glucose tolerance and diabetes in acute HF. Heart 2008;94:296-304. (330) 17664189	To investigate the nature and importance of blood glucose abnormalities in an unselected HF population	Cohort	N/A	454	N/A	N/A	N/A	Inhospital mortality	N/A	p=0.0023; (95% CI: 1.03-1.13)	1.08, aHR per 2 mmol/L increase in glucose
Anemia											

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Blood Transfusions for Acute Decompensated HF: Friend or Foe? Garty et al. Am Heart J 2009;158:653-8. (331) 19781427	To assess the impact of blood transfusion among pts with ADHF	Propensity score analysis, national HF survey	Unknown	2335	~85% ischemic	ADHF	Chronic HF admitted for another reason	Mortality; 39.6 vs. 28.5% in BT vs. no BT pts	N/A	In hosp 0.08 (95% CI: 0.21-1.11); 30 d 0.02 (95% CI: 0.13-0.64); 1 y 0.12 (95% CI: 0.50-1.09); 4 y 0.29 (95% CI: 0.64-1.14)	aOR for BT: 0.48; 0.29; 0.74; 0.86
COPD											
Bronchodilator Therapy in ADHF in Pts without a History of Chronic Obstructive Pulmonary Disease. Singer AJ et al. Ann Emerg Med. 2008;51:25-34. (332) 17949853	The association between inhaled bronchodilators and HF pts with and without COPD	Registry (ADHF National Registry Emergency Module registry)	N/A	10,978	N/A	ED discharge diagnosis of ADHF as a primary condition, adult	N/A	Mortality (inhospital)	N/A	For pts without COPD bronchodilator use associated with mortality (95% CI: 0.67–1.56); mechanical ventilation (95% CI: 1.21–2.37) [adjusted, propensity-scored model]. For pts with COPD, no significant difference	1.02; 1.69
Should acute treatment with inhaled beta agonists be withheld from patients with dyspnea who may have heart failure? Maak CA et al. J Emerg Med. 2011 Feb;40(2):135-45. (333) 18572345	To determine the safety and efficacy of acute administration of inhaled beta-2 agonists to pts with HF	Review; evidence synthesis from MEDLINE and EMBASE searches	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

ACM indicates all cause mortality; ADHF, acute decompensated heart failure; BT, blood transfusion; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; ED, emergency department; EMBASE, Excerpta Medica Database; HF, heart failure; ICU, intensive care unit; MEDLINE, Medical Literature Analysis and Retrieval System Online; N/A, not applicable; NICE-SUGAR, Normoglycaemia in Intensive Care Evaluation and Survival Using Glucose Algorithm Regulation; pt, patient; and RCT, randomized control trial.

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Data Supplement 38. Worsening Renal Function, Mortality and Readmission in Acute HF (Section 8.5)

Study Name, Author, Year	Aim of Study	Study Type	Study Size	Patient Population		Endpoints		Statistical Analysis (Results)
				Inclusion Criteria	*Exclusion Criteria*	*Primary Endpoint*	*Secondary Endpoint*	
Damien Logeart, 2008 (334) 17651843	Study prevalence, causes and consequences of WRF during hospitalization for acute HF	Observational	416 pts admitted for acute HF	Pts hospitalized for acute HF	Chronic and severe renal failure (admission SCr >230 µmol/lol/L); cardiogenic shock or severe low output requiring inotropic agents during the hospitalization; inhospital death	Combined death; first unscheduled readmission for HF Outcome during the 6 mo after discharge was determined by contacting the pts or their general practitioners by telephone.	N/A	WRF occurred in 152 cases (37%), 5±3 d after admission. Old age, DM, HTN and acute coronary syndromes increased the risk of WRF. Inhospital furosemide doses as well as discharge treatment were similar in WRF and no-WRF pts. Serum Crelevation was the strongest independent determinant of a longer hospital stay (p=0.001). AEs occurred in 158 pts (38%) during follow-up, with 23 deaths and 135 readmissions. Cox analysis showed that WRF, transient or not, was an independent predictor of the risk of death or readmission (HR: 1.74 95%CI: 1.14–2.68; p=0.01).
Grace L. Smith, 2006 (335) 16697315	Estimate prevalence of renal impairment in HF pts and the magnitude of associated mortality risk using a systematic review of published studies.	Meta-analysis	80,098 hospitalized and non-hospitalized HF pts.	Cohort studies and secondary analyses of several RCTs.	Studies with <6 mo follow-up and a study that defined renal impairment using ICD-9 code but no direct serum measures	All-cause mortality risks associated with any renal impairment (Cr>1.0 mg/dL, CrCl or estimated eGFR <90 mL/min, or cystatin-clopidogrel >1.03 mg/dL) and moderate to severe impairment (Cr≥1.5, CrCl or eGFR <53, or cystatin-clopidogrel ≥1.56)	Cardiovascular mortality (all cardiovascular mortality and HF or pump failure mortality) and functional decline by validated functional status scales such as NYHA functional class or activities of daily living assessment	A total of 63% of pts had any renal impairment, and 29% had moderate to severe impairment. After follow-up ≥1 y, 38% of pts with any renal impairment and 51% with moderate to severe impairment died vs 24% without. Adjusted all-cause mortality was increased with any impairment (aHR: 1.56; 95% CI: 1.53-1.60, p <0.001) and moderate to severe impairment (aHR: 2.31; 95% CI: 2.18-2.44, p<0.001). Mortality worsened incrementally across the range of renal function, with 15% (95% CI: 14%-17%) increased risk for every 0.5 mg/dL increase in Crand 7% (95% CI: 4%-10%) increased risk for every 10 mL/min decrease in eGFR.
Marco Metra, 2008 (336) 18279773	Association between hospitalizations for acute HF and WRF	Observational	318 consecutive pts admitted for acute HF.	Diagnosis of acute HF, as established by the ESC guidelines; treatment with an IV agent, which in all cases included furosemide with or without other vasoactive medications.	Inability to give informed consent and those with evidence of ACS, acute arrhythmia, myocarditis, valve stenosis, cardiac tamponade, aortic dissection, pulmonary embolism, high output syndrome or evidence of non-cardiovascular factors	Cardiac death and urgent, unplanned hospitalizations	N/A	53 pts (17%) died and 132 (41%) were rehospitalized for HF. WRF-Abs-% occurred in 107 (34%) pts. In multivariable survival analysis, WRF-Abs-% was an independent predictor of death or HF rehospitalization (aHR: 1.47; 95%CI: 1.13–1.81; p=0.024). The independent predictors of WRF-Abs-%, evaluated using multivariable logistic regression, were history of chronic kidney disease (p=0.002), LVEF (p=0.012), furosemide daily dose (p=0.03) and NYHA class (p=0.05) on admission.

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					as main cause of symptoms development of complications or undergoing procedures which may cause a rise in Cr during the hospitalization			
Cowie MR, 2006 16624834 (337)	To determine the prevalence and risk factors for WRF among pts hospitalized for decompensated HF and the association with subsequent rehospitalization and mortality.	Observational	299	Age >20 y, documented history of chronic HF defined according to the ESC criteria; documented evidence of impaired LVSF, as demonstrated by an EF 40% on TTE or other imaging technique on the index admission or within the preceding 6 mo	Pts with a planned discharge within 24 h of admission; an investigator-defined history of ACS or cardiogenic shock within 1 mo prior to the index admission; receiving a new prescription for potentially nephrotoxic drugs within 2 d prior to admission; severe aortic stenosis, valvular disease anticipated to require surgery within 6 mo, 'high output' cardiac failure, or those undergoing chronic renal replacement therapy or cancer chemotherapy	All-cause mortality during the initial hospitalization and within 30+7 d and 180+7 d of the index hospitalization; date and cause of subsequent hospital re-admissions were also recorded.	N/A	1/3 of pts [72 of 248 pts, 29% (95% CI: 26-32%)] developed WRF during hospitalization. The risk of WRF was independently associated with SCr levels on admission (OR: 3.02, 95% CI: 1.58-5.76), pulmonary edema OR: 3.35, 95% CI: 1.79-6.27, and a history of AF: OR 0.35: 95% CI: 0.18-0.67. Although the mortality of WRF pts was not increased significantly, the length of stay was 2 d longer [median 11 d (90% range (4-41) vs 9 d (4-34), p=0.006]. The rehospitalization rate was similar in both groups.
Komukai K, 2008 18577827 (338)	To investigate whether renal dysfunction is associated with rehospitalization for CHF after successful discharge	Observational	109 pts	Pts with CHF who had been admitted and followed up after discharge at the outpatient clinic were reviewed. CHF was diagnosed by ≥2 cardiologists on the basis of the Framingham criteria	HF complicated by acute MI, undergoing or starting dialysis during the follow-up period, or undergoning cardiac surgery during the follow-up period	Rehospitalization for HF after discharge	N/A	Pts with decreased renal function (estimated GFR on admission <45ml Emin.1 E1.73m2) were rehospitalized more frequently than were pts with preserved renal function (estimated GFR on admission .45). Pts with decreased renal function were older and had higher rates of anemia, WRF during hospitalization, and previous HF hospitalization. Independent predictors of rehospitalization for HF identified with multivariate analysis were age, previous hospitalization for HF, decreased renal function, and non-use of an ACEI or ARB.
Akhter MW, 2004 15464689 (339)	Evaluate the relation between elevated SCr at baseline, as well as WRF during hospitalization, and	Secondary analysis of the VMAC trial	481 (215 had RI and 266 did not)	Patients with dyspnea at rest caused by acute HF	N/A	Length of hospitalization, 30 d readmission rate as well as 30-d and 6-mo mortality	N/A	Elevated baseline Cr was associated with length of hospital stay (median 6 vs 7 d, p=0.003). RI was associated with a 59% increase in 30-d readmissions (17% vs 27%, p=0.016). Higher Cr on admission was associated with both morbidity and mortality. All-cause mortality at 6 mo increased

