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ESC GUIDELINES

2013 ESC guidelines on the management of stable coronary artery disease

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Abbreviations and acronyms

^{99m}Tc	technetium-99m
^{201}Tl	thallium 201
ABCB1	ATP-binding cassette sub-family B member 1
ABI	ankle-brachial index
ACC	American College of Cardiology
ACCF	American College of Cardiology Foundation
ACCOMPLISH	Avoiding Cardiovascular Events Through Combination Therapy in Patients Living With Systolic Hypertension
ACE	angiotensin converting enzyme
ACIP	Asymptomatic Cardiac Ischaemia Pilot
ACS	acute coronary syndrome
ADA	American Diabetes Association
ADP	adenosine diphosphate
AHA	American Heart Association
ARB	angiotensin II receptor antagonist
ART	Arterial Revascularization Trial
ASCOT	Anglo-Scandinavian Cardiac Outcomes Trial
ASSERT	Asymptomatic atrial fibrillation and Stroke Evaluation in pacemaker patients and the atrial fibrillation Reduction atrial pacing Trial
AV	atrioventricular
BARI 2D	Bypass Angioplasty Revascularization Investigation 2 Diabetes
BEAUTIFUL	Morbidity-Mortality Evaluation of the I_f Inhibitor Ivabradine in Patients With Coronary Artery Disease and Left Ventricular Dysfunction
BIMA	bilateral internal mammary artery
BMI	body mass index
BMS	bare metal stent
BNP	B-type natriuretic peptide
BP	blood pressure
b.p.m.	beats per minute
CABG	coronary artery bypass graft
CAD	coronary artery disease
CAPRIE	Clopidogrel vs. Aspirin in Patients at Risk of Ischaemic Events
CASS	Coronary Artery Surgery Study
CCB	calcium channel blocker
CCS	Canadian Cardiovascular Society
CFR	coronary flow reserve
CHARISMA	Clopidogrel for High Atherothrombotic Risk and Ischaemic Stabilization, Management and Avoidance
CI	confidence interval
CKD	chronic kidney disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CMR	cardiac magnetic resonance
CORONARY	The CABG Off or On Pump Revascularization Study
COURAGE	Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation
COX-1	cyclooxygenase-1
COX-2	cyclooxygenase-2
CPG	Committee for Practice Guidelines
CT	computed tomography
CTA	computed tomography angiography
CV	cardiovascular
CVD	cardiovascular disease
CXR	chest X-ray
CYP2C19*2	cytochrome P450 2C19
CYP3A	cytochrome P3A

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CYP3A4	cytochrome P450 3A4
CYP450	cytochrome P450
DANAMI	Danish trial in Acute Myocardial Infarction
DAPT	dual antiplatelet therapy
DBP	diastolic blood pressure
DECOPI	Desobstruction Coronaire en Post-Infarctus
DES	drug-eluting stents
DHP	dihydropyridine
DSE	dobutamine stress echocardiography
EACTS	European Association for Cardiothoracic Surgery
EECP	enhanced external counterpulsation
EMA	European Medicines Agency
EASD	European Association for the Study of Diabetes
ECG	electrocardiogram
Echo	echocardiogram
ED	erectile dysfunction
EF	ejection fraction
ESC	European Society of Cardiology
EXCEL	Evaluation of XIENCE PRIME or XIENCE V vs. Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization
FAME	Fractional Flow Reserve vs. Angiography for Multivessel Evaluation
FDA	Food & Drug Administration (USA)
FFR	fractional flow reserve
FREEDOM	Design of the Future Revascularization Evaluation in patients with Diabetes mellitus: Optimal management of Multivessel disease
GFR	glomerular filtration rate
HbA1c	glycated haemoglobin
HDL	high density lipoprotein
HDL-C	high density lipoprotein cholesterol
HR	hazard ratio
HRT	hormone replacement therapy
hs-CRP	high-sensitivity C-reactive protein
HU	Hounsfield units
ICA	invasive coronary angiography
IMA	internal mammary artery
IONA	Impact Of Nicorandil in Angina
ISCHEMIA	International Study of Comparative Health Effectiveness with Medical and Invasive Approaches
IVUS	intravascular ultrasound
JSAP	Japanese Stable Angina Pectoris
KATP	ATP-sensitive potassium channels
LAD	left anterior descending
LBBB	left bundle branch block
LIMA	Left internal mammary artery
LDL	low density lipoprotein
LDL-C	low density lipoprotein cholesterol
LM	left main
LMS	left main stem
LV	left ventricular
LVEF	left ventricular ejection fraction
LVH	left ventricular hypertrophy
MACE	major adverse cardiac events
MASS	Medical, Angioplasty, or Surgery Study
MDRD	Modification of Diet in Renal Disease
MERLIN	Metabolic Efficiency with Ranolazine for Less Ischaemia in Non-ST-Elevation Acute Coronary Syndromes
MERLIN-TIMI 36	Metabolic Efficiency with Ranolazine for Less Ischemia in Non-ST-Elevation Acute Coronary Syndromes: Thrombolysis In Myocardial Infarction
MET	metabolic equivalents
MI	myocardial infarction
MICRO-HOPE	Microalbuminuria, cardiovascular and renal substudy of the Heart Outcomes Prevention Evaluation study
MPI	myocardial perfusion imaging
MRI	magnetic resonance imaging
NO	nitric oxide
NSAIDs	non-steroidal anti-inflammatory drugs
NSTE-ACS	non-ST-elevation acute coronary syndrome
NYHA	New York Heart Association
OAT	Occluded Artery Trial
OCT	optical coherence tomography
OMT	optimal medical therapy
PAR-1	protease activated receptor type 1
PCI	percutaneous coronary intervention
PDE5	phosphodiesterase type 5
PES	paclitaxel-eluting stents
PET	positron emission tomography
PRECOMBAT	Premier of Randomized Comparison of Bypass Surgery vs. Angioplasty Using Sirolimus-Eluting Stent in Patients with Left Main Coronary Artery Disease
PTP	pre-test probability
PUFA	polyunsaturated fatty acid
PVD	peripheral vascular disease
QoL	quality of life
RBBB	right bundle branch block
REACH	Reduction of Atherothrombosis for Continued Health
RITA-2	Second Randomized Intervention Treatment of Angina
ROOBY	Veterans Affairs Randomized On/Off Bypass
SAPT	single antiplatelet therapy
SBP	systolic blood pressure
SCAD	stable coronary artery disease
SCORE	Systematic Coronary Risk Evaluation
SCS	spinal cord stimulation
SES	sirolimus-eluting stents
SIMA	single internal mammary artery
SPECT	single photon emission computed tomography
STICH	Surgical Treatment for Ischaemic Heart Failure
SWISSI II	Swiss Interventional Study on Silent Ischaemia Type II
SYNTAX	SYNergy between percutaneous coronary intervention with TAXus and cardiac surgery
TC	total cholesterol

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TENS	transcutaneous electrical neural stimulation
TERISA	Type 2 Diabetes Evaluation of Ranolazine in Subjects With Chronic Stable Angina
TIME	Trial of Invasive vs. Medical therapy
TIMI	Thrombolysis In Myocardial Infarction
TMR	transmyocardial laser revascularization
TOAT	The Open Artery Trial
WOEST	What is the Optimal antiplatElet and anticoagulant therapy in patients with oral anticoagulation and coronary StenTing

1. Preamble

Guidelines summarize and evaluate all evidence available, at the time of the writing process, on a particular issue with the aim of assisting physicians in selecting the best management strategies for an individual patient with a given condition, taking into account the impact on outcome, as well as the risk–benefit ratio of particular diagnostic or therapeutic means. Guidelines are not substitutes but are complements for textbooks, and cover the ESC Core Curriculum topics. Guidelines and recommendations should help physicians to make decisions in their daily practice: however, the final decisions concerning an individual patient must be made by the responsible physician(s).

A great number of Guidelines have been issued in recent years by the European Society of Cardiology (ESC) as well as by other societies and organisations. Because of the impact on clinical practice, quality criteria for the development of guidelines have been established in order to make all decisions transparent to the user. The recommendations for formulating and issuing ESC Guidelines can be found on the ESC website (http://www.escardio.org/guidelines-surveys/esc-guidelines/about/Pages/rules-writing.aspx). ESC Guidelines represent the official position of the ESC on a given topic and are regularly updated.

Members of this Task Force were selected by the ESC to represent professionals involved with the medical care of patients with this pathology. Selected experts in the field undertook a comprehensive review of the published evidence for the diagnosis, management and/or prevention of a given condition according to the ESC Committee for Practice Guidelines (CPG) policy. A critical evaluation of diagnostic and therapeutic procedures was performed, including assessment of the risk–benefit ratio. Estimates of expected health outcomes for larger populations were included, where data exist. The level of evidence and the strength of recommendation of particular treatment options were weighed and graded according to predefined scales, as outlined in *Tables 1* and *2*.

The experts of the writing and reviewing panels completed Declaration of Interest forms where real or potential sources of conflicts of interest might be perceived. These forms were compiled into one file and can be found on the ESC website (http://www.escardio.org/guidelines). Any changes in declarations of interest that arise during the writing period must be notified to the ESC and updated. The Task Force received its entire financial support from the ESC, without any involvement from healthcare industry.

The ESC CPG supervises and co-ordinates the preparation of new Guidelines produced by Task Forces, expert groups or consensus panels. The Committee is also responsible for the endorsement process of these Guidelines. The ESC Guidelines undergo extensive review by the CPG and external experts. After appropriate revisions, they are approved by all the experts involved in the Task Force. The finalized document is approved by the CPG for publication in the *European Heart Journal*.

The task of developing ESC Guidelines covers not only the integration of the most recent research, but also the creation of educational tools and implementation programmes for the recommendations. To implement the guidelines, condensed pocket editions, summary slides, booklets with essential messages, electronic versions for digital applications (smartphones etc.) are produced. These versions are abridged and thus, if needed, one should always refer to the full

Table 1 Classes of recommendations

Classes of recommendations	Definition	Suggested wording to use
Class I	**Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective.**	**Is recommended/is indicated**
Class II	**Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure.**	
Class IIa	***Weight of evidence/opinion is in favour of usefulness/efficacy.***	**Should be considered**
Class IIb	***Usefulness/efficacy is less well established by evidence/opinion.***	**May be considered**
Class III	**Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful.**	**Is not recommended**

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Table 2 Levels of evidence

Level of evidence A	Data derived from multiple randomized clinical trials or meta-analyses.
Level of evidence B	Data derived from a single randomized clinical trial or large non-randomized studies.
Level of evidence C	Consensus of opinion of the experts and/or small studies, retrospective studies, registries.

text version, which is freely available on the ESC website. The National Societies of the ESC are encouraged to endorse, translate and implement the ESC Guidelines. Implementation programmes are needed because it has been shown that the outcome of disease may be favourably influenced by the thorough application of clinical recommendations.

Surveys and registries are needed to verify that real-life daily practice is in keeping with what is recommended in the guidelines, thus completing the loop between clinical research, writing of guidelines and implementing them into clinical practice.

The Guidelines do not, however, override the individual responsibility of health professionals to make appropriate decisions in the circumstances of the individual patient, in consultation with that patient and, where appropriate and necessary, the patient's guardian or carer. It is also the health professional's responsibility to verify the rules and regulations applicable to drugs and devices at the time of prescription.

2. Introduction

These guidelines should be applied to patients with stable known or suspected coronary artery disease (SCAD). This condition encompasses several groups of patients: (i) those having stable angina pectoris or other symptoms felt to be related to coronary artery disease (CAD) such as dyspnoea; (ii) those previously symptomatic with known obstructive or non-obstructive CAD, who have become asymptomatic with treatment and need regular follow-up; (iii) those who report symptoms for the first time and are judged to already be in a chronic stable condition (for instance because history-taking reveals that similar symptoms were already present for several months). Hence, SCAD defines the different evolutionary phases of CAD, excluding the situations in, which coronary artery thrombosis dominates clinical presentation (acute coronary syndromes).