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	outcomes pts hospitalized for decompensated HF in the VMAC trial							(37.4% vs 12.3%, p <0.0001). Baseline RI was an independent predictor of 6-mo mortality with a RR: 2.72; 95% CI 1.76-4.21; p=0.0001.
Nohria A, 2008 18371557 (340)	Examine the ESCAPE database to assess the impact of renal dysfunction in patients with acute HF	Secondary analysis of the ESCAPE trial	A total of 433 pts were enrolled at 26 sites	LVEF ≤30%, recent hospitalization or escalation of outpatient diuretic therapy, and SBP ≤125 mm Hg who were admitted to the hospital with at least 1 sign and 1 symptom of HF, despite adequate treatment with ACEIs and diuretics	Creatinine >3.5 mg/dL, the use of dobutamine/dopamine >3 μg/kg/min or milrinone before randomization, and requirement for early right heart catheterization.	D alive and out of the hospital for 6 mo after randomization	30-d mortality and length of stay	Baseline and discharge RI, but not WRF, were associated with an increased risk of death and death or rehospitalization. Among the hemodynamic parameters measured in pts randomized to the PAC arm (n=194), only right atrial pressure correlated weakly with baseline SCr (r=0.165; p=0.03). There was no correlation between baseline hemodynamics or change in hemodynamics and WRF. A PAC-guided strategy was associated with less average increase in Cr, but did not decrease the incidence of defined WRF during hospitalization or affect renal function after discharge relative to clinical assessment alone.
Owan et al., 2006 16679257	Whether the severity of renal dysfunction, the incidence of WRF or outcomes has changed over time (secular trends) in pts hospitalized for HF therapy.	Observational	6440	All consecutive HF pts admitted to Mayo Clinic hospitals in Rochester, MN, between January 1, 1987, and December 31, 2002	N/A	Change in the incidence of WRF or outcomes over time	N/A	The incidence of WRF, defined as an increase in Crof >0.3 mg/dL increased slightly over the study period (p=0.01). Renal dysfunction and development of WRF were associated with mortality. When adjusted for the changes in baseline characteristics, later admission year was associated with lower 3-mo (aOR: 0.98 per y; 95% CI: 0.96–0.99; p=0.008) and overall mortality (HR: 0.99 per y; 95% CI 0.98–1.00; p 0.002).
Krumholz, 2000 10781761 (341)	To determine the incidence and identify factors associated with the development of worsening renal function in elderly patients with acute HF and to examine the impact of WRF on clinical and economic outcomes.	Retrospecrive	1,681 pts from 18 Connecticut hospitals	Age ≥65 y; discharge with HF without having clear precipitants for renal dysfunction	Pts <65 y of age; pts whose diagnosis could not be validated by medical record review, pts with severe aortic stenosis, severe mitral stenosis, or HF secondary to a medical illness (e.g., sepsis); major complications (stroke, acute MI shock, heart arrest, hypotension, pneumonia, and infection) or underwent a cardiac procedure requiring contrast (cardiac catheterization or angioplasty) or bypass	The outcome variable for the first phase of the study was worsening renal function, defined as in the ELITE study as an increase in SCr level during hospitalization of >0.3 mg/dL from admission. The principal endpoints for the 2nd phase of the study were inhospital mortality, length of stay and cost, 30-d mortality and readmission, and 6-mo mortality and readmission	N/A	WRF occurred in 28% of the cohort and was associated with male gender, HTN, rales > basilar, pulse >100 beats/min, SBP >200 mm Hg, and admission Cr>1.5 mg/dL. Based on the number of these factors, a pt's risk for developing WRF ranged between 16% (≤1 factor) and 53% (≥5 factors). After adjusting for confounding effects, WRF was associated with a significantly longer length of stay by 2.3 d, higher inhospital cost by $1,758, and an increased risk of inhospital mortality (aOR:2.72; 95% CI:1.62-4.58)

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					surgery during hospitalization			
Forman , 2004 14715185 (342)	To determine the prevalence of WRF among hospitalized HF pts, clinical predictors of WRF, and hospital outcomes associated with WRF.	Cohort (retrospective)	1,004	HF pts hospitalized between July 1, 1997, and June 30, 1998, at 11 academic medical centers.	Pts were excluded if their hospitalizations were for an elective procedure (e.g., percutaneous transluminal coronary angioplasty, pacemaker, or cardioversion) or if their hospital length of stay was <2 d. Other exclusion criteria included severe aortic stenosis, anticipated cardiac transplantation, transfer from another inhospital setting, chronic dialysis, use of a LV assist device, high-output HF, age <20 y, concomitant use of an investigational product or device, and patients receiving chemotherapy. Subjects were also excluded if Crvalues were not documented at admission.	The principal outcome was WRF, defined as an increase in SCr of >0.3 mg/dL (26.5 μmol/L) from admission, consistent with several previous investigations; hospital length of stay, inhospital mortality, and complications occurring after the rise in creatinine. Complications were defined as shock, MI, stroke, major infection/sepsis, clinically significant hypotension, and new onset AF with ventricular rates >100 beats/min.	N/A	Among 1,004 HF pts studied, WRF developed in 27%. In the majority of cases, WRF occurred within 3 d of admission. History of HF or DM, admission Cr≥1.5 mg/dL (132.6 μmol/L), and SBP >160 mm Hg were independently associated with higher risk of WRF. A point score based on these characteristics and their RR ratios predicted those at risk for WRF. Hospital deaths aRR: 7.5; 95% CI: 2.9-19.3), complications (aRR: 2.1; 95% CI: 1.5-3.0), and length of hospitalizations >10 d (aRR: 3.2, 95% CI: 2.2-4.9) were greater among pts with WRF

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Klein, 2008 19808267 (343)	To investigate the relation between admission values and changes in BUN and eGFR and rate of death by 60 d after discharge	Retrospective analysis of OPTIME-CHF (multicenter, randomized, double-blind, placebo-controlled trial)	949	Pts >18 y who had known systolic HF and had been hospitalized for exacerbation of no more than 48 h earlier	Active myocardial ischemia within the past 3 mo, AF with poor ventricular rate control (>110/min), sustained ventricular tachycardia or ventricular fibrillation, baseline SBP <80 mm Hg or SCr level >3.0 mg/dL (265 μmol/L)	Total no. of d hospitalized for cardiovascular causes within 60 d of randomization. D lost to follow-up and d deceased were prospectively included in the primary endpoint to avoid bias toward a therapy with an increased death rate.	N/A	Although both lower admission eGFR and higher admission BUN were associated with higher risk of death by 60 d after discharge, multivariable proportional-hazards analysis showed that BUN was a stronger predictor of death by 60 d than was eGFR (χ^2 =11.6 and 0.6 for BUN and eGFR, respectively). Independently of admission values, an increase of ≥10 mg/dL in BUN during hospitalization was associated with worse 60-d survival rate: BUN (per 5-mg/dL increase) had a HR: 1.08; 95% CI: 1.01-1.16). Although milrinone treatment led to a minor improvement in renal function by discharge, the 60-d death and readmission rates were similar between the milrinone and placebo groups

ACEI indicates angiotensin-converting-enzyme inhibitor; ACS, acute coronary syndrome; AE, adverse event; AF, atrial fibrillation; BUN, blood urea nitrogen; CHF, congestive heart failure; Cr, creatinine; CrCL, creatinine clearance; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; ELITE, Evaluation of Losartan in the Elderly; ESC, European Society of Cardiology; ESCAPE, Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness; HTN, hypertension; ICD-9, international classification of diseases – 9th edition; IV, intravenous; LVSF, left ventricular systolic function; MI, myocardial infarction; NYHA, New York Heart Association; OPTIME-CHF, the Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure study ; Pts, patients; RCT, randomized clinical trial; RI, renal insufficiency; SBP, systolic blood pressure; SCr, serum creatinine; TTE, transthoracic echocardiography; VMAC, Vasodilation in the Management of Acute Congestive Heart Failure; and WRF, worsening renal function.

Data Supplement 39. Nesiritide (Section 8.7)

Study Name, Author, Year	Aim of study	Study Type	Background Therapy	Study Size	Etiology	Pt Population		Severity		Endpoints		Mortality	Trial Duration (Years)	Statistical Analysis (Results)	Study Limitations	Complications /AEs
			Pre-trial standard treatment.	*N (Total) n (Experimental) n (Control)*	*Ischemic/ Non-Ischemic*	*Inclusion Criteria*	*Exclusion Criteria*	*Severity of HF Symptoms*	*Study Entry Sverity Criteria*	*Primary Endpoint*	*Secondary Endpoint*	*1st Year Mortality*				
Nesiritide Study Group (NSGT), Colucci WS, 2000. 10911006 (344)	Determine efficacy/clinical use of nesiritide for short term treatment of ADHF.	RCT	Chronic medication regimen N/A; any IV medication (dobutamine, milrinone, dopamine, or vasodilator) was	Efficacy trial: 127 Comparative trial: 305. NESIRITIDE Efficacy trial: 43 (0.015 g/kg/min), 42 (0.03 mg/kg/min) Comparative trial: 103 (0.015mg/kg/min)	Efficacy trial: 46% ICM, Comparative trial: 54% ICM.	Symptomatic HF warranting hospitalization for ≥1 IV medication in addition to diuretics. Efficacy trial: PCWP ≥18 mmHg, CI, ≤2.7L/min/m,	MI/UA within prior 48 h. Clinically important valvular stenosis, HCM or RCM, constrictive pericarditis, primary pHTN, or active myocarditis.	Efficacy trial: 98% NYHA III-IV mean PCWP 28 mmHg, mean CI 1.9 L/min/m2, mean SBP 116 mmHg. Comparativ	Symptomatic ADHF requiring ≥1 intravenous medication in addition to diuretics.	Efficacy: change from baseline PCWP @ 6 h after treatment Comparative: Global clinical status (independen	Efficacy trial: Global clinical status. Clinical symptoms. Other hemodynamic measure	N/A	<1y (10 mo enrollment 10/96-7/97); Comparative trial: 68-73% rx with nesiritide x 1-2 d 14-21%	Efficacy trial: PCWP - 6.0±7.2mm Hg (@ 0.015 g/kg/min) vs. - 9.6±6.2mm Hg (@ 0.03 g/kg/min) vs. +2.0±7.2mm Hg (placebo) Comparative	Subjective measurements of global clinical status and clinical symptoms. Background medical therapy not reported. 3. Change in	Asymptomatic/ mildly symptomatic hypotension. NSVT (Comparative trial).

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			discontinued; diuretics were held 4 h before, during, and 6 h after study drug infusion in Efficacy trial.	, 100 (0.03 mg/kg/min). Efficacy trial: 42 placebo, Comparative Trial: 102 standard rx (investigator choice of up to 2 IV agents---milrinone, dobutamine, nitroglycerin, or nitroprusside, along with diuretics and other oral HF medications).		2, SBP, ≥90 mmHg.		e: 92% NYHA III-IV.		t assessment by pt and investigator, 5-point scale: markedly better, better, no change, worse, or markedly worse). Clinical symptoms (dyspnea and fatigue, jointly pt and investigator assessment, 3 point scale: improved, no change, or worse).	ments.		x 3-5d, 9-14% x 5d.	trial: none. Efficacy trial: p<0.001 (pairwise with placebo).	PCWP is a surrogate outcome.	

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Vasodilation in the Management of Acute CHF (VMAC), 2002. 11911755 (345)	To compare the efficacy and safety of intravenous nesiritide, intravenous nitroglycerin, and placebo.	RCT	Diuretics 86%, ACEI 60%, ARB 11%, beta blockers 33%, oral nitrates 35%, CCB 14%, digoxin 60%, warfarin 33%, ASA 45%, statins 25%.	489 204(nesiritide) 143 (nitroglycerin) 142 (placebo)	Ischemic 55%	Dyspena at rest due to decompensated CHF Severe enough dyspnea to require hospitalization & IV therapy. A cardiac etiology for dyspnea was established by estimated or measured elevation of cardiac filling pressures (PCWP ≥20 mm Hg in catheterized pts) and ≥ 2 of the following: (a) JVD, (b) PND or 2-pillow orthopnea within 72 h before study entry, (c) abdominal discomfort due to mesenteric congestion, or (d) a CXR consistent with decompensated CHF.	SBP <90 mm Hg, cardiogenic shock or volume depletion, any condition that would contraindicate an IV vasodilator, acutely unstable clinical status that would not permit a 3 h placebo period, use of IV nitroglycerin that could not be withheld, mechanical ventilation, and anticipated survival of <30-35 d.	100% NYHA IV at time of presentation/entry or at least dyspneic at rest, 84% chronic NYHA III-IV (prior to decompensation), 19% SBP <100mmHg .	NYHA IV at presentation (dyspnea at rest).	PCWP Pt self-assessment of dyspnea @ 3 h of study drug infusion (3 point scale: improved, no change, worse).	Comparisons between nesiritide and nitroglycerin: Onset of effect on PCWP. Effect on PCWP @ 24 hr after start of study drug. Self-assessed dyspnea and global clinical status. Overall safety profile. Use of other IV vasoactive agents or diuretics. Effects on other hemodynamic variables.	N/A	Enrollment October 1999 and July 2000 (10 mo); study drug infusion, median time 24-25 h.	PCWP at 3 h (mean (SD)) Nesiritide: −5.8 (6.5) mmHg* Nitroglycerin : −3.8 (5.3) mmHg Placebo: −2 (4.2) mmHg ABSOLUTE BENEFIT IN PCWP Nesiritde vs. Placebo : -3.8 mmHg. *p<0.05 (compared with placebo, compared with nitroglycerin) . N/A	Subjective measurements of global clinical status and clinical symptoms. Change in PCWP is a surrogate outcome.	Generalized headache (8% nesiritide group vs. 20% nitroglycerin group) Asymptomatic (8%) and symptomatic (4%) hypotension in nesiritide group.

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Prospective Randomized Outcomes Study of Acutely Decompensated Congestive HF Treated Initially as Outpts With Nesiritide (PROACTION), Peacock IV WF, 2005. 16183441 (346)	To evaluate the safety and efficacy of a standard care treatment regimen with the addition of either nesiritide or placebo in ED/OU pts with decompensated HF.	RCT	Diuretics 77%, ACEI 58%, ARB 14%, beta blockers 46%, aldosterone antagonist 14%, CCB 22%, digoxin 48% placebo vs. 34% nesiritide, nitrates 45%, statins 29%, ASA 46%.	237 120 117	N/A	1. Pt presented to ED with a medical Hx with HF, along with fluid overload or elevated cardiac filling pressures by clinical assessment, dyspnea at rest or with minimal exertion (defined as walking 20 ft), and judged to require ≥12 h of hospital therapy for HF. 2. Evidence of HF as primary etiology of the dyspnea required ≥2 of the following: a) PND or 2-pillow orthopnea within 72 h before the start of study drug; b) JVD; c) abdominal symptoms, as manifest by	1. Pt not a candidate for observation (e.g., presented with any condition that obviously mandated hospital admission, such as acute MI, or requirement for invasive monitoring or mechanical ventilation, including BPAP); 2. SBP <90 mmHg; 3. Admitted to the ED primarily for a diagnostic evaluation (e.g., rule out ACS); 4. Receiving chronic dialysis; 5. Had cardiac markers indicative of myocardial necrosis; 6. Medical condition so severe that 30 d survival was unlikely; 7. Medical condition	61% NYHA III-IV at baseline.	Dyspnea at rest or with <20 feet ambulation.	No pre-defined primary endpoints. Efficacy measures included admission to the hospital after the index visit, readmission within 30 d for any reason, length of stay in the hospital, assessment of dyspnea, and resource utilization. Safety measures included: vital signs, AEs (defined as any pre-existing medical event that worsened or any new medical event that occurred during administration of study drug,	N/A	N/A	11 mo enrollment period (3/01-1/02); mean study drug infusion time ~20 h (same for both groups); 30d follow-up period.	Total hospital LOS through study Day 30 excluding index visit (days) Mean ± SD: 7.1 ± 4.25 (placebo + standard care) vs. 3.1 ± 2.20 (nesiritide + standard care); 2. Subjects readmitted after index hospitalization, excluding those who died or were lost to follow- up: 23% (placebo + standard care) vs. 9% (nesiritide + standard care). 1. p=0.032 2. p=0.049 N/A	No pre-defined primary end-points; 49% of pts were NYHA I-II or without any Hx of HF.	Asymptomatic hypotension (10% with nesiritide vs 3% with placebo, p=0.03).

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						discomfort, decreased appetite, or nausea attributed by the investigator to be due to hepatosplanchnic congestion; d) ≥5lb weight gain in the previous month; e) CXR with findings indicative of HF; or f) pulmonary rales.	(such as cardiogenic shock or volume depletion) that contraindicated use of IV vasodilatators. 8. If within 2 h before the start of study drug administration pt received IV vasodilatators or oral ACEI; or they were anticipated to require either IV vasodilators during the first 3 h after the start of study drug or oral ACEI during the first 30 min after the start of study drug.			whether or not related to study drug), and SAEs (defined as AEs that were life-threatening, resulted in hospitalization, or death).						
Risk of Worsening Renal Function With Nesiritide in Pts With Acutely Decompensated HF, Sackner-Bernstein JD, 2005. 15781736 (347)	To investigated the renal effects of nesiritide as treatment for ADHF.	Meta-analysis	Variable (see original RCTs included in meta-analysis).	1269 797 472	N/A (see original RCTs)	Five RCTs (1288 pts were enrolled and randomized, 1269 underwent assessment of renal function) reported the effects of nesiritide on renal function as measured	N/A	See original RCTs	See original RCTs	Studies were reviewed for the incidence of worsening renal function (increase in SCr >0.5 mg/dL recorded at any time during the input portion	N/A	N/A	N/A	WRF: 21% (nesiritide) vs. 15% (control). WRF requiring medical intervention: 11% (nesiritide) vs. 4% (control) WRF requiring	Meta-analysis Inability to adjust statistically for differences in other factors beyond treatment group assignment that could have	N/A

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						by the frequency of increased (SCr) ≥0.5 mg/dL forming the basis of meta-analyses.				of the trial).				hemodialysis: 2% vs 2%. 1) p=0.001 2) p=0.03 3) p=0.71 1) RR_{MH}: 1.54; 95% CI: 1.19 to 1.98; 2) RR_{MH}: 2.29; 95% CI: 1.07-4.89; 3) 95% CI: 0.50- 2.76;	influenced the development of renal dysfunction. WRF is a surrogate marker for clinical outcome.	
Short-term Risk of Death After Treatment With Nesiritide for Decompensated HF A Pooled Analysis of RCTs, Sackner-Bernstein JD, 2005. 15840865 (348)	To investigate the safety of nesiritide relative to noninotrope-based control therapies, primarily consisting of diuretics or vasodilators.	Meta-analysis	Variable (see original RCTs included in meta-analysis).	862 485 377	N/A (see original RCTs)	Randomized double-blind study of pts with acutely decompensated HF, therapy administered as single infusion (≥6 h), inotrope not mandated as control, and reported 30 d mortality (NSGET, VMAC, PROACTION).	N/A	Variable: 60-98% NYHA III-IV, overall 79% NYHA III-IV.	See original RCTs	30 d survival was assessed by meta-analysis using a fixed-effects model and time-dependent risk by Kaplan-Meier analysis with Cox proportional hazards regression modeling.	N/A	N/A	N/A	1) 30 d mortality: 7.2% (nesiritide) vs. 4.0% (control). 1) p=0.059. 1) RR: 1.74; 95% CI: 0.97-3.12.	1) The NSGET, VMAC, and PROACTION studies were not de-signed to definitively determine whether nesiritide is associated with risk of death, although each prospectively monitored for deaths following therapy. 2) None of the 3 studies collected complete information on the use	

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															of additional medications or procedures through the 30 d follow-up period. (possible confounders). 3) It is possible that these results are due to chance.	
BNP-CARDS, Witteles RM, 2007. 17980248 (349)	To evaluate the impact of nesiritide on renal function in pts with acute decompensated HF and baseline renal dysfunction.	RCT	Beta blocker 65%, ACEI/ARB 49%, aldosterone antagonist 13%, digoxin (26%), amiodarone (21% nesiritide vs. 6% placebo), CCB 24%, hydralazine (5% nesiritide vs. 25% placebo).	75 39 36	CAD: 77% (nesiritide) vs. 56% (control)	Newly admitted with primary dx of ADHF. Calculated GFR (using the Cockcroft-Gault formula) between 15 to 60 ml/min (changed from 15 to 50 ml/min in December 2004 to be consistent with the published definition of “moderate renal impairment”). Age ≥18 y.	Baseline SBP <90 mm Hg. Hemodynamically significant aortic stenosis. Need for IV vasodilator therapy. Admission to ICU. Hx of cardiac transplantation Allergy to nesiritide. Prior enrollment in the trial.	N/A	N/A	A significant decline in renal function (defined as a peak SCr increase of ≥20% at any time during the first 7 d of hospitalization compared with the admission creatinine). Change in SCr from the admission value to discharge and/or Day 7 of hospitalization, whichever	Net negative diuresis ≥1 l/day while on the infusion. Change in weight during the infusion. Need to discontinue the infusion due to hypoten-sion. Total diuretic use while receiving the infusion. Median length of stay. Death or	N/A	30 mo (3/04 - 8/06); up to 30 d follow up.	No significant differences in the incidence of a 20% creatinine rise (23% nesiritide vs. 25% placebo). No significant difference in the change in SCr (-0.05 vs. +0.05 mg/dl). No significant differences in the secondary end points of 3a) weight (-2.19 vs. -1.58 kg), 3b) IV	Small # of participants still could allow for a type II error. Exclusion of important subgroups of ADHF pts, including those needing intensive care and those requiring IV vasodilator therapy; the results of this trial certainly do not exclude a potentially important effect of nesiritide (positive or	13% discontinued infusion d/t hypotension; 10% transferred to ICU; 10% 30 d mortality; 33% 30 d mortality/readmission (of note: no difference in these SAE/complications compared with placebo control).