However, patients who have a first or recurrent manifestation of angina but can be categorized as having a low-risk acute coronary syndrome (ACS) according to the current ACS guidelines of the ESC [no recurrence of chest pain, no signs of heart failure, no abnormalities in the resting electrocardiogram (ECG), no rise in markers of myocardial necrosis (preferably troponin) and hence are not candidates for swift intervention][1] should also be managed according to the algorithms presented in these Guidelines. Although routine screening of asymptomatic patients is discouraged,[2] these guidelines can also be applied to asymptomatic patients presenting for further evaluation due to an abnormal test. The scope of the present Guidelines, therefore, spans from asymptomatic individuals to patients after stabilisation of an ACS.

The traditional understanding of SCAD is that of a disease causing exercise- and stress-related chest symptoms due to narrowings of $\geq$50% in the left main coronary artery and $\geq$70% in one or several of the major coronary arteries. Compared with the previous version of the Guidelines[3], the present edition considers not only such atherosclerotic narrowings, but also microvascular dysfunction and coronary vasospasm in the diagnostic and prognostic algorithms; the present Guidelines also distinguish diagnostic testing from prognostic assessment; they give increased importance to the pre-test probability (PTP) of disease strongly influencing the diagnostic algorithms and they take into account recent advances in technology, the importance of physiological assessment of CAD in the catheterization laboratory and the increasing evidence that the prognostic benefit of revascularization may be less than has been traditionally expected.

In order to limit the length of the printed text, additional information, tables, figures and references are available as web addenda at the ESC website (www.escardio.org).

3. Definitions and pathophysiology (see web addenda)

Stable coronary artery disease is generally characterized by episodes of reversible myocardial demand/supply mismatch, related to ischaemia or hypoxia, which are usually inducible by exercise, emotion or other stress and reproducible—but, which may also be occurring spontaneously. Such episodes of ischaemia/hypoxia are commonly associated with transient chest discomfort (angina pectoris). SCAD also includes the stabilized, often asymptomatic, phases that follow an ACS.

Because the transition from unstable to stable syndromes is a continuum, without a clear boundary, angina at rest caused by coronary vasospasm may be regarded within the scope of SCAD,[3–5] as in the present document or, conversely, within the scope of ACS as in some,[6] but not in other,[1] ACS guidelines. Recent use of ultrasensitive troponin tests has shown that episodes of minute troponin release—below the threshold for acute myocardial infarction— often occur in patients with stable CAD and this has been shown to have prognostic implications,[7,8,9] thus also demonstrating the continuum of CAD subgroups.

The various clinical presentations of SCAD (see also section 6.1) are associated with different underlying mechanisms that mainly include: (i) plaque-related obstruction of epicardial arteries; (ii) focal or diffuse spasm of normal or plaque-diseased arteries; (iii) microvascular dysfunction and (iv) left ventricular dysfunction caused by prior acute myocardial necrosis and/or hibernation (ischaemic cardiomyopathy) (*Table 3*). These mechanisms may act singly or in combination. However, stable coronary plaques with and without previous revascularization may also be completely clinically silent. Additional information on the relationship between symptoms and underlying disease mechanisms, the histology of epicardial lesions, the definitions and pathogenesis of vasospasm, the

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Table 3 Main features of stable coronary artery disease

Pathogenesis
Stable anatomical atherosclerotic and/or functional alterations of epicardial vessels and/or microcirculation
Natural history
Stable symptomatic or asymptomatic phases which may be interrupted by ACS
Mechanisms of myocardial ischaemia
Fixed or dynamic stenoses of epicardial coronary arteries;
Microvascular dysfunction;
Focal or diffuse epicardial coronary spasm;
The above mechanisms may overlap in the same patient and change over time.
Clinical presentations
Effort induced angina caused by: • epicardial stenoses; • microvascular dysfunction; • vasoconstriction at the site of dynamic stenosis; • combination of the above.
Rest angina caused by: • Vasospasm (focal or diffuse) • epicardial focal; • epicardial diffuse; • microvascular; • combination of the above.
Asymptomatic: • because of lack of ischaemia and/or of LV dysfunction; • despite ischaemia and/or LV dysfunction.
Ischaemic cardiomyopathy

ACS = acute coronary syndrome; LV = left ventricular; SCAD = stable coronary artery disease.

definition of microvascular dysfunction and ischaemic cardiomyopathy is available in sections 3.1–3.5 of the web addenda.

Myocardial ischaemia and hypoxia in SCAD are caused by a transient imbalance between blood supply and metabolic demand. The consequences of ischaemia occur in a predictable temporal sequence that involves:

(1) Increased H+ and K+ concentration in the venous blood that drains the ischaemic territory
(2) Signs of ventricular diastolic and subsequently systolic dysfunction with regional wall motion abnormalities
(3) Development of ST–T changes
(4) Cardiac ischaemic pain (angina).[10]

This sequence explains why imaging techniques based on perfusion, metabolism or wall motion are more sensitive than an ECG or symptoms in detecting ischaemia. Angina is ultimately caused by the release of ischaemic metabolites—such as adenosine—that stimulate sensitive nerve endings, although angina may be absent even with severe ischaemia owing, for instance, to impaired transmission of painful stimuli to the cortex and other as-yet-undefined potential mechanisms.[11]

The functional severity of coronary lesions can be assessed by measuring coronary flow reserve (CFR) and intracoronary artery pressures (fractional flow reserve, FFR). More detailed descriptions can be found in the web addenda.

4. Epidemiology

As SCAD is so multifaceted, its prevalence and incidence have been difficult to assess and numbers vary between studies, depending on the definition that has been used. For epidemiologic purposes, stable angina is essentially a diagnosis based on history and therefore relies on clinical judgement. The Rose angina questionnaire has a specificity of ~80–95%,[12] but its sensitivity varies substantially from 20–80% when compared with clinical diagnosis, ECG findings and coronary angiography.

The prevalence of angina in population-based studies increases with age in both sexes, from 5–7% in women aged 45–64 years to 10–12% in women aged 65–84 and from 4–7% in men aged 45–64 years to 12–14% in men aged 65–84.[13] Interestingly, angina is more prevalent in middle-aged women than in men, probably due to the higher prevalence of functional CAD—such as microvascular angina—in women,[14,15] whereas the opposite is true in the elderly.

Available data suggest an annual incidence of uncomplicated angina pectoris of 1.0% in male western populations aged 45–65 years, with a slightly higher incidence in women under the age of 65.[13,16] There is a steep increase with age and the incidence in men and women 75–84 years of age reaches almost 4%.[16] The incidence of angina varies in parallel with observed international differences in CAD mortality.[16,17]

Temporal trends suggest a decrease in the annual death rate due to CAD.[18] However, the prevalence of a history of diagnosed CAD does not appear to have decreased, suggesting that the prognosis of those with established CAD is improving. Improved sensitivity of diagnostic tools may additionally contribute to the contemporary high prevalence of diagnosed CAD.

Epidemiological data on microvascular angina and vasospastic angina are missing. However, recent clinical data suggest that abnormal coronary vasomotion is present in two-thirds of patients who suffer from stable angina but have no coronary stenoses at angiography.[19]

5. Natural history and prognosis

In many patients, early manifestations of CAD are endothelial dysfunction and microvascular disease. Both are associated with an increased risk of complications from CAD.[20–22]

Contemporary data regarding prognosis can be derived from clinical trials of anti-anginal and preventive therapy and/or revascularization, although these data are biased by the selected nature of the populations studied. From these, estimates for annual mortality rates range from 1.2–2.4% per annum,[23–28] with an annual incidence of cardiac death between 0.6 and 1.4% and of non-fatal myocardial infarction (MI) between 0.6% in the Second Randomized Intervention Treatment of Angina (RITA-2)[26] and 2.7% in the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trials.[23] These estimates are consistent with observational registry data.[13,29]

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However, within the population with stable CAD, an individual's prognosis can vary considerably, depending on baseline clinical, functional and anatomical characteristics. This is exemplified in the Reduction of Atherothrombosis for Continued Health (REACH) registry,[30], which included very high-risk patients, many with peripheral arterial disease or previous MI and almost 50% with diabetes. Consequently, annual mortality rate was as high as 3.8% in this population[30], whereas patients with non-obstructive plaques within the coronary arteries have an annual mortality rate of only 0.63%.

Prognostic assessment is an important part of the management of patients with SCAD. On the one hand, it is important to reliably identify those patients with more severe forms of disease, who may have an improvement in outcome with more aggressive investigation and—potentially—intervention, including revascularization. On the other hand, it is also important to identify those patients with a less-severe form of disease and a good prognosis, thereby avoiding unnecessary invasive and non-invasive tests and revascularization procedures.

Conventional risk factors for the development of CAD[31–33]—hypertension,[34] hypercholesterolaemia,[35] diabetes,[36] sedentary lifestyle,[37], obesity,[37] smoking,[34,38] and a family history[39]—have an adverse influence on prognosis in those with established disease, presumably through their effect on the progression of atherosclerotic disease processes. However, appropriate treatment can reduce these risks.[40–42] An elevated resting heart rate is also indicative of a worse prognosis in those with suspected or proven CAD.[43] In general, the outcome is worse in patients with reduced left ventricular ejection fraction (LVEF) and heart failure, a greater number of diseased vessels, more proximal locations of coronary stenoses, greater severity of lesions, more extensive ischaemia, more impaired functional capacity, older age, significant depression and more severe angina.[44–47]

6. Diagnosis and assessment (see web addenda)

The diagnosis and assessment of SCAD involves clinical evaluation, including identifying significant dyslipidaemia, hyperglycaemia or other biochemical risk factors and specific cardiac investigations such as stress testing or coronary imaging. These investigations may be used to confirm the diagnosis of ischaemia in patients with suspected SCAD, to identify or exclude associated conditions or precipitating factors, assist in stratifying risk associated with the disease and to evaluate the efficacy of treatment. In practice, diagnostic and prognostic assessments are conducted simultaneously, rather than separately, and many of the investigations used for diagnosis also offer prognostic information. However, for the purpose of clarity, the processes of obtaining diagnostic and prognostic information are dealt with separately in this text.

6.1 Symptoms and signs (see web addenda)

A careful history remains the cornerstone of the diagnosis of chest pain. In the majority of cases, it is possible to make a confident diagnosis on the basis of the history alone, although physical examination and objective tests are often necessary to confirm the diagnosis, exclude alternative diagnoses,[48] and assess the severity of underlying disease.

The characteristics of discomfort-related to myocardial ischaemia (angina pectoris) may be divided into four categories: location, character, duration and relationship to exertion and other exacerbating or relieving factors. The discomfort caused by myocardial ischaemia is usually located in the chest, near the sternum, but may be felt anywhere from the epigastrium to the lower jaw or teeth, between the shoulder blades or in either arm to the wrist and fingers.

The discomfort is often described as pressure, tightness or heaviness; sometimes strangling, constricting or burning. It may be useful to directly ask the patient for the presence of 'discomfort' as many do not feel 'pain' or 'pressure' in their chest. Shortness of breath may accompany angina, and chest discomfort may also be accompanied by less-specific symptoms such as fatigue or faintness, nausea, burning, restlessness or a sense of impending doom. Shortness of breath may be the sole symptom of SCAD and it may be difficult to differentiate this from shortness of breath caused by bronchopulmonary disease.

The duration of the discomfort is brief—no more than 10 min in the majority of cases and more commonly even minutes or less—but chest pain lasting for seconds is unlikely to be due to angina. An important characteristic is the relationship to exercise, specific activities or emotional stress. Symptoms classically appear or become more severe with increased levels of exertion—such as walking up an incline or against a breeze or in cold weather—and rapidly disappear within a few minutes when these causal factors abate. Exacerbations of symptoms after a heavy meal or after waking up in the morning are classical features of angina. Angina may be reduced with further exercise (walk-through angina) or on second exertion (warm-up angina).[49] Buccal or sublingual nitrates rapidly relieve angina. The angina threshold—and hence symptoms—may vary considerably from day to day and even during the same day.