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										was sooner.	rehospitalization within 30 d. Resource utilization—defined by need for dialysis, intensive care monitoring, pulmonary artery catheterization, and intubation.			furosemide (125 vs. 107 mg), 3c) discontinuation of infusion due to hypotension (13% vs. 6%), 3d) 30 d death/hospital readmission (33% vs. 25%) 1) p=0.85 2) p=0.46 3a) p=0.26 3b) p=0.53 3c) p=0.28 3d) p=0.43	negative) on renal function in those pts. Although trial was not powered to evaluate mortality and hospital readmission, there were nonsignificant trends observed in favor of placebo. Due to the relatively small sample size, the lack of statistical significance does not rule out differences in these outcomes.	
Follow-Up Serial Infusions of Nesiritide, FUSION I, Yancy CW, 2006. 16828598 (350)	To test the feasibility of nesiritide as adjunctive therapy for pts with advanced HF and a Hx of recurrent hospitalizations.	RCT	Diuretics 100%, beta blockers 75%, ACEI 56%, ARB 17%, oral nitrates 49%, aldosterone antagonist 36%, IV milrinone 28%, IV	138 49 (0.005 g/kg/min) 46 (0.010 g/kg/min) 43 (standard care)	65% ICM	Adults (aged ≥18 y). NYHA III or IV HF for ≥60 d before randomization. ≥2 hospital admissions or unscheduled outpt visits requiring IV vasoactive	SBP<90 mm Hg. Recipient of or listed for cardiac transplantation Placement of a BiV PM within previous 60 d or AICDd within previous 30 d. Currently	100% NYHA III-IV	N/A	Safety, as predetermined by the ability to tolerate out-pt infusions of nesiritide without evidence of an increased AE rate compared with SC.	N/A	N/A	Enrollment period N/A; 12 wk follow-up.	The frequency of all-cause hospitalization through wk 12 was lower in pts receiving SC plus either nesiritide 0.005 g/kg/min or nesiritide 0.010	The study was not powered to assess outcomes.	AEs related to renal function (i.e., abnormal renal function, acute renal failure, increased blood urea nitrogen, increased SCr, and oliguria, as defined in Coding Symbols for a

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			dobutamine 10%, IV dopamine 11%.			treatment for ADHF within the 12 mo preceding randomization. 4. ≥1 admission in the preceding 5 to 30 d. 5. 6MWT <400 m. 6. Currently receiving optimal HF treatment with long-term oral medications.	receiving long-term dialysis or likely to require dialysis during the study period. Inability to complete a 6 m walk test. Evidence of acute MI within previous 30 d.							g/kg/min than in those receiving SC only. Also, pts in the nesiritide groups were alive and out of the hospital for more days (median 84 d for the 2 groups) than those in the SC-only group (median 77 d). All cause hospitalization: p=0.037 (nesiritide 0,005 mg/kg/min vs. standard care alone), p=0.011 (nesiritide 0,010 mg/kg/min vs. standard care alone). Days alive and out of hospital: p=0.005 (nesiritide vs. standard care only).		Thesaurus of Adverse Reaction Terms), occurred in 22% of all pts. An increase in SCr to >0.5 mg/dl higher than baseline occurred at some time during the study in 18 of 41 pts (44%) in the standard care-only group, 17 of 49 pts (35%) in the nesiritide 0.005 g/kg/min group, and 16 of 46 pts (35%) in the nesiritide 0.010 g/kg/min group (p=0.614). The most frequently reported AEs among all pts with RI were worsening HF (42%), asymptomatic hypotension (16%), dyspnea (13%), and symptomatic hypotension (12%).

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Second Follow-Up Serial Infusions of Nesiritide, FUSION II, Yancy CW, 2008. 19808265 (351)	To evaluate the potential clinical utility of outpt, intermittent nesiritide infusions in ACCF/AHA stage C/D HF pts.	RCT	Loop diuretics 75%, ACEI 43%, ARB 14%, beta blocker 65%, aldosterone antagonist 37%, nitrates 18%, ICD 39%, CRT 24%.	911 605 306	64% Ischemic	≥2 HF hospitalizations or the equivalent within 12 mo, with the most recent within the prior 60 d. (A hospitalization equivalent was defined as an unscheduled outpt treatment for ADHF with an intravenous vasoactive drug or 3 unscheduled intravenous diuretic treatments for ADHF within 60 d.) LVEF <40% within 24 wk. Investigator documentation of consistent NYHA III or IV symptoms during the previous 60 d (estimated creatinine clearance <60 mL/min calculated by the	SBP <90 mmHg. Dependence on (or inability to discontinue) intermittent or continuous IV vasoactive medications. >2 output infusions of vasoactive therapy within 30 d without a hospitalization Biventricular pacemaker within 45 d or a single- or dual-chamber pacemaker, ICD within 15 d. Cardiogenic shock or volume depletion. Chronic dialysis.	100% NYHA III-IV	N/A	Time to all-cause death or the first hospitalization for cardiovascular or renal causes from randomization through Week 12.	No. of cardiovascular and renal hospital admissions. D alive and out of the hospital. Time to cardiovascular death, all evaluated through Wk 12. QoL as assessed by change in the KCCQ summary score from baseline to Wk 13.	N/A	Enrollment 4/04-6/06. Follow-up ended in 12/06.	All-cause mortality or cardiovascular and renal hospitalizations through Week 12 occurred in 36.8% of the placebo combined group and 36.7% of the nesiritide combined group. No statistically significant difference in secondary end-points. Log-rank test p=0.79. HR: 1.03; 95% CI: 0.82-1.3.	"Because of the much lower than expected event rates, FUSION II was underpowered to evaluate the effect of nesiritide on the primary end point. The resulting power calculation based on the observed placebo event rates yielded only 37% power to detect a conservative relative risk reduction of 15% between groups. In retrospect, a sample size of 3500 pts would have been needed for 90% power to detect this treatment effect. However, it	SCr >0.5 mg/dl in 32.1% (nesiritide) vs. 38.8% (placebo), p=0.046.

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						Cockcroft-Gault equation; 24 h urine collection was also required for NYHA class III pts). Optimal treatment with oral medications and device therapy unless a documented contraindication or intolerance was present.									should be noted that on the basis of the actual results, the wide confidence limits with a nearly indistinguishable event rate between active treatment and placebo exclude a benefit in the primary end point as small as 15%, making it relatively unlikely that an important positive effect was missed."	
Acute Study of Clinical Effectiveness of Nesiritide in Decompensated HF, ASCEND-HF, O'Connor CM, 2011. 21732835 (352)	To evaluate the effect of nesiritide, in addition to standard care, on rates of self-reported dyspnea at 6 and 24 h, rehospitalization for HF or death from any cause at	RCT	ACEI/ARB 60%, beta blocker 58%, Aldosterone antagonist 28%, nitrate 23%, hydralazine 7.4%, loop diuretic 95%,	7007 3496 (nesiritide) 3511 (placebo)	60% ICM	Age >17 y. Pts hospitalized for ADHF. Pts hospitalized for a reason other than ADHF, but diagnosed with ADHF within 48 h of admission.	Hospitalized >48 h before randomization. Probable discharge in <24h. Hypotension risk. Uncontrolled hypertension. Experimental medication (including nesiritide) or	100% NYHA III-IV at time of enrollment.	NYHA III-IV; at least 1 of following signs: respiratory rate ≥20 breaths/min or pulmonary congestion or edema with rales ≥1/3 way	Two coprimary end points: Composite of HF rehospitalization and all-cause mortality from randomization through D 30. Change in	Self-reported overall well-being at 6 and 24 h after study drug initiation. Composite of persistent or worsening	30 d mortality: 4.0% placebo vs. 3.6% nesiritide.	Enrollment 5/07-12/10; study drug infusion, at least 24 h and up to 7 d.	No significant effect on 30 d rehospitalization (6.0% nesiritide vs. 6.1% placebo) or 30 d mortality (3.6% nesiritide vs. 4.0%	Primarily addressed safety concerns, thus broad range of pts. Rudimentary, pt assessment of dyspnea. Low clinical event rate.	30 d all-cause mortality and worsening renal function: 31.4% vs. 29.5% (Nesiritide vs. Placebo, p=0.11). 2. Higher rate of hypotensive events amongst nesiritide group

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	30 d, and renal dysfunction.		inotropic agent 4%, vasodilator 15%.				device use. Pregnant or suspected pregnancy.		up lung field; at least 1 of following objective measures: congestion or edema on CXR, BNP ≥400 pg/ml or NT-pro-BNP ≥1000 pg/ml, PCWP >20 mmHg, LVEF <40% in prior 12 mo.	self-reported dyspnea symptom at 6 and 24 h after study drug initiation.	HF and all-cause mortality from randomization through hospital discharge. 3. # of days alive and outside the hospital from randomization through Day 30. Composite of CV death and rehospitalization due to CV causes from randomization through Day 30.			placebo). p=0.31 Nesiritide improved dyspnea at 6 h and 24 h after treatment compared to placebo but did not reach prespecified level for significance. p=0.03 (6hr), p=0.007 (24hr) 3) No difference in rate of worsening renal function. p=0.11.		(26.6% vs. 15.3%, p<0.001).

ACCF/AHA indicates American College of Cardiology Foundation/American Heart Association; ACEI, angiotensin-converting enzyme inhibitor; ACS, acute coronary syndrome; ADHF, acute decompensated heart failure; AE, adverse events; ARB, angiotensin-receptor blocker; ASA, aspirin; BPAP, bilevel positive airway pressure; BNP, b-type natriuretic peptide; CAD, coronary artery disease; CCB, calcium channel blocker; CHF, congestive heart failure; CI, confidence interval; CRT, cardiac resynchronization therapy; CV, cardiovascular; CXR, chest X-ray; ED, emergency department; FUSION, Follow-Up Serial Infusions of Nesiritide; GFR, glomerular filtration rate; HCM, hypertrophic cardiomyopathy; HF, heart failure; HR, hazard ratio; Hx, history; ICD, implantable cardioverter-defibrillator; ICM, ischemic cardiomyopathy; ICU, intensive-care unit; IV, intravenous; JVD, jugular venous distention; KCCQ, Kansas City Cardiomyopathy Questionnaire; LOS, length of stay; MI, myocardial infarction; N/A, not applicable; NSGET, Nesiritide Study Group Efficacy Trial; NSVT, non-sustained ventricular tachycardia; NYHA, New York Heart Association; OU, observation unit; PCWP, pulmonary capillary wedge pressure; pHTN, pulmonary hypertension; PND, paroxysmal nocturnal dyspnea; PROACTION, Prospective Randomized Outcomes study of Acutely decompensated CHF Treated Initially as Outpatients with Nesiritide; Pt, patient; RCM, restrictive cardiomyopathy; RCT, randomized controlled trial; RI, renal insuficiency; RR, relative risk; RR_{MH}, relative risk Mantel-Haenszel fixed-effects model; SAE, serious adverse event; SBP, systolic blood pressure; SC; SCr, serum creatinine; SD, standard deviation; UA, unstable angina; and VMAC, Vasodilator in the Management of Acute Heart Failure.