Definitions of typical and atypical angina have been previously published and are summarized in *Table 4*.[50] Atypical angina is most frequently chest pain resembling that of typical angina in location and character, that is responsive to nitrates but has no precipitating factors. Often, the pain is described as starting at rest from a low level of intensity, which slowly intensifies, remains at its maximum for up to 15 min and then slowly decreases in intensity. This characteristic description should alert the clinician to the possibility that coronary vasospasm is present.[51] Another atypical presentation is pain of anginal location and quality, which is triggered by exertion

Table 4 Traditional clinical classification of chest pain

Typical angina (definite)	Meets all three of the following characteristics: • substernal chest discomfort of characteristic quality and duration; • provoked by exertion or emotional stress; • relieved by rest and/or nitrates within minutes.
Atypical angina (probable)	Meets two of these characteristics.
Non-anginal chest pain	Lacks or meets only one or none of the characteristics.

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Table 5 Classification of angina severity according to the Canadian Cardiovascular Society

Class I	Ordinary activity does not cause angina such as walking and climbing stairs. Angina with strenuous or rapid or prolonged exertion at work or recreation.
Class II	Slight limitation of ordinary activity. Angina on walking or climbing stairs rapidly, walking or stair climbing after meals, or in cold, wind or under emotional stress, or only during the first few hours after awakening. Walking more than two blocks on the level and climbing more than one flight of ordinary stairs at a normal pace and in normal conditions.
Class III	Marked limitation of ordinary physical activity. Angina on walking one to two blocks[a] on the level or one flight of stairs in normal conditions and at a normal pace.
Class IV	Inability to carry on any physical activity without discomfort' – angina syndrome may be present at rest'.

[a]Equivalent to 100–200 m.

but occurs some time after exertion and may be poorly responsive to nitrates. This presentation is often seen in patients with microvascular angina.[52]

Non-anginal pain lacks the characteristic qualities described, may involve only a small portion of the left or right hemithorax, and last for several hours or even days. It is usually not relieved by nitroglycerin (although it may be in the case of oesophageal spasm) and may be provoked by palpation. Non-cardiac causes of pain should be evaluated in such cases.[48]

The Canadian Cardiovascular Society classification is widely used as a grading system for stable angina,[53] to quantify the threshold at which symptoms occur in relation to physical activities (*Table 5*). It is, however, important to keep in mind that the grading system explicitly recognizes that rest pain may occur in all grades as a manifestation of associated and superimposed coronary vasospasm.[5] It is also important to remember that the class assigned is indicative of the maximum limitation and that the patient may do better on other days.

Patients with chest pain are often seen in general practice. Applying a well-validated prediction rule containing the five determinants [*viz.* age/sex (male $\geq$ 55 years, female $\geq$ 65 years); known vascular disease; patient assumes pain is of cardiac origin; pain is worse during exercise and pain is not reproducible by palpation: one point for each determinant] leads to accurate ruling-out of CAD at a specificity of 81% ($\leq$2 points) and a sensitivity of 87% (3–5 points).[54] This rule should be used in the context of other clinical information, such as the presence of cough or stinging pain (making CAD more unlikely). In contrast, clinical features such as radiation of pain into the left arm, known heart failure and diabetes mellitus make CAD more likely.[55]

Physical examination of a patient with (suspected) angina pectoris is important to assess the presence of anaemia, hypertension, valvular heart disease, hypertrophic obstructive cardiomyopathy or arrhythmias. It is also recommended that practitioners obtain the body mass index (BMI) and search for evidence of non-coronary vascular disease—which may be asymptomatic [includes palpation of peripheral pulses and auscultation of carotid and femoral arteries as well as assessment of the ankle brachial index (ABI)]—and other signs of comorbid conditions such as thyroid disease, renal disease or diabetes. One should also try to reproduce the symptoms by palpation (this makes SCAD less likely: see above).[54] However, there are no specific signs in angina pectoris. During or immediately after an episode of myocardial ischaemia, a third or fourth heart sound may be heard and mitral insufficiency may also be apparent during ischaemia. Such signs are, however, elusive and non-specific.

6.2 Non-invasive cardiac investigations

Although many non-invasive cardiac investigations can be used to support the diagnosis of SCAD, the optimal use of resources is only achieved if pre-test probabilities, based on simple clinical findings, are first taken into consideration. Once the diagnosis of SCAD has been made, further management decisions depend largely on the severity of symptoms, the patient's risk for adverse cardiac events and on patient preferences. The choice is between preventive medication plus symptomatic medical management only or, additionally, revascularization, in which case the type of revascularization has to be determined. These management decisions will be dealt with in separate chapters. As there are few randomized trials assessing health outcomes for diagnostic tests, the available evidence has been ranked according to evidence from non-randomized studies or meta-analyses of these studies.

6.2.1 Basic testing

Before any testing is considered one must assess the general health, comorbidities and quality of life (QoL) of the patient. If assessment suggests that revascularization is unlikely to be an acceptable option, further testing may be reduced to a clinically indicated minimum and appropriate therapy should be instituted, which may include a trial of anti-anginal medication even if a diagnosis of SCAD has not been fully demonstrated.

Basic (first-line) testing in patients with suspected SCAD includes standard laboratory biochemical testing (*Table 6*), a resting ECG (*Table 8*), possibly ambulatory ECG monitoring (if there is clinical suspicion that symptoms may be associated with a paroxysmal arrhythmia) (*Table 10*), resting echocardiography (*Table 9*) and, in selected patients, a chest X-ray (CXR) (*Table 11*). Such testing can be done on an outpatient basis.

6.2.1.1 Biochemical tests (see web addenda)

Laboratory investigations are used to identify possible causes of ischaemia, to establish cardiovascular (CV) risk factors and associated conditions and to determine prognosis.

Haemoglobin as part of a full blood count and—where there is a clinical suspicion of a thyroid disorder—thyroid hormone levels provide information related to possible causes of ischaemia. The full blood count, incorporating total white cell count as well as haemoglobin, may also add prognostic information.[56]

Fasting plasma glucose and glycated haemoglobin (HbA1c) should be measured in every patient with suspected CAD. If both are inconclusive, an additional oral glucose tolerance test is recommended.[57,58] Knowledge of glucose metabolism is important because of the well-recognized association between adverse cardiovascular (CV) outcome and diabetes. Moreover, elevations of fasting

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Table 6 Blood tests in assessment of patients with known or suspected SCAD in order to optimize medical therapy

Recommendations	Class [a]	Level [b]	Ref. [c]
If evaluation suggests clinical instability or ACS, repeated measurements of troponin preferably using high sensitivity or ultrasensitive assays are recommended to rule out myocardial necrosis associated with ACS.	I	A	73, 74
Full blood count including haemoglobin and white cell count is recommended in all patients.	I	B	75
It is recommended that screening for potential T2DM in patients with suspected and established SCAD is initiated with HbA1c and fasting plasma glucose and that an OGTT is added if HbA_{1c} and fasting plasma glucose are inconclusive	I	B	57, 58, 76
Creatinine measurement and estimation of renal function (creatinine clearance) are recommended in all patients	I	B	77
A fasting lipid profile (including LDL) is recommended in all patients[d]	I	C	-
If indicated by clinical suspicion of thyroid disorder assessment of thyroid function is recommended	I	C	-
Liver function tests are recommended in patients early after beginning statin therapy	I	C	-
Creatine kinase measurement are recommended in patients taking statins and complaining of symptoms suggestive of myopathy	I	C	-
BNP/NT-proBNP measurements should be considered in patients with suspected heart failure	IIa	C	-

ACS = acute coronary syndrome; BNP = B-type natriuretic peptide; HbA1c = glycated haemoglobin; LDL = low density lipoprotein; NT-proBNP = N-terminal pro B-type natriuretic peptide; SCAD = stable coronary artery disease; T2DM = type 2 diabetes mellitus.
[a] Class of recommendation.
[b] Level of evidence.
[c] Reference(s) supporting class I (A + B) and IIa + IIb (A + B) recommendations.
[d] For details please refer to dyslipidaemia guidelines.[62]

or post-glucose challenge glycaemia have been shown to predict adverse outcome in SCAD, independently of conventional risk factors.[59] Finally, glycated haemoglobin (HbA1c) predicts outcome in diabetics, as well as in non-diabetic subjects.[60,61] Patients with diabetes should be managed according to the ESC/European Association for the Study of Diabetes (EASD) Guidelines on diabetes.[57]

Fasting lipid profile, including total cholesterol (TC), high density lipoprotein (HDL) cholesterol, low density lipoprotein (LDL) cholesterol and triglycerides should also be evaluated in all patients with suspected or established ischaemic disease, including stable angina, to establish the patient's risk profile and ascertain the need for treatment.[62]

The lipid profile and glycaemic status should be re-assessed periodically to determine efficacy of treatment and, in non-diabetic patients, to detect new development of diabetes (*Table 7*). There is no evidence to support recommendations for the frequency of re-assessment of these risk factors. Consensus suggests annual measurement.[62]

Renal dysfunction may occur in association with hypertension, diabetes or renovascular disease and has a negative impact on prognosis in patients with stable angina pectoris.[63–65] Hence, baseline renal function should be evaluated with estimation of the glomerular filtration rate (GFR) using a creatinine (or cystatin C)-based method such as the Cockcroft–Gault,[66] Modification of Diet in Renal Disease (MDRD),[67] or Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formulas.[68]

If there is a clinical suspicion of CAD instability, biochemical markers of myocardial injury—such as troponin T or troponin I—should be measured, preferably using high sensitivity or ultrasensitive assays. If troponin is elevated, further management should follow the non-ST-elevation acute coronary syndrome (NSTE-ACS) guidelines.[1] As troponins have a central role in identifying unstable patients,[1,7] it is recommended that troponin measurements be performed in every patient hospitalised for symptomatic SCAD.

Table 7 Blood tests for routine re-assessment in patients with chronic stable coronary artery disease

Recommendations	Class [a]	Level [b]	Ref. [c]
Annual control of lipids, glucose metabolism (see recommendation 3 in Table 6) and creatinine is recommended in all patients with known SCAD.	I	C	-

SCAD = stable coronary artery disease.
[a] Class of recommendation.
[b] Level of evidence.
[c] Reference(s) supporting class I (A + B) and IIa + IIb (A + B) recommendations.

Very low levels of troponin can be detected in many patients with SCAD when high-sensitive assays are employed. These levels are usually below the levels defined as being elevated. Although there is some prognostic value associated with the amount of troponin found in stable patients,[8,9] troponin does not have enough independent prognostic value to recommend systematic measurement in out-of-hospital patients with SCAD.

Elevated levels of high-sensitivity C-reactive protein (hs-CRP) have also been reported to be associated with an increased event risk in patients with SCAD. However, a recent analysis of 83 studies found multiple types of reporting and publication bias, making the magnitude of any independent association between hs-CRP and prognosis among patients with SCAD sufficiently uncertain that no recommendation can be made to routinely measure this parameter.[69]

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Table 8 Resting electrocardiogram for initial diagnostic assessment of stable coronary artery disease

Recommendations	Class [a]	Level [b]	Ref. [c]
A resting ECG is recommended in all patients at presentation.	I	C	-
A resting ECG is recommended in all patients during or immediately after an episode of chest pain suspected to indicate clinical instability of CAD.	I	C	-

ECG = electrocardiogram; SCAD = stable coronary artery disease.
[a] Class of recommendation.
[b] Level of evidence.
[c] Reference(s) supporting class I (A + B) and IIa + IIb (A + B) recommendations.

Table 9 Echocardiography

Recommendations	Class [a]	Level [b]	Ref. [c]
A resting transthoracic echocardiogram is recommended in all patients for: a) exclusion of alternative causes of angina; b) identification of regional wall motion abnormalities suggestive of CAD; c) measurement of LVEF for risk stratification purpose; d) evaluation of diastolic function.	I	B	27, 79, 80
Ultrasound of the carotid arteries should be considered to be performed by adaequately trained clinicians to detect increased IMT and/or plaque in patients with suspected SCAD without known atherosclerotic disease.	IIa	C	-

CAD = coronary artery disease; IMD = Intima-media thickness; LVEF = left ventricular ejection fraction; SCAD = stable coronary artery disease.
[a] Class of recommendation.
[b] Level of evidence.
[c] Reference(s) supporting class I (A + B) and IIa + IIb (A + B) recommendations.

Although there may be some additional prognostic value in other biomarkers, there is insufficient evidence to recommend the routine use of natriuretic peptides, haemostasis markers or genetic testing in the management of patients with SCAD (for additional information see web addenda).[70–72]

6.2.1.2 Resting electrocardiogram

All patients with suspected CAD should have a resting 12-lead ECG recorded. A normal resting ECG is not uncommon, even in patients with severe angina, and does not exclude the diagnosis of ischaemia. However, the resting ECG may show signs of CAD, such as previous MI or an abnormal repolarization pattern. An ECG will establish a baseline for comparison in future situations.

The ECG may assist in clarifying the differential diagnosis if taken in the presence of pain, allowing detection of dynamic ST-segment changes in the presence of ischaemia. An ECG during chest pain and immediately afterwards is always useful and can be diagnostic in patients with vasospasm, since ST segment shifts tend to be at least partially reversible once spasm is relieved. The ECG may also show other abnormalities such as left ventricular hypertrophy (LVH), left or right bundle branch block (LBBB or RBBB), pre-excitation, arrhythmias, or conduction defects. Such information may be helpful in defining the mechanisms responsible for chest pain (atrial fibrillation may be associated with chest discomfort without epicardial coronary disease)[78] in selecting appropriate further investigations, or in tailoring individual patient treatment. The resting ECG also has a role in risk stratification, as outlined later.

6.2.1.3 Echocardiography at rest (see web addenda)

Resting two-dimensional and Doppler transthoracic echocardiography provide information on cardiac structure and function. Although left ventricular (LV) function is often normal in these patients, regional wall motion abnormalities may be detected, which increase the likelihood of CAD. Furthermore other disorders, such as valvular heart disease (aortic stenosis) or hypertrophic cardiomyopathy, can be ruled out as an alternative cause of symptoms. Finally, global ventricular function, an important prognostic parameter in patients with SCAD,[29,79] can be measured. Echocardiography is particularly useful in patients with murmurs[80], previous MI or symptoms/signs of heart failure.

Once resting echocardiography has been performed, ultrasound of the carotid arteries using an appropriate probe may be added by clinicians trained in the examination.[81,82] The detection of increased intima-media thickness and/or plaques establishes the presence of atherosclerotic disease, with consequent implications for preventive therapy,[37] and increases the pre-test probability of CAD in subsequent diagnostic tests.[83]

Tissue Doppler imaging and strain rate measurements may also be helpful in detecting heart failure with preserved EF as an explanation for physical activity-associated symptoms.[84] Impaired diastolic filling is the first sign of active ischaemia and may point to the presence of microvascular dysfunction in patients who complain about shortness of breath, as a possible angina equivalent.[85,86]

Although the diagnostic yield of echocardiography in patients with angina is mainly concentrated in specific subgroups, estimation of ventricular function is important in all patients for risk stratification (see section 6.4). Hence, echocardiography (or alternative methods of assessment of ventricular function if echocardiography is of insufficient quality) should be performed in all patients with a first presentation with symptoms of SCAD.

There is no indication for repeated use of resting echocardiography on a regular basis in patients with uncomplicated SCAD in the absence of a change in clinical status.

6.2.1.4 Cardiac magnetic resonance at rest

Cardiac magnetic resonance (CMR) may also be used to define structural cardiac abnormalities and evaluate ventricular function.[87] Use of

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Table 10 Ambulatory electrocardiogram monitoring for initial diagnostic assessment of stable coronary artery disease

Recommendations	Class [a]	Level [b]	Ref. [c]
Ambulatory ECG monitoring is recommended in patients with SCAD and suspected arrhythmia.	I	C	-
Ambulatory ECG monitoring should be considered in patients with suspected vasospastic angina.	IIa	C	-

ECG = electrocardiogram; SCAD = stable coronary artery disease.
[a] Class of recommendation.
[b] Level of evidence.
[c] Reference(s) supporting class I (A + B) and IIa + IIb (A + B) recommendations.

CMR is recommended in patients in whom, despite the use of echo contrast agents, transthoracic echocardiography is unable to answer the clinical question (usually because of a restricted acoustic window) and who have no contra-indications for CMR.

6.2.1.5 Ambulatory electrocardiogram monitoring

Ambulatory ECG (Holter) monitoring may reveal evidence of myocardial ischaemia during normal daily activities but, in SCAD, rarely adds important diagnostic information over and above that provided by the stress test.[88] Neither is there good evidence to support routine deployment of ambulatory ECG monitoring as a tool for refined prognostication.

Ambulatory monitoring, however, has a role in patients in whom arrhythmias or vasospastic angina are suspected (equipment for ST-segment evaluation required).

6.2.1.6 Chest X-ray

A CXR is frequently used in the assessment of patients with chest pain: however, in SCAD, the CXR does not provide specific information for diagnosis or event risk stratification. The test may occasionally be helpful in assessing patients with suspected heart failure.[89] The CXR may also be useful in patients with pulmonary problems, which often accompany SCAD, or to rule out another cause of chest pain in atypical presentations.

Table 11 Chest X-ray for initial diagnostic assessment of SCAD

Recommendations	Class [a]	Level [b]	Ref. [c]
CXR is recommended in patients with atypical presentation or suspicion of pulmonary disease.	I	C	-
CXR should be considered in patients with suspected heart failure.	IIa	C	-

CXR = chest X-ray.
[a] Class of recommendation.
[b] Level of evidence.
[c] Reference(s) supporting class I (A + B) and IIa + IIb (A + B) recommendations.

6.2.2 Three major steps used for decision-making

These guidelines recommend a stepwise approach for decision making in patients with suspected SCAD. The process begins with a clinical assessment of the probability that SCAD is present in a particular patient (determination of PTP; Step 1) (see below). Step 1 is followed by non-invasive testing to establish the diagnosis of SCAD or non-obstructive atherosclerosis (typically by performing carotid ultrasound) in patients with an intermediate probability of disease (Step 2). Once the diagnosis of SCAD has been made, optimal medical therapy (OMT) is instituted and stratification for risk of subsequent events (referred to as 'event risk' in the following text) is carried out (Step 3)—usually on the basis of available non-invasive tests— in order to select patients who may benefit from invasive investigation and revascularization. Depending on the severity of symptoms, early invasive coronary angiography (ICA) may be performed with appropriate invasive confirmation of the significance of a stenosis (FFR) and subsequent revascularization, bypassing non-invasive testing in Steps 2 and 3.

6.2.3 Principles of diagnostic testing

Interpretation of non-invasive cardiac tests requires a Bayesian approach to diagnosis. This approach uses clinicians' pre-test estimates [termed pre-test probability (PTP)] of disease along with the results of diagnostic tests to generate individualized post-test disease probabilities for a given patient. The PTP is influenced by the prevalence of the disease in the population studied, as well as clinical features (including the presence of CV risk factors) of an individual.[90] Major determinants of PTP are age, gender and the nature of symptoms.[90]

Sensitivity and specificity are often used to describe the accuracy of a given diagnostic method, but they incompletely describe how a test performs in the clinical setting. First, some diagnostic methods may perform better in some patients than in others—such as coronary computed tomography angiography (CTA), which is sensitive to heart rate, body weight and the presence of calcification. Second, although sensitivity and specificity are mathematically independent from the PTP, in clinical practice many tests perform better in low-risk populations; in the example used above, coronary CTA will have higher accuracy values when low-likelihood populations—which are younger and have less coronary calcium—are subjected to the examination.

Because of the interdependence of PTP (the clinical likelihood that a given patient will have CAD) and the performance of the available diagnostic methods (the likelihood that this patient has disease if the test is positive, or does not have disease if the test is negative), recommendations for diagnostic testing need to take into account the PTP. Testing may do harm if the number of false test results is higher than the number of correct test results. Non-invasive, imaging-based diagnostic methods for CAD have typical sensitivities and specificities of approximately 85% (*Table 12*). Hence, 15% of all diagnostic results will be false and, as a consequence, performing no test at all will provide fewer incorrect diagnoses in patients with a PTP below

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Table 12 Characteristics of tests commonly used to diagnose the presence of coronary artery disease

	Diagnosis of CAD	
	Sensitivity (%)	Specificity (%)
Exercise ECG [a, 91, 94, 95]	45–50	85–90
Exercise stress echocardiography[96]	80–85	80–88
Exercise stress SPECT[96-99]	73–92	63–87
Dobutamine stress echocardiography[96]	79–83	82–86
Dobutamine stress MRI[b,100]	79–88	81–91
Vasodilator stress echocardiography[96]	72–79	92–95
Vasodilator stress SPECT[96, 99]	90–91	75–84
Vasodilator stress MRI[b,98, 100-102]	67–94	61–85
Coronary CTA[c,103-105]	95–99	64–83
Vasodilator stress PET[97, 99, 106]	81–97	74–91

CAD = coronary artery disease; CTA = computed tomography angiography; ECG = electrocardiogram; MRI = magnetic resonance imaging; PET = positron emission tomography; SPECT = single photon emission computed tomography.
[a] Results without/with minimal referral bias.
[b] Results obtained in populations with medium-to-high prevalence of disease without compensation for referral bias.
[c] Results obtained in populations with low-to-medium prevalence of disease.

Table 13 Clinical pre-test probabilities[a] in patients with stable chest pain symptoms[108]

	Typical angina		Atypical angina		Non-anginal pain	
Age	Men	Women	Men	Women	Men	Women
30–39	59	28	29	10	18	5
40–49	69	37	38	14	25	8
50–59	77	47	49	20	34	12
60–69	84	58	59	28	44	17
70–79	89	68	69	37	54	24
>80	93	76	78	47	65	32

ECG = electrocardiogram; PTP = pre-test probability; SCAD = stable coronary artery disease.
[a] Probabilities of obstructive coronary disease shown reflect the estimates for patients aged 35, 45, 55, 65, 75 and 85 years.
• Groups in white boxes have a PTP <15% and hence can be managed without further testing.
• Groups in blue boxes have a PTP of 15–65%. They could have an exercise ECG if feasible as the initial test. However, if local expertise and availability permit a non-invasive imaging based test for ischaemia this would be preferable given the superior diagnostic capabilities of such tests. In young patients radiation issues should be considered.
• Groups in light red boxes have PTPs between 66–85% and hence should have a non-invasive imaging functional test for making a diagnosis of SCAD.
• In groups in dark red boxes the PTP is >85% and one can assume that SCAD is present. They need risk stratification only.

15% (assuming all patients to be healthy) or a PTP above 85% (assuming all patients to be diseased). In these situations, testing should only be done for compelling reasons. This is the reason why this Task Force recommends no testing in patients with (i) a low PTP <15% and (ii) a high PTP >85%. In such patients, it is safe to assume that they have (i) no obstructive CAD or (ii) obstructive CAD.

The low sensitivity of the exercise ECG—only 50% (despite an excellent specificity of 90%, values obtained from studies avoiding verification bias)[91]—is the reason why the number of false test results will become higher than the number of correct test results in populations with a PTP >65%.[92] Therefore, this Task Force recommends not employing the exercise stress test in such higher-risk populations for *diagnostic* purposes. However, the test may nevertheless provide valuable *prognostic* information in such populations.[93]

In this new version of the Guidelines, more weight is given to testing based systematically on consideration of pre-test probabilities.[107] This Task Force selected the most recent estimates of CAD prevalences as the basis of these Guidelines' clinical algorithm,[108] as discussed in the web addenda and shown in *Table 13*. The web addenda also contains more information about changes from the previous Stable Angina guidelines of the ESC and the reasons why ECG exercise testing was kept in the algorithm.