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Data Supplement 40. Hospitalized Patients – Oral Medications (Section 8.8)

Study Name, Author, Year	Aim of Study	Study Type	Study Size	Patient Population		Results	P Values & 95% CI:	OR: HR: RR:	Study Limitations
				Inclusion Criteria	*Exclusion Criteria*				
Beta Blockers During and at Discharge of HF Hospitalization									
Fonarow GC, Abraham WT, Albert NM et al. Influence of Beta blocker Continuation or Withdrawal on Outcomes in Pts Hospitalized with HF: Findings From the OPTIMIZE-HF Program. J Am Coll Cardiol 2008 July 15;52(3):190-9. 18617067 (353)	To determine whether beta-blocker therapy should be continued or withdrawn during hospitalization for decompensated HF.	Registry (OPTIMIZE-HF)	5791 pts admitted with HF at 91 academic and community hospitals throughout the U.S.	Hospitalization for episode of worsening HF as primary cause of admission.	N/A	Among 2373 pts eligible for beta blockers at discharge: 1350 (56.9%) receiving beta blockers before admission and continued on therapy, 632 (26.6%) newly started, 79 (3.3%) in which therapy was withdrawn, and 303 (12.8%) eligible but not treated. Continuation of beta blockers with lower risk for death (HR: 0.60; p=0.04) and death/rehospitalization (HR: 0.69; p=0.01). Withdrawal of beta blocker associated with higher risk for mortality (HR: 2.3; p=0.01), but with similar risk as HF pts eligible but not treated with beta blockers.	95% CI: 0.37-0.99; p=0.04	HR: 0.60	Registry
Fonarow GC, Abraham WT, Albert NM et al. Dosing of Beta blocker Therapy Before, During, and After Hospitalization for HF (OPTIMIZE-HF). *Am J Cardiol* 2008 December 1;102(11):1524-9. 19026308 (354)	The doses of beta blockers used in pts with HF in routine clinical practice before, during, and after hospitalization for HF.	Registry (OPTIMIZE-HF).	5791 pts admitted with HF at 91 academic and community hospitals throughout the U.S.	Hospitalization for episode of worsening HF as primary cause of admission.	None	The mean total daily dose for beta blockers before hospital admission <1/2 the recommended target dose (carvedilol 21.5 +/- 17.8 mg and metoprolol succinate 69.2 +/- 51.9 mg), with infrequent up- or down-titration during the HF hospitalization. 2/3 of pts had no change in their beta blocker doses in the first 60-90 d after hospital discharge. At 60-90 d postdischarge follow-up, only 17.5% and 7.9% of pts treated with recommended target doses of carvedilol and metoprolol succinate	N/A	N/A	Registry

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Gattis WA, O'Connor CM, Gallup DS, Hasselblad V, Gheorghiade M. Predischarge Initiation of Carvedilol in Pts Hospitalized for Decompensated HF: Results of the Initiation Management Predischarge: Process for Assessment of Carvedilol Therapy in HF (IMPACT-HF) trial. *J Am Coll Cardiol* 2004 May 5;43(9):1534-41. 15120808 (355)	To evaluate if predischarge carvedilol initiation in stabilized pts hospitalized for HF increased the number of pts treated with beta-blockade at 60 d after randomization without increasing side effects or length of hospital stay.	RCT (IMPACT-HF)	363	Pts hospitalized for HF.	N/A	At 60 d 165 pts (91.2%) randomized to predischarge carvedilol initiation treated with a beta blocker, compared with 130 pts (73.4%) randomized to initiation postdischarge (p < 0.0001). Predischarge initiation was not associated with increased risk of SAEs. The median length of stay was 5 d in both groups.	p<0.0001	N/A	N/A
Metra M, Torp-Pedersen C, Cleland JG et al. Should Beta-blocker Therapy be Reduced or Withdrawn After an Episode of Decompensated HF? Results From COMET. *Eur J Heart Fail* 2007 September;9(9):901-9. 17581778 (356)	To study the relationship between changes in beta blocker dose and outcome in pts surviving a HF hospitalization in COMET.	Retrospective subgroup analysis of RCT.	3029	Pts with LVEF <35, NYHA class II-IV HF hospitalized for HF were subdivided on the basis of the beta blocker dose administered at the visit following hospitalization, compared to that administered before.	Intolerance to beta blockers	752/3029 pts (25%) with HF hospitalization. 61 (8%) had beta-blocker treatment withdrawn, 162 (22%) had a dose reduction and 529 (70%) maintained on the same dose. 1 and 2 y cumulative mortality rates 28.7% and 44.6% for pts withdrawn from study medication, 37.4% and 51.4% for those with a reduced dosage, 19.1% and 32.5% for those maintained on the same dose (HR: 1.59; 95% CI: 1.28 to 1.98; p<0.001). No interaction with the beneficial effects of carvedilol, compared to metoprolol.	95%CI: 1.28-1.98; p<0.001	HR:1.59	Post-hoc analysis
Fonarow GC, Abraham WT, Albert NM et al. Prospective Evaluation of Beta-blocker use at the Time of Hospital Discharge as a HF Performance Measure: Results From OPTIMIZE-HF.J Card Fail 2007;13:722-31. 17996820 (357)	To prospectively evaluate beta blocker use at hospital discharge as an indicator of quality of care and outcomes in pts with HF.	Registry	20118	Data from the OPTIMIZE-HF registry for pts hospitalized with HF from 259 hospitals were prospectively collected and analyzed. 20118 pts with systolic dysfunction were included.	N/A	At discharge, 90.6% of pts eligible to receive beta blockers, 83.7% ACEI or ARB. Eligible pts discharged with beta blockers significantly more likely to be treated at follow-up than those not discharged with beta blockers (93.1% vs. 30.5%; P<0.0001). Discharge use of beta blockers in eligible pts lowers risk of death (HR: 0.48; 95% CI: 0.32-0.74; p<0.001) and death/rehospitalization (OR: 0.74; 95% CI: 0.55-0.99; p=0.04).	95% CI: 0.32-0.74; p<0.001	HR: 0.48	Registry

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Fonarow GC, Abraham WT, Albert NM et al. Carvedilol use at Discharge in Pts Hospitalized for HF is Associated With Improved Survival: an Analysis From OPTIMIZE-HF. *Am Heart J* 2007 January;153(1):82-11. 17174643 (358)	Examine effects on mortality and rehospitalization of carvedilol use at discharge in pts hospitalized for HF and LVSD compared with outcomes in pts who are eligible for, but do not receive, beta blockers before discharge.	Registry	5791	OPTIMIZE-HF program enrolled 5791 pts admitted with HF, web-based registry at 91 hospitals participating with prespecified 60-90 d follow-up from March 2003 to December 2004.	N/A	2373 (87.2%) eligible to receive a beta blocker at discharge. Carvedilol prescribed in 1162 (49.0%). Discharge carvedilol associated with a significant reduction in mortality (HR: 0.46; p=0.0006) and mortality and rehospitalization (OR: 0.71, p=0.0175) compared to no predischarge beta blocker.	p=0.0006	HR: 0.46	N/A
Ace-Inhibitors During and at Discharge of HF Hospitalization									
Willenheimer R, van Veldhuisen DJ, Silke B et al. Effect on Survival and Hospitalization of Initiating Treatment for Chronic HF With Bisoprolol Followed by Enalapril, as Compared With the Opposite Sequence: Results of the Randomized CIBIS III. Circulation 2005;112:2426-35. 16143696 (186)	To determine whether the sequence of initiation of beta blockers or ACEI during hospitalization make a difference in outcomes.	RCT	101	Mild to moderate HF and LVEF ≤35%, who were not receiving ACEI, beta blocker, or ARB therapy randomized to open-label bisoprolol (target dose 10 mg QD; n=505) or enalapril (target dose 10 mg BID; n=505) for 6 mo, followed by their combination for 6 to 24 mo.	N/A	Bisoprolol-first treatment noninferior to enalapril-first treatment (HR: 1.17). Primary end point in 178 pts allocated to bisoprolol-first treatment vs 186 allocated to enalapril-first treatment (HR: 0.94; 95% CI: 0.77-1.16). Bisoprolol-first treatment: 65 pts died, vs 73 with enalapril-first treatment (HR: 0.88; 95% CI: 0.63 to 1.22), and 151 vs 157 pts hospitalized (HR: 0.95; 95% CI: 0.76-1.19).	p=ns	HR: 0.94	N/A
Thilly N, Briançon S, Juillière Y, Dufay E, Zannad F. Improving ACE inhibitor use in patients hospitalized with systolic heart failure: a cluster randomized controlled trial of clinical practice guideline development and use. J Eval Clin Pract. 2003 Aug; 9(3):373-82. 12895159 (359)	To evaluate the effect of developing and implementing CPGs on the quality of care given to pts receiving ACEI for systolic HF.	RCT	20 cardiology units in France (Experimental group (n=10) in each experimental unit, doctors were involved in drafting and implementing CPGs; those at control units were not.)	HF pts <75 y old	Age >75 y	Compliance with the CPG relating to ACEI dose on discharge higher in the experimental group (p=0.003).	N/A	N/A	N/A
Spironolactone During and at Discharge of HF Hospitalization									

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Hamaguchi S, Kinugawa S, Tsuchihashi-Makaya M et al. Spironolactone use at Discharge was Associated With Improved Survival in Hospitalized Pts With Systolic HF. Am Heart J 2010;160:1156-62. 21146672 (360)	Whether the discharge use of spironolactone is associated with better mortality and rehospitalization among hospitalized s ystolic HF pts.	Prospective cohort	946	Hospitalized HF pts with reduced LVEF <40%.	N/A	Spironolactone prescribed at discharge in 435 pts (46%). Discharge use of spironolactone associated with reduction in death (HR: 0.612; p=0.020) and cardiac death (HR: 0.524; p=0.013).	p=0.02	HR: 0.612	N/A
Ko DT, Juurlink DN, Mamdani MM et al. Appropriateness of Spironolactone Prescribing in HF Pts: a Population-Based Study. J Card Fail 2006;12:205-10. 16624686 (361)	Appropriateness of spironolactone prescription at discharge.	Population based Cohort	9165	Hospitalized HF pts in Ontario, Canada, 1999-2001.	N/A	1502 pts prescribed spironolactone at discharge. 18% had hyperkalemia during hospitalization and 23% were discharged on concurrent potassium supplements. Although only 8% of pts with SCr >2.5 mg/dL, many with stage III (53.1%), stage IV (12.8%), or stage V (3.9%) chronic renal insufficiency.	N/A	N/A	N/A
Digoxin During and at Discharge of HF Hospitalization									
Dhaliwal AS, Bredikis A, Habib G, Carabello BA, Ramasubbu K, Bozkurt B. Digoxin and Clinical Outcomes in Systolic HF Pts on Contemporary Background HF Therapy. Am J Cardiol 2008;102:1356-60. 18993155 (362)	To determine the effect of digoxin at discharge in pts hospitalized with HF.	Cohort	347	Hospitalized pts with HF.	Competing non-HF diagnoses	HF hospitalizations (HR: 1.08; 95% CI: 0.77-1.50; p=0.66), total mortality (HR: 1.03; 95% CI: 0.78-1.35, p=0.85), or the combined end point of HF hospitalization and total mortality (HR: 1.11, 95% CI: 0.81-1.53, p=0.52) not different in pts treated with digoxin compared with those not treated with digoxin.	p=0.66	HR: 1.08	Retrospective cohort
Ahmed A, Allman RM, DeLong JF. Inappropriate use of Digoxin in Older Hospitalized HF Pts. J Gerontol A Biol Sci Med Sci 2002;57:M138-M143. 11818435 (363)	To determine the correlates of inappropriate dig oxin use in older HF pts.	Cohort	603	Older hospitalized HF pts with documented LVEF and EKG.	N/A	Digoxin use considered inappropriate if pts had preserved LVEF (≥40%) or if they had no AF. 376 pts (62%) discharged on digoxin, and 223 (37%) without indication for use. Of 132 pts without an indication and not already on digoxin, 38 (29%) initiated on it.	N/A	N/A	N/A
Adherence to Performance Measurements or Guidelines for Evidence Based Medication Use During Hospitalization									
Krantz MJ, Ambardekar AV, Kaltenbach L, Hernandez AF, Heidenreich PA, Fonarow GC. Patterns and Predictors of	To assess noncontraindicated use patterns for ACEI/ARBs, beta	Registry (GTWG-HF)	9474	N/A	N/A	Of those treated before hospitalization, continuation rates: 88.5% for ACEI/ARBs, 91.6% for beta blockers, and 71.9% for aldosterone-antagonists.	N/A	N/A	N/A