If the pain is clearly non-anginal other diagnostic testing may be indicated to identify gastrointestinal, pulmonary or musculoskeletal causes of chest pain (*Figure 1*). Nevertheless, these patients should also receive risk factor modification based on commonly applied risk charts such as SCORE (http://www.heartscore.org/Pages/welcome.aspx) or the Framingham risk score (http://hp2010.nhlbihin.net/atpiii/calculator.asp). Patients with suspected SCAD, in whom comorbidities make revascularization inadvisable, should be treated medically but pharmacologic stress imaging may be an option if it appears necessary to verify the diagnosis. Patients with a reduced left ventricular ejection fraction (LVEF) of <50% and typical angina are at high risk for cardiovascular events (see later in the text) and they should be offered ICA without previous testing (see *Figure 1*).

Patients in whom anginal pain may be possible but who have a very low probability of significant CAD <15% should have other cardiac causes of chest pain excluded and their CV risk factors adjusted, based on risk score assessment.[37] No specific non-invasive stress testing should be performed.[92] In patients with repeated, unprovoked attacks of chest pain only at rest, vasospastic angina should be considered and diagnosed, and treated appropriately (see below). Patients with an intermediate PTP of 15–85% should undergo further non-invasive testing. In patients with a clinical PTP >85%, the diagnosis of CAD should be made clinically and further testing will not improve accuracy. Further testing may, however, be indicated for stratification of risk of events, especially if no satisfactory control of symptoms is possible with initial medical therapy (*Figure 1*). In patients with severe angina at a low level of exercise and those with a clinical constellation indicating a high event risk,[109] proceeding directly to ICA is a reasonable option. Under such circumstances, the indication for revascularization should depend on the result of intraprocedural fractional flow reserve (FFR) testing when indicated.[110]

The very high negative predictive value of a coronary CTA showing no stenoses can reassure patients and referring physicians that instituting medical therapy and *not* proceeding to further testing or invasive therapies is a good strategy. This makes the test potentially useful, especially for patients at low intermediate PTPs (*Figure 2*). One should remember that there may be overdiagnosis of stenoses in patients with Agatston scores >400,[104,105] and it seems prudent to call a coronary CTA 'unclear' if severe focal or diffuse calcifications

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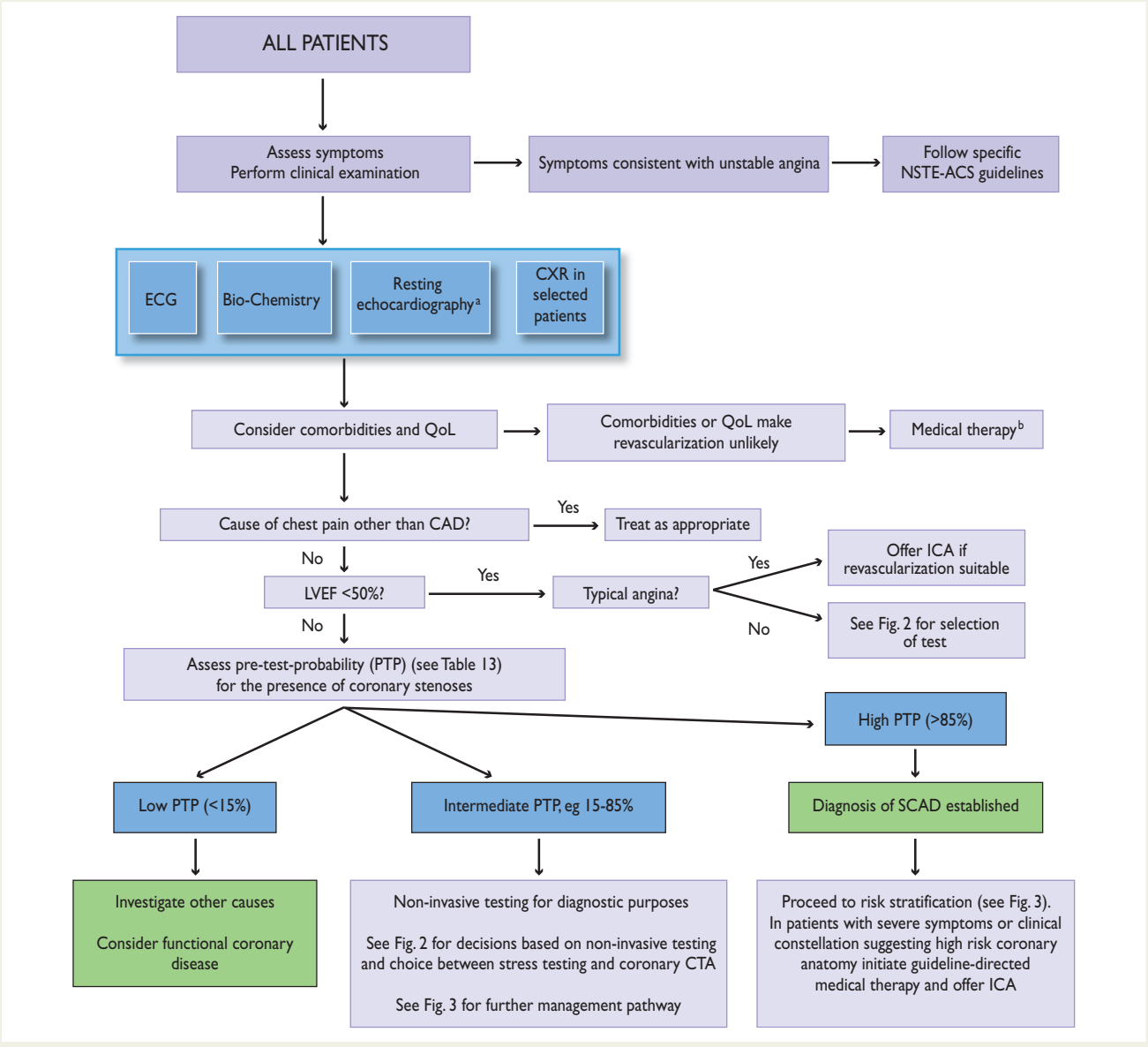

Figure 1 Initial diagnostic management of patients with suspected SCAD. CAD = coronary artery disease; CTA = computed tomography angiography; CXR = chest X-ray; ECG = electrocardiogram; ICA = invasive coronary angiography; LVEF = left ventricular ejection fraction; PTP = pre-test probability; SCAD = stable coronary artery disease.

[a] May be omitted in very young and healthy patients with a high suspicion of an extracardiac cause of chest pain and in multimorbid patients in whom the echo result has no consequence for further patient management

[b] If diagnosis of SCAD is doubtful, establishing a diagnosis using pharmacologic stress imaging prior to treatment may be reasonable.

prevent an unambiguous identification of the vessel lumen (see *Figure 2*). To obtain optimal results, published professional standards need to be meticulously adhered to.[111] With these caveats in mind, coronary CTA may be considered to be an alternative to ischaemia testing, especially in patients with chest pain symptoms at intermediate PTPs lower than 50%.[112]

6.2.4 Stress testing for diagnosing ischaemia

6.2.4.1 Electrocardiogram exercise testing

Because of its simplicity and widespread availability, treadmill or bicycle exercise testing, using 12-lead ECG monitoring, remains a useful option (*Table 14*) in patients with suspected SCAD and a PTP (15–65%) at which the test performs well (see above). A detailed description of the exercise procedure, its interpretation, the influence of drugs and other factors on test performance, and test performance in special groups can be found in the previous version of these Guidelines on the ESC website.[3]

The main diagnostic ECG abnormality during ECG exercise testing consists of a horizontal or down-sloping ST-segment depression ≥0.1mV, persisting for at least 0.06–0.08s after the J-point, in one or more ECG leads. It is worth noting that, in about 15% of patients, diagnostic ST-segment changes appear only during the recovery

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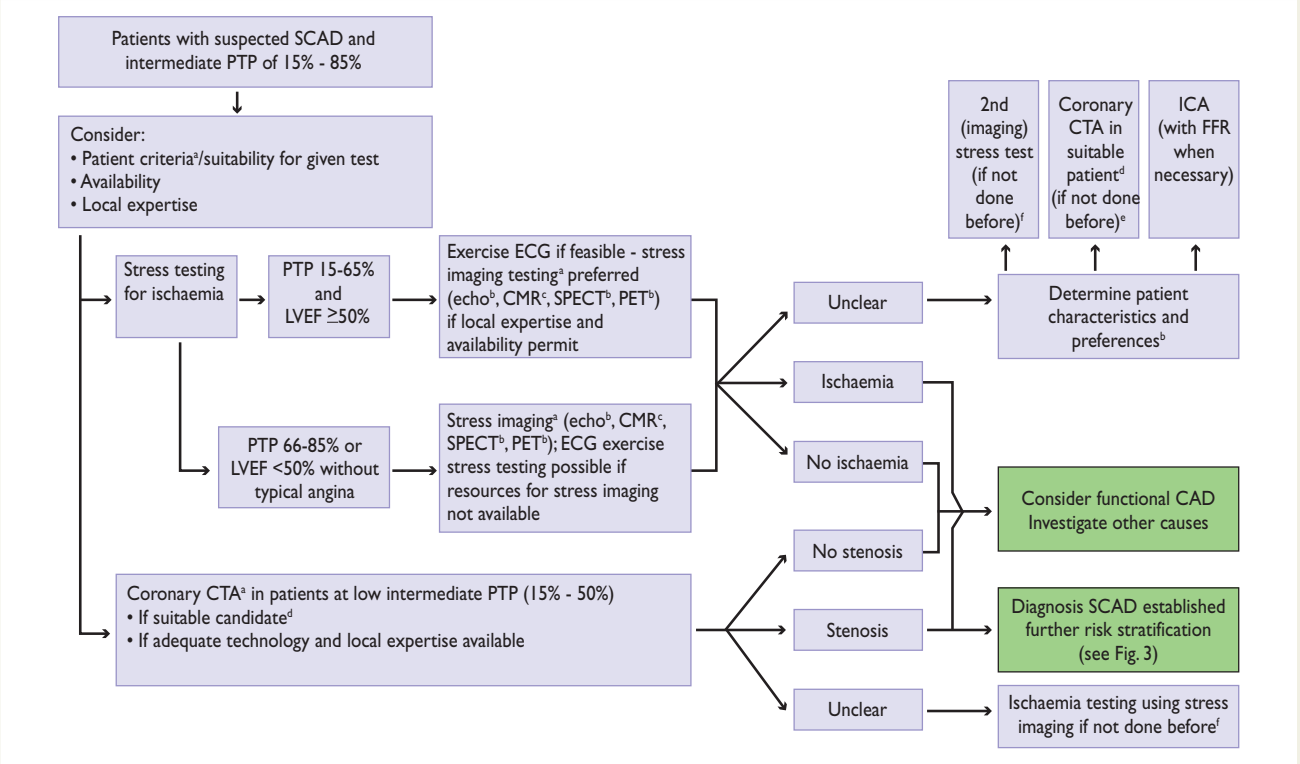

Figure 2 Non-invasive testing in patients with suspected SCAD and an intermediate pre-test probability. CAD = coronary artery disease; CTA = computed tomography angiography; CMR = cardiac magnetic resonance; ECG = electrocardiogram; ICA = invasive coronary angiography; LVEF = left ventricular ejection fraction; PET = positron emission tomography; PTP = pre-test probability; SCAD = stable coronary artery disease; SPECT = single photon emission computed tomography.
[a]Consider age of patient versus radiation exposure.
[b]In patients unable to exercise use echo or SPECT/PET with pharmacologic stress instead.
[c]CMR is only performed using pharmacologic stress.
[d]Patient characteristics should make a fully diagnostic coronary CTA scan highly probable (see section 6.2.5.1.2) consider result to be unclear in patients with severe diffuse or focal calcification.
[e]Proceed as in lower left coronary CTA box.
[f]Proceed as in stress testing for ischaemia box.

phase. The test also provides additional information, such as heart rate response, blood pressure response, symptoms, and workload achieved, which has both diagnostic and prognostic relevance.

To obtain maximal diagnostic information from exercise ECG testing, the latter should be symptom/sign-limited and performed without the influence of anti-ischaemic drugs. There are numerous reviews and meta-analyses of the performance of exercise ECG for the diagnosis of coronary disease, showing variable diagnostic yield according to the threshold selected for the diagnosis. Using exercise ST-depression ≥0.1 mV or 1 mm to define a positive test, the reported sensitivities and specificities for the detection of significant CAD (usually diameter stenoses ≥50%) range between 23–100% (mean 68%) and 17–100% (mean 77%), respectively[91]. Restricting the analysis to those studies designed to avoid work-up bias, sensitivities between 45–50% and specificities of 85–90% were reported (*Table 12*).[94,95] Adding cardiopulmonary exercise testing may improve sensitivity significantly,[113] but this combination of tests is not widely used.

It is important to remember that these numbers are valid only in patients without significant ECG abnormalities at baseline. Exercise ECG testing is not of diagnostic value in the presence of LBBB, paced rhythm and Wolff-Parkinson-White syndrome, in which cases the ECG changes are not interpretable. Additionally, false-positive results are more frequent in patients with abnormal resting ECG in the presence of LVH, electrolyte imbalance, intraventricular conduction abnormalities, atrial fibrillation,[78,114] and use of digitalis.

Exercise ECG testing is also less sensitive and specific in women.[95] However, a recent randomized trial, comparing an initial diagnostic strategy of exercise nuclear myocardial perfusion imaging (MPI) with standard exercise treadmill testing, in symptomatic women with suspected CAD and preserved functional capacity who were able to exercise, did not show an incremental benefit of the more expensive MPI strategy on clinical outcomes.[115]

In some patients, the exercise ECG may be inconclusive; for example, when 85% of maximum heart rate is not achieved in the absence of symptoms or signs of ischaemia, when exercise is

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Table 14 Performing an exercise electrocardiogram for initial diagnostic assessment of angina or evaluation of symptoms

Recommendations	Class [a]	Level [b]	Ref. [c]
Exercise ECG is recommended as the initial test for establishing a diagnosis of SCAD in patients with symptoms of angina and intermediate PTP of CAD (Table 13, 15–65%), free of anti-ischaemic drugs, unless they cannot exercise or display ECG changes which make the ECG non evaluable.	I	B	115, 116
Stress imaging is recommended as the initial test option if local expertise and availability permit.	I	B	117–120
Exercise ECG should be considered in patients on treatment to evaluate control of symptoms and ischaemia.	IIa	C	-
Exercise ECG in patients with ≥0,1 mV ST-depression on resting ECG or taking digitalis is not recommended for diagnostic purposes.	III	C	-

CAD = coronary artery disease; ECG = electrocardiogram; PTP = pre-test probability; SCAD = stable coronary artery disease.
[a] Class of recommendation.
[b] Level of evidence.
[c] Reference(s) supporting levels of evidence.

Table 15 Use of exercise or pharmacologic stress testing in combination with imaging

Recommendations	Class [a]	Level [b]	Ref. [c]
An imaging stress test is recommended as the initial test for diagnosing SCAD if the PTP is between 66–85% or if LVEF is <50% in patients without typical angina.	I	B	143, 144
An imaging stress test is recommended in patients with resting ECG abnormalities which prevent accurate interpretation of ECG changes during stress.	I	B	117, 145
Exercise stress testing is recommended rather than pharmacologic testing whenever possible.	I	C	-
An imaging stress test should be considered in symptomatic patients with prior revascularization (PCI or CABG).	IIa	B	146, 147
An imaging stress test should be considered to assess the functional severity of intermediate lesions on coronary arteriography.	IIa	B	148, 149

CABG = coronary artery bypass graft; ECG = electrocardiogram; PCI = percutaneous coronary intervention; PTP = pre-test probability.; SCAD = stable coronary artery disease.
[a] Class of recommendation.
[b] Level of evidence.
[c] Reference(s) supporting levels of evidence.

limited by orthopaedic or other non-cardiac problems, or when ECG changes are equivocal. In these patients, an alternative non-invasive imaging test with pharmacologic stress should be selected (*Figure 2*). In patients who are appropriately selected (*Figure 2*), coronary CTA is another option. Furthermore, a 'normal' ECG stress test in patients taking anti-ischaemic drugs does not rule out significant coronary disease.

Exercise stress testing can also be useful to evaluate the efficacy of medical treatment or after revascularization, or to assist prescription of exercise after control of symptoms. For these indications, exercise stress testing should be performed on treatment to evaluate control of ischaemia or effort performance. The effect of routine periodic exercise testing on patient outcomes has not been formally evaluated.

6.2.4.2 Stress imaging (see web addenda)

6.2.4.2.1 Stress echocardiography. Stress echocardiography is performed with exercise (treadmill or bicycle ergometer) or with pharmacological agents.[121] Exercise provides a more physiological environment than pharmacological tests and provides additional physiological data, such as exercise time and workload, as well as information about changes in heart rate, blood pressure and ECG. Thus, exercise is the test of choice when feasible (*Table 15*).

On the other hand, a pharmacological test is preferred when there is already a significant resting wall motion abnormality (dobutamine for viability assessment) and/or if the patient is unable to exercise adequately. Until recently, stress echocardiography relied on inducible wall thickening abnormalities as a marker of ischaemia (supply–demand mismatch). As most data on diagnostic accuracy were obtained using this standard, there is a caveat, in that the values for sensitivity and specificity assumed in these guidelines (*Table 12*) rely heavily on old studies, carried out at a time when contrast media were not broadly utilized in clinical practice.

The pharmacological agent of choice to produce supply-demand mismatch is dobutamine. Myocardial contrast echocardiography, which utilizes microbubbles, allows assessment of myocardial perfusion, which provides information beyond wall thickening assessment during both vasodilator and inotropic stress echocardiography.[122,123] This approach, however, is not widely employed clinically.

Contrast agents must be used in all patients undergoing all forms of stress echocardiography when two or more continuous segments (17 segment LV model) are not well visualised at rest.[122] The use of contrast during stress echocardiography not only enhances image quality, but improves reader confidence and enhances

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accuracy for the detection of CAD.[122,124] Tissue Doppler imaging and strain rate imaging may also improve the diagnostic performance of stress echocardiography by improving the capability of echocardiography to detect ischaemia beyond wall motion assessment.[125]

6.2.4.2.2 Myocardial perfusion scintigraphy (single photon emission computed tomography and positron emission tomography). Technetium-99m (^{99m}Tc) radiopharmaceuticals are the most commonly used tracers, employed with single photon emission computed tomography (SPECT) in association with a symptom-limited exercise test on either a bicycle ergometer or a treadmill (*Table 15*). Thallium 201 (^{201}Tl) is associated with a higher radiation and is less commonly used today. New SPECT cameras reduce radiation and/or acquisition time significantly.[126]

Regardless of the radiopharmaceutical or camera used, SPECT perfusion scintigraphy is performed to produce images of regional tracer uptake, which reflect relative regional myocardial blood flow. With this technique, myocardial hypoperfusion is characterized by reduced tracer uptake during stress, in comparison with the uptake at rest. Increased uptake of the myocardial perfusion agent in the lung field identifies stress-induced ventricular dysfunction in patients with severe and extensive CAD.[127] As with all stress imaging techniques, SPECT perfusion also provides a more sensitive prediction of the presence of CAD than the exercise ECG (*Table 12*). Transient ischaemic dilatation and reduced post-stress ejection fraction (EF) are important non-perfusion predictors of severe CAD.

Pharmacological stress testing with perfusion scintigraphy is indicated in patients who are unable to exercise adequately or may be used as an alternative to exercise stress. Adenosine may precipitate bronchospasm in asthmatic individuals by activating A_1, A_{2B} and A_3 receptors in addition to activation of the A_{2A} adenosine receptor, which produces hyperaemia. This limitation exists irrespective of the imaging technique used but, in such cases, dobutamine or regadenoson,[128] a selective A_{2A} receptor agonist, may be used as an alternative stressor.

MPI using positron emission tomography (PET) is superior to SPECT imaging for the detection of SCAD in terms of image quality, interpretative certainty and diagnostic accuracy.[129] However, SPECT scanners and imaging radiotracers are more widely available and less expensive than PET scanners and positron-emitting radiotracers (e.g. ^{82}Rb, ^{13}N-ammonia).[130] Hence, as compared with the other stress imaging techniques, PET is less commonly used for diagnosing SCAD. PET has the unique ability to quantify blood flow in mL/min/g, which allows detecting microvascular disease.[131]

6.2.4.2.3 Stress cardiac magnetic resonance. Cardiac magnetic resonance (CMR) stress testing, in conjunction with a dobutamine infusion, can be used to detect wall motion abnormalities induced by ischaemia.[132] The technique has been shown to have a comparable safety profile to dobutamine stress echocardiography (DSE).[133,134] Dobutamine stress CMR may be useful in patients with sub-optimal acoustic windows,[132,135] especially those in whom pharmacologic perfusion imaging using adenosine is contra-indicated (*Table 15*).

Perfusion CMR is more widely used than dobutamine stress CMR. Recent studies have confirmed the good diagnostic accuracy of CMR perfusion imaging at 1.5 Tesla (T), as compared with nuclear perfusion imaging.[102,136]

Details regarding stress and imaging protocols were recently reviewed.[137] Analysis is either visual, to identify low signal areas of reduced perfusion, or with computer assistance to determine the up-slope of myocardial signal increase during the first pass. Quantitative CMR perfusion measurements demonstrate good correlations with FFR measurements.[138] Although not widely available, the use of high-strength magnets at 3.0 T provides higher diagnostic accuracy, as compared with 1.5 T machines.[139,140]

6.2.4.2.4 Hybrid techniques. Hybrid SPECT/CT, PET/CT and PET/CMR imaging are now available at a few selected centres. Hybrid imaging is a novel technique combining functional and anatomical aspects, which holds much promise for future clinical application. The limited evidence available today indicates a higher diagnostic accuracy, as compared with single techniques.[141] Initial reports also point to the prognostic value of hybrid imaging.[142]

6.2.5 Non-invasive techniques to assess coronary anatomy

6.2.5.1 Computed tomography

Spatial resolution and temporal resolution, as well as volume coverage of modern multidetector row CT systems, are sufficient to allow robust imaging of the coronary arteries in many patients.[150] Radiation dose is a matter of concern and special measures need to be undertaken to avoid unnecessarily high radiation doses when CT is used for coronary artery imaging.[151] CT imaging of the coronary arteries can be performed without contrast injection (coronary calcium scoring) or after intravenous injection of iodinated contrast (coronary CTA).

6.2.5.1.1 Calcium scoring. Multidetector row CT permits the detection of coronary calcification in non-contrast enhanced data sets. By consensus, pixels above a threshold of 130 Hounsfield units (HU) are defined as representing coronary calcium. Calcified lesions are usually quantified using the 'Agatston score'.[152]

With the exception of patients with renal failure—who may have medial calcification—coronary calcium is exclusively a consequence of coronary atherosclerosis. The amount of calcium correlates roughly to the total amount of atherosclerosis present in the coronary arteries,[153] but correlation with the degree of luminal narrowing is poor. Even with severe calcification, luminal stenosis is not necessarily present and a 'zero' calcium score cannot be used to rule out coronary artery stenoses in symptomatic individuals (*Table 16*), especially when young and with acute symptoms.[154]

6.2.5.1.2 Coronary computed tomography angiography. After intravenous injection of contrast agent, CT can visualize the coronary artery lumen. Adequate technology (at least 64-slice CT) and patient selection, as well as careful patient preparation, are mandated. According to expert consensus, only patients with adequate breath holding capabilities, without severe obesity, with a favourable calcium score (e.g. Agatston score <400) and distribution, in sinus rhythm and with a heart rate of 65 beats per minute (b.p.m.) or less (preferably 60 b.p.m. or less), should be considered for coronary CTA.[111] If necessary, the use of short-acting β-blockers or other heart rate-lowering medication is recommended.