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Evidence-Based Medication Continuation Among Hospitalized HF Pts (from Get With the Guidelines-HF). Am J Cardiol 2011 June 15;107(12):1818-23. 21482418 (364)	blockers, and aldosterone antagonists using the GWTG-HF registry.					Of pts untreated before admission, 87.4% started on ACEI/ARBs, 90.1% beta blocker and 25.2% on an aldosterone antagonist during hospitalization or at discharge. Admission therapy most strongly associated with discharge use (OR: 7.4, 6.0, and 20.9 for ACEI/ARBs, beta blockers, and aldosterone antagonists, respectively)			
Fonarow GC, Gheorghiade M, Abraham WT. Importance of In-hospital Initiation of Evidence-based Medical Therapies for HF-a Review. *Am J Cardiol* 2004 November 1;94(9):1155-60. 15518610 (365)	Review of AHF therapies.	Review	N/A	N/A	N/A	Message: Adopting in-hospital initiation of HF therapies as the standard of care could improve treatment rates, decrease the risk of future hospitalizations, and prolong life.	N/A	N/A	Review paper
Fonarow GC, Yancy CW, Heywood JT. Adherence to HF Quality-of-care Indicators in US Hospitals: Analysis of the ADHERE Registry. *Arch Intern Med* 2005 July 11;165(13):1469-77. 16009861 (366)	To determine the current rates of conformity with quality of care indicators or their variability across hospitals.	Registry (ADHERE)	81142 admissions	81142 admissions occurring between July 1, 2002, and December 31, 2003, at 223 academic and non-academic hospitals in the US participating in the ADHERE.	N/A	Median rates of conformity with HF-1, HF-2, HF-3, and HF-4 24.0%, 86.2%, 72.0%, and 43.2%, respectively.	N/A	N/A	Registry
Fonarow GC, Abraham WT, Albert NM et al. Association Between Performance Measures and Clinical Outcomes for Pts Hospitalized With HF. JAMA 2007 January 3;297(1):61-70. 17200476 (367)	To examine the relationship between current (ACCF/AHA) performance measures for pts hospitalized with HF and relevant clinical outcomes.	Registry (OPTIMIZE-HF)	5791 pts at 91 US hospitals	OPTIMIZE-HF, a registry and performance improvement program.	Incomplete data	Mortality during follow-up 8.6% and mortality/rehospitalization 36.2%. None of the 5 ACCF/AHA HF performance measures was significantly associated with reduced early mortality risk. Only ACEI or ARB use at discharge was associated with 60 to 90 d postdischarge mortality or rehospitalization. Beta-blockade at the time of hospital discharge, (not a HF performance measure then) strongly associated with reduced mortality (HR: 0.48; 95% CI: 0.30-0.79; p=0.004).	p=0.004 for beta- blocker, p<0.05 for ACEI.		Registry

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Lappe JM, Muhlestein JB, Lappe DL et al. Improvements in 1 y Cardiovascular Clinical Outcomes Associated With a Hospital-based Discharge Medication Program. *Ann Intern Med* 2004 September 21;141(6):446-53. 15381518 (368)	To develop and implement a program ensuring appropriate prescription of aspirin, statins, beta blockers, ACEI, and warfarin at hospital discharge.	Prospective cohort	57465 enrolled from 10 largest hospitals in the Utah-based Intermountain Health Care system.	A nonrandomized / before-after study comparing pts hospitalized before (1996-1998) and after (1999-2002) implementation of a DMP.		Rate of prescription of each medication increased significantly to >90% (p<0.001). RR for death and readmission at 30 d decreased after DMP implementation; HRs for death and readmission: 0.81 (95% CI: 0.73-0.89) and 0.92 (95% CI: 0.87-0.99) (p<0.001 and p=0.017, respectively). At 1 y, risk for death still low (HR: 0.79; 95% CI: 0.75-0.84; p<0.001) while risk for readmission stabilized (HR: 0.94; 95% CI: 0.90-0.98; p=0.002).	95% CI: 0.75-0.84; p<0.001	HR: 0.79	Observational and nonrandomized, authors could not control for potential confounders or determine the extent to which secular trends accounted for the observed improvements.
AHA Scientific Statement for Treatment of Acute HF Syndromes									
Weintraub NL, Collins SP, Pang PS et al. Acute HF Syndromes: ED Presentation, Treatment, and Disposition: Current Approaches and Future Aims: a Scientific Statement From the AHA. Circulation 2010 November 9;122(19):1975-96. 20937981 (369)	To characterize acute HF syndromes: from presentation, treatment, and disposition.	AHA scientific statement	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Recent Studies with Other Oral Medications for Treatment of Acute HF									
Gheorghiade M, Konstam MA, Burnett JC, Jr. et al. Short-term Clinical Effects of Tolvaptan, an Oral Vasopressin Antagonist, in Pts Hospitalized for HF: the EVEREST Clinical Status Trials. *JAMA* 2007 March 28;297(12):1332-43. 17384438 (153)	To evaluate short-term effects of tolvaptan when added to standard therapy in pts hospitalized with HF.	RCT (EVEREST)	2048 trial A, 2085 (trial B) 4133 tolvaptan (30 mg/d), or matching placebo, within 48 h of admission.	Age ≥18 y; current hospitalization for CHF with admission up to 48 h prior to randomization; chronic HF is defined as requiring treatment for a minimum of 30 d prior to hospitalization. Subject must have signs of extracellular volume expansion, defined as ≥2 of the following: a) JVD; b) pitting edema (>1+); or c) dyspnea. NYHA Class III or IV	Women who will not adhere to the reproductive precautions as outlined in the ICF. Positive urine pregnancy test. Inability to provide written informed consent. Cardiac surgery within 60 d of potential study enrollment, excluding PCI. Planned revascularization procedures, EP device implantation, cardiac mechanical support implantation, cardiac transplantation, or other cardiac surgery within 30 d following study enrollment. Subjects who are on cardiac mechanical support. Hx of biventricular pacer placement	Tolvaptan had no effect on long-term mortality or HF-related morbidity. Mortality for tolvaptan vs placebo not different (HR: 0.98; 95% CI: 0.87-1.11; p=0.68). Composite of CV death or hospitalization for HF not different (HR: 1.04; 95% CI: 0.95-1.14; p=0.55). Secondary end points CV mortality, CV death or hospitalization, and worsening HF not different between tolvaptan and placebo. Tolvaptan significantly improved secondary end points of Day 1 pt-assessed dyspnea, Day 1 body weight, and Day 7 edema. In pts with hyponatremia, serum sodium levels significantly increased.	95% CI: 0.87-1.11; p=0.68	HR: 0.98	N/A

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				at the time of hospitalization. LVEF ≤40% within 1 y.	within the last 60 d. Co-morbid condition with an expected survival less than 6 mo. Subjects with acute STEMI at the time of hospitalization. Hx of sustained ventricular tachycardia or ventricular fibrillation within 30 d, unless in the presence of an automatic ICD. Hx of a cerebrovascular accident within the last 30 d. Hemodynamically significant uncorrected primary cardiac valvular disease. Hypertrophic cardiomyopathy (obstructive or non-obstructive). CHF due to uncorrected thyroid disease, active myocarditis or known amyloid cardiomyopathy. Subjects with progressive or episodic neurological disease such as multiple sclerosis or Hx of multiple strokes. Hx of primary significant liver disease or acute hepatic failure, as defined by the investigator. Hx of poorly controlled DM. Morbid obesity, defined as >159 kg (or 350 lbs) or BMI >40. Supine systolic arterial blood pressure <90 mmHg. SCr >3.5 mg/dL or >309.4 mmol/L. Serum potassium >5.5 mEq/L or >5.5 mmol/L. Hgb <9 g/dL or <90 g/L. Hx of hypersensitivity and/or idiosyncratic reaction to benzazepine derivatives (such			

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					as benazapril). Hx of drug or medication abuse within the past year, or current alcohol abuse. Inability to take oral medications. Participation in another clinical drug or device trial within the past 30 d. Previous participation in this or any other tolvaptan clinical trial..				
Konstam MA, Gheorghiade M, Burnett JC, Jr. et al. Effects of Oral Tolvaptan in Pts Hospitalized for Worsening HF: the EVEREST Outcome Trial. JAMA 2007 March 28;297(12):1319-31. 17384437 (154)	To investigate the effects of tolvaptan initiated in pts hospitalized with HF.	RCT (EVEREST-Outcome)	4133 (tolvaptan, 30 mg once per day (n=2072) or placebo (2062) within 48 h of admission.	Age ≥18 y. Current hospitalization for chronic CHF with admission up to 48 h prior to randomization. Chronic HF is defined as requiring treatment for a minimum of 30 d prior to hospitalization. The subject must have signs of extracellular volume expansion, defined as ≥2 of the following: a) JVD; b) pitting edema (>1+); or c) dyspnea. NYHA Class III or IV at the time of hospitalization. LVEF ≤40% within 1 y.	Women who will not adhere to the reproductive precautions as outlined in the ICF. Positive urine pregnancy test. Inability to provide written informed consent. Cardiac surgery within 60 d of potential study enrollment, excluding PCI. Planned revascularization procedures, EP device implantation, cardiac mechanical support implantation, cardiac transplantation, or other cardiac surgery within 30 d following study enrollment. Subjects who are on cardiac mechanical support. Hx of biventricular pacer placement within the last 60 d. Comorbid condition with an expected survival less than 6 mo. Subjects with acute STEMI at the time of hospitalization. Hx of sustained ventricular tachycardia or ventricular fibrillation within 30 d, unless in the presence of an automatic ICD. Hx of a cerebrovascular accident within the last 30 d. Hemodynamically significant uncorrected primary cardiac	Tolvaptan had no effect on long-term mortality or HF-related morbidity. Mortality for tolvaptan versus placebo not different (HR: 0.98; 95% CI: 0.87-1.11; p=0.68). Composite of CV death or hospitalization for HF not different (HR: 1.04; 95% CI: 0.95-1.14; p=0.55). Secondary end points CV mortality, CV death or hospitalization, and worsening HF not different between tolvaptan and placebo. Tolvaptan significantly improved secondary end points of Day 1 pt-assessed dyspnea, Day 1 body weight, and Day 7 edema. In pts with hyponatremia, serum sodium levels significantly increased.	95% CI: 0.87-1.11; p=0.68	HR: 0.98	N/A

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					valvular disease. Hypertrophic cardiomyopathy (obstructive or non-obstructive). CHF due to uncorrected thyroid disease, active myocarditis or known amyloid cardiomyopathy. Subjects with progressive or episodic neurological disease such as multiple sclerosis or Hx of multiple strokes. Hx of primary significant liver disease or acute hepatic failure, as defined by the investigator. Hx of poorly controlled DM. Morbid obesity, defined as >159 kg (or 350 lbs) or BMI >40. Supine systolic arterial blood pressure <90 mmHg. SCr >3.5 mg/dL or >309.4 mmol/L. Serum potassium >5.5 mEq/L or >5.5 mmol/L. Hgb <9 g/dL or <90 g/L. Hx of hypersensitivity and/or idiosyncratic reaction to benzazepine derivatives (such as benazapril). Hx of drug or medication abuse within the past y, or current alcohol abuse. Inability to take oral medications. Participation in another clinical drug or device trial within the past 30 d. Previous participation in this or any other tolvaptan clinical trial.			