Since the specificity of coronary CTA decreases with increasing amounts of coronary calcium,[103,155,156] and the prevalence of coronary artery stenosis was found to be high in symptomatic individuals with an Agatston score >400,[157] it is reasonable not to proceed with coronary CTA if the calcium score exceeds 400.[158] However, on a patient level, per-segment calcification has a stronger influence on diagnostic accuracy than calcium,[159] and the influence of calcium

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Table 16 Use of coronary computed tomography angiography for the diagnosis of stable coronary artery disease

Recommendations	Class [a]	Level [b]
Coronary CTA should be considered as an alternative to stress imaging techniques for ruling out SCAD in patients within the lower range of intermediate PTP for SCAD in whom good image quality can be expected.	IIa	C
Coronary CTA should be considered in patients within the lower range of intermediate PTP for SCAD after a non conclusive exercise ECG or stress imaging test or who have contraindications to stress testing in order to avoid otherwise necessary invasive coronary angiography if fully diagnostic image quality of coronary CTA can be expected.	IIa	C
Coronary calcium detection by CT is not recommended to identify individuals with coronary artery stenosis.	III	C
Coronary CTA is not recommended in patients with prior coronary revascularization.	III	C
Coronary CTA is not recommended as a 'screening' test in asymptomatic individuals without clinical suspicion of coronary artery disease.	III	C

CTA = computed tomography angiography; ECG = electrocardiogram; PTP = pre-test probability; SCAD = stable coronary artery disease.
[a] Class of recommendation.
[b] Level of evidence.

on the accuracy of coronary CTA is less pronounced in low heart rates and for modern CT systems.[160,161] In the event that a calcium score is not obtained and calcifications are only seen on the completed coronary CTA scan, it may be prudent to refrain from stenosis quantification in areas of extensive calcifications and call the test 'unclear' (see *Figure 2*).

In patients with suspected CAD, multicentre studies using 64-slice CT have demonstrated sensitivities of 95–99% and specificities of 64–83% (*Table 12*) as well as negative predictive values of 97–99% for the identification of individuals with at least one coronary artery stenosis by ICA.[103,105] Meta-analyses of smaller trials confirm a high sensitivity (98–99%) and negative predictive value (99–100%), paired with lower specificity (82–89%) and positive predictive value (91–93%).[162] In a multicentre study, which included patients with previously known CAD, previous PCI and MI, diagnostic accuracy was lower (sensitivity 85% and specificity 90%).[104] Severe coronary calcium negatively impacts the accuracy of coronary CTA.[155,159] Also, coronary CTA remains less reliable in patients with coronary stents, due to artefacts caused by metal and the limited spatial resolution of CT. The assessment of coronary artery bypass grafts (CABG) is highly accurate while the evaluation of native coronary vessels in post-bypass patients is difficult and prone to false positive findings.[163,164]

Whilst prospective trials—which have randomized patients to the use or non-use of coronary CTA looking at hard clinical endpoints in stable chest pain patients—are currently not available (just as for the other imaging techniques), registry data confirm an excellent prognosis if coronary CTA demonstrates the absence of coronary artery stenoses.[165–167] Indications for coronary CTA are summarized in *Figure 2*.

The diagnostic performance of coronary CTA is best for individuals at the lower range of intermediate PTP for the disease.[162,168] Thus, coronary CTA may be useful in ruling out coronary stenoses in such patients if—based on patient characteristics as described above—good image quality and a reasonably low radiation exposure can be expected and if adequate technology and expertise are available. Under the same prerequisites, coronary CTA should also be considered in patients with a stress test result that contradicts clinical judgement (especially a positive stress test result when clinical judgment speaks against the presence of severe stenoses) if ICA would otherwise be chosen to rule out CAD (*Table 16*).

Given the false-positive rate of stress tests in some populations, such as patients with LVH, coronary CTA may be warranted as a first-line test in selected individuals. However, coronary CTA cannot rule out functional CAD in these patients. No data are available to support 'screening' coronary CTA in asymptomatic individuals and CTA should not be used for this purpose.[2] New developments in coronary CTA, such as CT-FFR need further validation.[169]

6.2.5.2 *Magnetic resonance coronary angiography*

Coronary MR angiography allows for non-invasive visualization of the coronary arteries without exposing the patient to ionizing radiation. A recent small, multicentre study showed sensitivity, specificity and positive and negative predictive values of 88, 72, 71 and 88%, respectively, in a patient-based analysis.[170] However, long imaging times, lower spatial resolution and operator dependency remain major limitations.[171] Advantages of the technique include evaluation of overall cardiac anatomy and function in the same examination. However, at present, MR coronary arteriography must still be regarded primarily as a research tool and is not recommended for routine clinical practice in the diagnostic evaluation of SCAD.

6.3 Invasive coronary angiography (see web addenda)

Non-invasive testing can establish the likelihood of the presence of obstructive coronary disease with an acceptable degree of certainty. Thus, ICA will only rarely be necessary in stable patients with suspected CAD, for the sole purpose of establishing or excluding the diagnosis. Such situations may arise in patients who cannot undergo stress imaging techniques,[172] in patients with reduced LVEF <50% and typical angina (see *Figure 1*) or in those patients with special professions, such as pilots, due to regulatory issues. ICA may, however, be indicated following non-invasive risk stratification for determination of options for revascularization. In patients who have a high PTP and severe symptoms, or a clinical constellation suggesting high event risk, early ICA without previous non-invasive

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risk stratification may be a good strategy to identify lesions potentially amenable to revascularization (see *Figure 1*). FFR testing is advised if appropriate.[172]

Methods used to perform ICA have improved substantially, resulting in the reduction of complication rates with rapid ambulation. This is especially true for ICA performed via the radial artery.[173] The composite rate of major complications associated with routine femoral diagnostic catheterization—mainly bleeding requiring blood transfusions—is still between 0.5–2%.[174] The composite rate of death, MI, or stroke is of the order of 0.1–0.2%.[175]

ICA should not be performed in patients with angina who refuse invasive procedures, prefer to avoid revascularization, who are not candidates for PCI or CABG, or in whom revascularization is not expected to improve functional status or quality of life.

Intracoronary techniques for the diagnostic assessment of coronary anatomy are briefly mentioned in the web addenda of this document.

6.4 Stratification for risk of events

The long-term prognosis of SCAD depends upon a number of factors, such as clinical and demographic variables, LV function, the result of stress testing and coronary anatomy as determined by angiographic techniques.

When discussing risk stratification in patients with SCAD, event risk refers primarily to the risk of CV death and MI, although in some studies even wider combinations of CV endpoints are employed. As all-cause death is more precisely defined than other weaker endpoints—including MI—these guidelines stratify event risk according to this hard endpoint. The process of risk stratification serves to identify patients at high event risk who will benefit from revascularization beyond the amelioration of symptoms.

The definition of the high event risk group of patients who will benefit from revascularization has changed from the previous version of these Guidelines. Previously, identification of high event risk was solely based on the Duke treadmill score and a >2% annual risk of cardiac death was felt to be the threshold beyond which coronary angiography was recommended to identify the need for revascularization.[3] This value was based on the CV mortality in the placebo arms of studies in 'high-risk' populations, such as in the diabetic Microalbuminuria, cardiovascular, and renal sub-study of the Heart Outcomes Prevention Evaluation study (MICRO-HOPE)[176] and the Impact Of Nicorandil in Angina (IONA)[177] studies, where the annualized CV mortality rates were >2%.

In these Guidelines, patients with an annual mortality >3% are defined as high event risk patients. As shown in the web addenda, both ischaemia- and anatomy-oriented indices come to similar conclusions in identifying which patients are at such high event risk with medical treatment alone that revascularization procedures become beneficial in terms of prognosis. Therefore, in these Guidelines, it is the goal of a event risk-driven diagnostic strategy to identify patients with an annual mortality >3% per year.

For the purpose of these Guidelines, low event risk patients are those with an annual mortality <1% per year, similar to the definition chosen in the previous edition.[3] The intermediate event risk group has an annual mortality of ≥1% but ≤3% per year (*Table 17*).

The risk assessment sequence can be described as:

(1) Risk stratification by clinical evaluation
(2) Risk stratification by ventricular function
(3) Risk stratification by response to stress testing
(4) Risk stratification by coronary anatomy.

Event risk stratification generally follows a pyramidal structure, with all patients having event risk stratification by clinical evaluation as the most basic requirement, proceeding to assessment of ventricular function by resting echocardiography and, in the majority, to non-invasive assessment of ischaemia/coronary anatomy (which is usually obtained in the process of making a diagnosis of SCAD, as discussed above). ICA for risk stratification will only be required in a selected subgroup of patients.

Table 17 Definitions of risk for various test modalities[a]

Exercise stress ECG[b]	High risk Intermediate risk Low risk	CV mortality >3%/year. CV mortality between 1 and 3%/year. CV mortality <1%/year.
Ischaemia imaging	High risk Intermediate risk Low risk	Area of ischaemia >10% (>10% for SPECT; limited quantitative data for CMR – probably ≥2/16 segments with new perfusion defects or ≥3 dobutamine-induced dysfunctional segments; ≥ 3 segments of LV by stress echo). Area of ischaemia between 1 to 10% or any ischaemia less than high risk by CMR or stress echo. No ischaemia.
Coronary CTA[c]	High risk Intermediate rick Low risk	Significant lesions of high risk category (three-vessel disease with proximal stenoses, LM, and proximal anterior descending CAD). Significant lesion(s) in large and proximal coronary artery(ies) but not high risk category. Normal coronary artery or plaques only.

CAD = coronary artery disease; CMR = cardiac magnetic resonance; CTA = computed tomography angiography; CV = cardiovascular; ECG = electrocardiogram; ICA = invasive coronary angiography; LM = left main; PTP = pre-test probability; SPECT = single photon emission computed tomography.

[a] For detailed explanation on rationale for risk stratifcation scheme see web addenda.

[b] From nomogram (see web addenda, Figure W1) or http://www.cardiology.org/tools/medcalc/duke/

[c] See Fig 2 consider possible overestimation of presence of signifcant multivessel disease by coronary CTA in patients with high intermediate PTP (=50%) and/or severe diffuse or focal coronary calcifcations and consider performing additional stress testing in patients without severe symptoms before ICA.