ACCF/AHA indicates American College of Cardiology Foundation/American Heart Association; ACEI, angiotensin-converting enzyme inhibitor; ADHERE, Acute Decompensated HF National Registry; AF, atrial fibrillation; AHF, acute heart failure; ARB, angiotensin-receptor blocker; BMI, body mass index; CHF, congestive heart failure; CI, confidence interval; CIBIS, Cardiac Insufficiency Bisoprolol Study; COMET, Carvedilol or Metoprolol European Trial; CPG, clinical practice guidelines; CV, cardiovascular; DM, diabetes mellitus; DMP, discharge medication program; ED, emergency department; EKG, electrocardiogram; EP, electrophysiology; GWTG-HF, Get With the Guidelines-HF; HF, heart failure; Hx, history; ICD, implantable cardioverter-defibrillator; JVD, jugular venous distention; LVEF, left ventricular ejection fraction; LVSD, left ventricular systolic dysfunction; NS, not significant; NYHA, New York Heart Association; OPTIMIZE-HF, Organized Program to Initiate Lifesaving Treatment in Hospitalized Pts with HF; PCI, percutaneous coronary intervention; Pts, patients; RCT, randomized controlled trial; SAE, serious adverse event; SCr, serum creatinine, STEMI, ST segment elevation myocardial infarction; and US, United States.

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Data Supplement 41. Atrial Fibrillation (Section 9.1)

Study Name, Author, Year	Aim of Study	Study Type	Study Size	Patient Population		Endpoints		Statistical Analysis (Results)	Study Limitations	Findings/ Comments
				Inclusion Criteria	*Exclusion Criteria*	*Primary Endpoint*	*Secondary Endpoint*			
AF CHF Roy, 2008 19102036 (370)	Rhythm control reduces mortality as compared to rate control	Multi-center RCT	1,376	LVEF ≤35%, history of CHF, and history of AF	N/A	Death from CV causes	Death from any cause, worsening of CHF, or stroke.	Death from all CV causes: 27% in rhytm-control group vs. 25% in rate-control group HR: 1.0 6; p=0.59; 95% CI: 0.86-1.30	Results cannot be generalized to pts with HF and preserved LV function (in whom AF is common).	The use of rhythm-control did not reduce the rate of death from CV causes compared with rate-control. No significant differences in secondary outcomes either.
AFFIRM, 2002 12466506 (371)	Rhythm control reduces mortality as compared to rate control	Multi-center RCT	4,060	≥65 y with history of AF and other risk factors for stroke or death	N/A	Overall mortality	Composite death, dsabling stroke, diabling anoxic encephalopathy, major bleeding or cardiac arrest	Difference in mortality not statistically significant. HR: 1.15 95%CI: 0.99-1.34; ; p=0.08	Findings cannot be generalized to pts with more severe AF or to younger pts without risk factors for stroke	Rhythm-control strategy did not improve morality when compared to rate-control.
RE-LY, Eikelboom, 2011 21576658 (372)	Compare 2 doses (110 mg and 150 mg) of dabigatran 2 x d vs. warfarin for stroke prevention in pts with AF	Multi-center RCT	18,113	Pts with AF and at least 1 additional risk factor for stroke	N/A	Major bleeding	N/A	Dabigatran 110 mg twice d compared with warfain: 2.87% vs. 3.57 % (p=0.0002) Dabigatran 150 mg twice d vs warfarin: 3.31% vs. 3.57% (p=0.32) Dabigatran 150 mg twice d vs. Dabigatran 110 mg: 3.31% vs. 2.87%(p=0.04)	N/A	Both doses of Dabigatran were associated with lower risks of major bleeding than warfarin. Found an interaction between treatment and age for major bleeding. Both doses of Dabigatran associated with lower risk of extracranial bleeding in pts <75 y, though associated with similar or higher risks in pts ≥75 y. Risk of intracranial bleeding was lower with either dose of Dabigatran, regardless of age.
RE-LY, Connolly, SJ, 2009 19717844 (193)	Compare 2 doses (110 mg and 150 mg) of dabigatran 2x d vs. warfarin in pts with AF at increased risk of stroke	Mutli-center RCT	18,113	Pts with previous stroke or TIA, LVEF <40%, NYHA class II or higher	N/A	Stroke or systemic embolism	N/A	The 150 mg dose of Dabigatran was superior to warfarin in reducing stroke and systemic embolism (RR:0.66; 95% CI: 0.53-0.82; p<0.0001) but the 110 mg dose was not when compared to warafin (RR: 0.91; 95% CI: 0.74-1.11; p=0.34)	N/A	Both doses of Dabigatran were noninferior to warafin with respect to the primary outcome

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ROCKET AF, Fox KAA, 2011 21873708 (373)	Compare rivaroxaban with warfarin in prevention of stroke or systemic embolism in pts with AF	Double blind RCT	14,264; 2,950 pts with moderate renal impairment	Pts with non-valvular AF and moderate renal impairment (CrCl 30-49 mL/min)	N/A	Stroke or systemic embolism	N/A	Primary outcome occurred in 2.32 per 100 pt-y in rivaroxaban vs. 2.77 per 100 pt-y in warafin group. Fatal bleeding was 0.28% in rivaroxaban vs. 0.74% per 100 pt-y in warafin (ITT analysis HR: 0.86; 95% CI: 0.63-1.17; p=0.0047)	Analysis was not powered to detect differences between drugs in pts with renal insuficiency	While not able to show a difference between drugs, rivaroxaban was associated with reduction in fatal bleeding in pts with renal insufieniency.
ROCKET AF, Patel MR, 2011 21830957 (196)	Compare rivaroxaban with warfarin in prevention of stroke or systemic embolism in pts with AF	Double blind RCT	14,264	Non-valvular AF	N/A	Stroke or systemic embolism	N/A	Primary outcome occurred in less often in rivaroxaban group than warfarin group (2.1 % vs. 2.4% per y) ITT analysis noninferiority: HR: 0.88; 95% CI: 0.74-1.03; p<0.0001	No between group differences in the ITT analysis.	Showed noninferiority of rivaroxaban.

AF indicates atrial fibrillation; AFFIRM, Atrial Fibrillation Follow-up Investigation of Rhythm Management; CHF, congestive heart failure; CrCl , creatinine clearance; CV, cardiovascular; HR, hazard ratio; ITT, intent-to-treat; LV, left ventricular; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; Pts, patients; RCT, randomized control trial; RE-LY, randomized evaluation of long-term anticoagulant therapy trial; ROCKET-AF, Rivaroxaban Once Daily Oral Direct Factor Xa Inhibitor Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation; RR, relative risk; and TIA, transient ischemic attack;

Data Supplement 42. HF Disease Management (Section 11.2)

Study Name, Author, Year	Aim of study	Study Type	Study Size	Patient Population		Endpoints		Statistical Analysis (Results)	Study Limitations	Findings/ Comments
				Inclusion Criteria	*Exclusion Criteria*	*Primary Endpoint*	*Secondary Endpoint*			
What Works In Chronic Care Management: The Case Of HF 19124869 (374)	The effect of delivery methods in the management of HF care on hospital readmissions	Meta analysis of RCTs	2,028	Not Reported	Not Reported	All-cause hospital readmissions and readmission d	N/A	Pts enrolled in chronic care management programs using a multidisciplinary team in addition to in-person communication had a 2.9% reduction in readmissions/ mo and a 6.4% reduction in readmission d/mo compared to routine care (p < 0.001).	Possible study selection bias; were not able to evaluate cost savings; retrospective analysis.	A team-based approach in chronic care management programs for HF pts meets AHA's principles for high-quality disease management programs and the Disease Management Association of America's key components of disease management programs.

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CM in a heterogeneous CHF population: a RCT 12695272 (375)	Test the effect of CHF case management with the following 4 components: 1. early discharge planning, 2. pt and family CHF education, 3. 12 wk of telephone f/u, and, 4. promotion of optimal CHF medications	RCT	287	Primary or secondary diagnosis of CHF, LVD <40%, or radiologic evidence of pulmonary edema for which they underwent diuresis; had to be at risk for early readmission	Discharge to a long-term care facility, planned cardiac surgery, cognitive impairment, anticipated survival of <3 mo, and long-term hemodialysis	90-d readmission rate	Adherence to treatment plan and pt satisfaction	There was no difference between the 2 groups in 90-d re-admission rates (both were 37%, p>0.99). The intervention group showed greater adherence to most aspects of the treatment plan (p<0.01) and pts in this group reported greater pt satisfaction (p<0.01). Subgroup of pts who live in area and received care from local cardiologists decreased CHF readmission rate (2%vs. 14%; p=0.03).	Study was not blinded, adherence was assessed via pt self-report; and no consistent method for NYHA classification.	The intervention did not increase costs and study showed that strong working relationships between the CM and cardiologists decreased CHF hospital readmission rates.
CM for pts with chronic systolic HF in primary care: the HICMan exploratory RCT. 20478035 (376)	To compare CM vs. usual care on pt outcomes.	RCT	197	Adults with LVEF ≤45%	Not reported	HRQoL, HF self-care, and pt-reported quality of care.		Nonsignificant between group differences for the KCCQ overall summary scores favored CM: 1.7 (95%CI: -3.0-6.4; p=0.477). Heart failure self-care behavior scores were significant group differences favoring CM: -3.6 (95%CI: -5.7- -1.6; Cohen's d 0.55; p=0.001) Significant between group differences quality of chronic illness care (0.5; 95% CI : 0.3-0.7; p=0.000) and behavior counseling (0.5; 95%CI : 0.3-0.8; p=0.000), with moderate effect sizes (Cohen's d 0.7 for each summary score).	Small, unblended sample of patients from a non-representative sample of physicians.	The intervention failed to improve overall QoL, though showed significant improvements in pt-reported quality of care and chronic HF self-care.
Impact of a specialized outpatient HF follow-up program on hospitalization frequency and functional status of pts with AHF. 17695729	To evaluate the impact of a specialized outpatient HF follow-up program	Retrospective	147	Not reported	Not reported	Frequency and duration of hospitalization for HF and functional status		Significant improvement in NYHA class during the mean follow-up period: 55% of the pts were in class III, 37% in class II, 5% in class I and 3% in class IV (p<0.0001). Hospitalizations for acute decompensation of HF decreased: 87 at baseline vs. 25 (p<0.0001)	Small retrospective study	No significant differences were found in the proportion of pts on therapeutic drugs or in mean duration of hospitalization

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(377)										
Outpatient medical and nurse management program in pts with chronic HF in a large territorial area in Piedmont. 4 y of follow-up. 16444925 (378)	To evaluate an outpatient management program for pts with chronic HF	Prospective trial	115	Adults with chronic HF in the Piedmont region of Italy.		Hospitalization and ED admissions in the 12 mo before the 1st evaluation and every y after referral	MLWHF, NYHA functional class, pharmacological therapies at the referral time and at the end of follow-up.	EF improved from 31 +/- 10 to 36 +/- 12%. ED admissions and hospitalizations decreased ($p < 0.001$). NYHA classes I-II improved from 65.5 to 87.7% and NYHA classes III-IV were reduced from 34.5 to 12.3%. MLWHF score decreased from 25 to 21.9. Pts treated with ACEI + ARB increased from 91 to 96%, beta blockers from 35.2 to 69%, potassium sparing drugs increased from 54 to 64%.	Small trial, not generalizable to populations outside of Italy.	Showed a decrease in the number of hospitalizations and improvement in NYHA functional class and adherence to medical therapy. These results kept constant over time in the subsequent 4 y.

ACEI indicates angiotensin-converting-enzyme inhibitor; AHF, acute heart failure; ARB, angiotensin receptor blockers; CHF, congestive heart failure; CM, case management; ED, emergency department; EF, ejection fraction; HF, heart failure; HRQoL, health related quality of life; KCCQ, LVD, left ventricular dysfunction; MLHF, Minnesota Living with Heart Failure; NYHA, pts, patients; and QoL, quality of life.

Data Supplement 43. Telemonitoring (Section 11.2)

Study Name, Author, Year	Aim of study	Study Type	Study Size	Patient Population		Endpoints		Statistical Analysis (Results)	Study Limitations	Findings/ Comments
				Inclusion Criteria	*Exclusion Criteria*	*Primary Endpoint*	*Secondary Endpoint*			
Telemonitoring or structured telephone support programs for pts with chronic HF: systematic review and meta-analysis. 17426062 (379)	To determine whether remote monitoring (structured telephone support or telemonitoring) without regular clinic or home visits improves outcomes for pts with chronic HF.	Meta analysis	4,264	Published RCTs comparing remote monitoring programs with usual care in patients with chronic HF managed within the community.		All-cause mortality, all-cause rate of admission to hospital, and rate of admission to hospital as a result of chronic HF		20% reduction in all-cause mortality (95% CI: 8- 31%) with telemonitoring. No change in all-cause hospital admission rate. Hospital admissions due to chronic HF saw a reduction of 21% (95% CI: 11 -31%) with remote monitoring programmes	Relatively small number of studies and pts; few trials had follow-up beyond 6 mo.	Remote monitoring programs for pts with chronic HF reduced admissions to hospital and all-cause mortality by nearly 1/5.

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Structured telephone support or telemonitoring programs for pts with chronic HF 20687083 (380)	To examine the effect of telemonitoring and structured telephone support on HF outcomes.	Meta analysis	25 studies, 16 structured telephone support (n = 5613) and 11 of telemonitoring (n = 2710)	RCTs, adults ≥18 y, diagnosed with chronic HF.	Trials of general cardiac disorders rather than chronic HF were excluded.	All-cause mortality	All-cause readmissions to hospital and chronic HF-related admission to hospital	All-cause mortality: Telemonitoring RR: 0.66; 95% CI: 0.54-0.81, p< 0.0001 Structured telephone support RR: 0.88; 95% CI: 0.76-1.01; p=0.08 All-cause hospitalization: Telemonitoring RR:0.91; 95% CI: 0.84-0.99; p=0.02 Structured telephone support RR: 0.92; 95% CI: 0.85-0.99; p=0.02 Chronic HF-related hospitalizations: Telemonitoring RR: 0.79; 95% CI: 0.67-0.94; p=0.008. Structured telephone support RR: 0.77; 95% CI: 0.68-0.87; p<0.0001	Unable to stratify by age, sex, or NYHA class. Unable to adjust for the differing lengths of follow-up.	Telemonitoring and structured telephone support interventions for assisting with management of pts with chronic HF are beneficial and may play a significant role in the care of 'standard' management of chronic HF.
Effect of a standardized nurse case-management telephone intervention on resource use in patients with chronic HF. 11911726 (381)	To assess the effectiveness of a standardized telephonic case-management intervention in pts with chronic HF.	RCT	358; 130 (intervention); 228 (usual care)	N/A	N/A	HF hospitalization rates	All-cause hospitalization rates; HF readmission rate; HF hospital d	HF hospitalization rate was 45.7% lower in the intervention group at 3 mo (p=0.03) and 47.8% lower at 6 mo (p=0.01). HF hospital d (p=0.03) and multiple readmissions (p=0.03) were significantly lower in the intervention group at 6 mo – though not significant after adjustment for other covariates.	Selection bias due to randomization of physicians, rather than pts. Impossible to completely blind physicians to treatment.	Telephonic case management can reduce HF hospitalization resulting in significant cost savings.
RCT of telephone case management in Hispanics of Mexican origin with HF. 16624687 (382)	Tested the effectiveness of telephone case management in decreasing hospitalizations and improving HRQL and depression	RCT	134; 69 (intervention); 65 (usual care)	Hospitalized Hispanics with chronic HF	N/A	HF re-hospitalization	All-cause hospitalization, d in the hospital (HF and all-cause), multiple readmissions, acute care costs, all-cause mortality, HRQL, depression	No significant group differences were found in HF hospitalizations, HF readmission rate, d in the hospital, HF cost of care, all-cause acute care use or cost, mortality, HRQL, or depression.	Small sample size. Possible confounders included very ill population, poorly educated, economically poor, and unacculturated into US society.	None
Telemonitoring in pts with HF. 21080835 (383)	Test the effectiveness of telemonitoring vs. usual care.	RCT	1653; 826 (intervention); 827 (usual care)	Pts were enrolled from 2006-2009 at 33 cardiology practices across	Residence in a long-term nursing home; inability to participate in the protocol for any reason, including a low expected	All-cause readmission or all-cause mortality (within 180 d post enrollment)	HF hospitalization, d in the hospital, and number of	All-cause readmission or mortality: telemonitoring vs. usual care HR: 1.04; 95% CI: 0.91-1.19. No significant differences were seen between the 2 groups with respect to	Automated system with low adherence rate.	Telemonitoring did not improve outcomes among pts recently hospitalized for HF.

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				the US. Pts hospitalized for HF in the previous 30 d	probability of survival for the next 6 mo; inability to stand on a scale; severe cognitive impairment; and a planned hospitalization for a procedure		hospitalizations	the secondary endpoints		

HF indicates heart failure; HR, hazard ratio; HRQL, health related quality of life; NYHA, New York Heart Association; pts, patients; RCT, randomized control trial; RR, relative risk; and US, United States.

Data Supplement 44. Quality Metrics and Performance Measures (Section 12)

Study Name, Author, Year	Aim of study	Study Type	Study Size	Patient Population		Endpoints		Statistical Analysis (Results)	Study Limitations	Findings/ Comments
				Inclusion Criteria	*Exclusion Criteria*	*Primary Endpoint*	*Secondary Endpoint*			
Temporal trends in clinical characteristics, treatments, and outcomes for HF hospitalizations, 2002-2004: findings from ADHERE. 17540205 (384)	To assess temporal trends in clinical characteristics, treatments, quality indicators, and outcomes for HF hospitalizations.	Prospective	159,168	N/A	N/A	N/A	N/A	Inhospital treatment changed significantly over time with inotrope use decreasing from 14.7% to 7.9% (p<0 .0001). Discharge instructions increased 133%; smoking counseling, 132%; LV function measurement, 8%; and beta blocker use, 29% (all p<0.0001). Clinical outcomes improved over time, including need for mechanical ventilation, RR: 0.64, p < .0001); length of stay (mean), 6.3 to 5.5 d; and mortality, RR: 0.71, p<0.0001).	N/A	N/A
Improving evidence-based care for HF in outpatient cardiology practices: primary results of the Registry to Improve the Use of Evidence-Based HF Therapies in the Outpatient Setting (IMPROVE HF). 20660805 (385)	To evaluate the effectiveness of a practice-specific performance improvement intervention on the use of guideline-recommended therapies for pts with diagnosed HF and reduced LVEF or prior MI and reduced LVEF in outpatient cardiology practices	Prospective	34,810	HF or prior MI with LVEF ≤35%	Those with noncardiovascular medical condition associated with an estimated survival of <1 y and those who had undergone cardiac transplantation	7 quality measures: use of 1) ACEI or ARB, 2) Beta blocker, 3) aldosterone antagonist, 4) anticoagulant therapy for AF or flutter, 5) CRT with a defibrillator/CRT with a pacemaker, 6) ICD (ICD or CRT with a defibrillator), and 7) HF education for eligible pts.	N/A	Significant improvement was demonstrated in 5 of the 7 quality measures at the practice level at 24 mo after implementation of the performance improvement intervention, use of aldosterone antagonists, CRT, ICD, beta blocker, and HF education (p<0.001); Use of anticoagulation in eligible patients with AF did not improve over time. Use of ACEI/ARB increased (+6.8%), but this was not statistically significant (p=0.063)	Data collected by chart review, which may be incomplete; selection bias as eligible pts not included in analysis may differ by contraindication from those who were; analysis not adjusted for differing lengths of follow up.	Study demonstrates the positive impact of applying performance improvement techniques of guideline-driven care and improvement tools, in real-world cardiology practices.

ACEI indicates angiotensin-converting-enzyme inhibitor; ADHERE, Acute Decompensated Heart Failure National Registry; AF, atrial fibrillation; ARB, angiotensin receptor blockers; CRT, cardiac resynchronization therapy; HF, heart failure; ICD, implantable cardioverter-defibrillator; LV, left ventricular; MI, myocardial infarction; pt, patient; and RR, relative risk.

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2013 ACCF/AHA Guideline for the Management of Heart Failure—ONLINE AUTHOR LISTING OF COMPREHENSIVE RELATIONSHIPS WITH INDUSTRY AND OTHERS (May 2013)

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*Indicates significant relationship.
†No financial benefit.

ACC indicates American College of Cardiology; AHA, American Heart Association; AHEAD, Action For Health in Diabetes; AHRQ, Agency for Healthcare Research & Quality; ALECARDIO, Cardiovascular Outcomes Study to Evaluate the Potential of Aleglitazar to Reduce Cardiovascular Risk in Patients With a Recent Acute Coronary Syndrome Event and Type 2 Diabetes Mellitus; ALTITUDE, Aliskiren Trial in Type 2 Diabetes Using Cardio-Renal Endpoints; ASCEND-HF, Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure; CHAMPION, CardioMEMS Heart Sensor Allows Monitoring of Pressure to Improve Outcomes in NYHA Class III Patients; DCRI, Department of Clinical Research Informatics; DSMB, Data Safety Monitoring Board; EP, electrophysiology; EXSCEL, Exenatide Study of Cardiovascular Event Lowering; GWTG, Get With The Guidelines; HF, heart failure; HFSA, Heart Failure Society of America; IMPROVE HF, Registry to Improve the Use of Evidence-Based Heart Failure Therapies in the Outpatient Setting; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; NHLBI, National Heart, Lung, and Blood Institute; NIDDK, National Institute of Diabetes and Digestive and Kidney Diseases; NIH, National Institute of Health; NYU, New York University; PARADIGM-HF, Prospective Comparison of ARNI With ACEI to Determine Impact on Global Mortality and Morbidity in Patients With Heart Failure; PRIDE, Prolonging Remission in Depressed Elderly; SUNY, State University of New York; TECOS, Trial Evaluating Cardiovascular Outcomes with Sitagliptin in Patients with Type 2 Diabetes; UCLA, University of California, Los Angeles; UNOS, United Network for Organ Sharing; and VA, veterans affairs.

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