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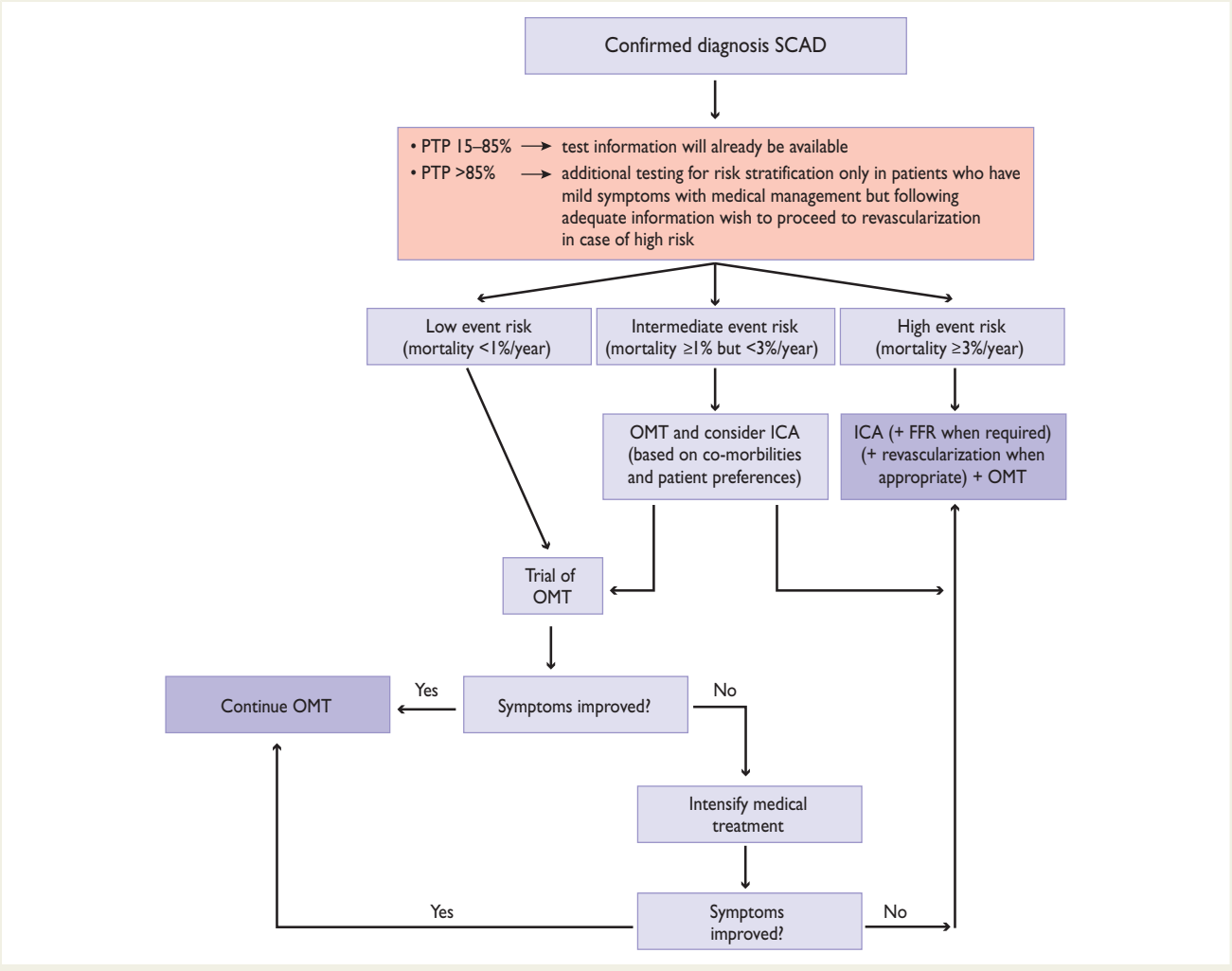

Figure 3 Management based on risk determination for prognosis in patients with chest pain and suspected SCAD (for choice of test see Fig. 2, for definitions of event risk see Table 17). ICA = invasive coronary angiography; OMT = optimal medical therapy; PTP = pre-test probability; SCAD = stable coronary artery disease.

6.4.1 Event risk stratification using clinical evaluation

Clinical history and physical examination can provide important prognostic information. The ECG can be conveniently incorporated into the event risk stratification at this level and the results of the laboratory tests discussed in the previous section may modify event risk estimation further. Diabetes, hypertension, current smoking and elevated TC (untreated or elevated despite treatment) have been shown to be predictive of adverse outcome in patients with SCAD or other populations with established coronary disease.[178] Increasing age is an important factor to consider, as are the presence of chronic kidney- or peripheral vascular disease,[65,179] prior MI,[180] symptoms and signs of heart failure,[180,181] and the pattern of occurrence (recent onset or progressive) and severity of angina, particularly if unresponsive to therapy.[45,182] However, this information is too complex to be placed into a clinically useful event risk score for patients with SCAD and the recommendation is therefore to use the data—especially the severity of angina—to modulate decisions made on the basis of PTP and non-invasive ischaemia/anatomy evaluation of the prognosis (*Figure 3*).

6.4.2 Event risk stratification using ventricular function

The strongest predictor of long-term survival is LV function. In patients with SCAD as LVEF declines, mortality increases. In the Coronary Artery Surgery Study (CASS) registry, the 12-year survival rates of patients with EF ≥50%, 35–49% and <35% were 73, 54 and 21%, respectively ($P < 0.0001$).[183] Hence, a patient with an LVEF <50% is already at high risk for CV death (annual mortality >3%), even without accounting for additional event risk factors, such as the extent of ischaemia. As a reduced LVEF <50% confers such an important increase in event risk, it may be important not to miss obstructed vessels causing ischaemia in such patients.[184,185] Hence, stress imaging should be employed instead of the exercise ECG (*Figure 2*).

Although the likelihood of preserved ventricular systolic function is high in patients with a normal ECG, a normal CXR and no history of prior MI,[186] asymptomatic ventricular dysfunction is not uncommon.[187] Therefore, as already discussed above, a resting echocardiogram is recommended in all patients with suspected SCAD (*Table 18*).

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Table 18 Risk stratification by resting echocardiography quantification of ventricular function in stable coronary artery disease

Recommendations	Class [a]	Level [b]
Resting echocardiography is recommended to quantify LV function in all patients with suspected SCAD.	I	C

LV = left ventricular; SCAD = stable coronary artery disease.
[a] Class of recommendation.
[b] Level of evidence.

6.4.3 Event risk stratification using stress testing

Symptomatic patients with suspected or known CAD should undergo stress testing to perform event risk stratification and use this as the basis for therapeutic decisions if they are candidates for coronary revascularization (*Table 19*). However, no randomized trials have been published demonstrating a better outcome for patients randomized to event risk stratification by stress testing, as compared with those without, and the evidence base therefore consists of observational studies only. As most patients will have undergone some form of diagnostic testing anyway, these results can also be used for event risk stratification. Patients with a high PTP >85%, who do not need diagnostic testing, should undergo stress imaging for event risk stratification purposes and the indication for revascularization should be discussed, considering the patient's risk of events, as appropriate (*Figure 3*). If patients with a PTP >85% have early ICA for symptomatic reasons, additional FFR may be required for event risk stratification as appropriate (*Figure 3*). For guidance about stress imaging for identifying myocardial viability we refer to the ESC Guidelines on heart failure.[89]

6.4.3.1 *Electrocardiogram stress testing*

The prognosis for patients with a normal exercise ECG and a low clinical risk for severe CAD[109] is excellent. In one study in which 37% of outpatients referred for non-invasive testing met the criteria for low event risk,[182] <1% had left main stem (LMS) artery disease or died within 3 years. Lower-cost options, such as treadmill testing, should therefore be used, whenever possible, for initial event risk stratification, and those at high event risk should be referred to coronary arteriography.

The prognostic exercise testing markers include exercise capacity, BP response and exercise-induced ischaemia (clinical and ECG). Maximum exercise capacity is a consistent prognostic marker. This measure is at least partly influenced by the extent of rest ventricular dysfunction and the amount of further LV dysfunction induced by exercise.[188] However, exercise capacity is also affected by age, general physical condition, comorbidities and psychological state. Exercise capacity may be measured by maximum exercise duration, maximum metabolic equivalent (MET) level achieved, maximum workload achieved, in Watts, maximum heart rate and double (rate–pressure) product. The specific variable used to measure exercise capacity is less important than the inclusion of this marker in the assessment.

The Duke treadmill score is well validated, combining exercise time, ST-deviation and angina during exercise to calculate the patient's event risk (for more information and a web based tool for calculating the Duke treadmill score see web addenda).[189] High event risk patients with an annual mortality >3% can also be identified using the Duke risk calculator (http://www.cardiology.org/tools/medcalc/duke/).

6.4.3.2 *Stress echocardiography*

Stress echocardiography is effective for stratifying patients according to their risk of subsequent CV events;[190,191] similarly, it has an excellent negative predictive value in patients with a negative test (no inducible wall motion abnormality),[192] having a hard event rate (death or

Table 19 Risk stratification using ischaemia testing

Recommendations	Class [a]	Level [b]	Ref. [c]
Risk stratification is recommended based on clinical assessment and the result of the stress test initially employed for making a diagnosis of SCAD.	I	B	109, 206–209
Stress imaging for risk stratification is recommended in patients with a non-conclusive exercise ECG[d]	I	B	210
Risk stratification using stress ECG (unless they cannot exercise or display ECG changes which make the ECG non evaluable) or preferably stress imaging if local expertise and availability permit is recommended in patients with stable coronary disease after a significant change in symptom level.	I	B	210–212
Stress imaging is recommended for risk stratification in patients with known SCAD and a deterioration in symptoms if the site and extent of ischaemia would influence clinical decision making.	I	B	146, 213–215
Pharmacological stress with echocardiography or SPECT should be considered in patients with LBBB.	IIa	B	216–218
Stress echocardiography or SPECT should be considered in patients with paced rhythm.	IIa	B	219, 220

ECG = electrocardiogram; LBBB = left bundle branch block; SCAD = stable coronary artery disease; SPECT = single photon emission computed tomography.
[a] Class of recommendation.
[b] Level of evidence.
[c] Reference(s) supporting levels of evidence.
[d] Stress imaging has usually been performed for establishing a diagnosis of SCAD in most of these patients.

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MI) of <0.5% per year. In patients with normal LV function at baseline, the risk of future events increases with the extent and severity of inducible wall motion abnormalities. Patients with inducible wall motion abnormalities in ≥3 of the 17 segments of the standard LV model should be regarded as being at high event risk (corresponding to an annual mortality >3%) and coronary angiography should be considered.[118,193,194]

6.4.3.3 Stress perfusion scintigraphy (single photon emission computed tomography and positron emission tomography)

Myocardial perfusion imaging using single photon emission computed tomography (SPECT) is a useful method of non-invasive risk stratification, readily identifying those patients at greatest risk for subsequent death and MI. Large studies have found that a normal stress perfusion study is associated with a subsequent rate of cardiac death and MI of <1% per year, which is nearly as low as that of the general population.[195] In contrast, large stress-induced perfusion defects, defects in multiple coronary artery territories, transient post-stress ischaemic LV dilatation and increased lung uptake of ^{201}Tl on post-stress images are all adverse prognostic indicators.[196] Patients with stress-induced reversible perfusion deficits >10% of the total LV myocardium (≥2 of the 17 segments) represent a high-risk subset.[194,197] Early coronary arteriography should be considered in these patients.

The extent and severity of ischaemia and scar on PET MPI in patients with known or suspected CAD also provides incremental event risk estimates of cardiac death and all-cause death, compared with traditional coronary risk factors.[198] Moreover, coronary vasodilator dysfunction quantified by PET is an independent correlate of cardiac mortality among both diabetics and non-diabetics.[199]

6.4.3.4 Stress cardiac magnetic resonance

There is an independent association between adverse cardiac outcomes in multivariate analysis for patients with an abnormal dobutamine stress CMR and >99% event-free survival in patients with no evidence of ischaemia over a 36-month follow-up.[200] Similar data exist for perfusion CMR using adenosine stress.[201] Assuming that the biological principles are the same for stress echocardiography and stress SPECT as they are for CMR, new wall motion abnormalities (≥3 segments in the 17 segment model) induced by stress or stress-induced reversible perfusion deficits >10% (≥2 segments) of the LV myocardium should be regarded as indicating a high event risk situation.[194] However, there are as yet no data providing proof that this distinction can be made by CMR in the same way as with SPECT. In fact CMR estimates of the extent of perfusion deficit as a percentage of the entire LV are imprecise, as compared with SPECT, as only three slices of the LV are currently examined by standard CMR machines.

6.4.4 Event risk stratification using coronary anatomy

6.4.4.1 Coronary computed tomography angiography

In one study, patients harbouring positively remodelled coronary segments with low attenuation plaque on coronary CTA had a higher risk of developing ACS than patients having only lesions without such characteristics.[202] The number of coronary arteries affected by non-obstructive plaque seems to have prognostic significance and plaque in all three main coronary vessels, when visualised by coronary CTA, is associated with increased mortality (risk ratio 1.77 when compared with individuals without any detectable plaque).[203] However, the actual clinical utility of coronary CTA wall imaging for event risk stratification, beyond the detection of significant coronary stenosis, remains currently uncertain.

Large prospective trials have established the prognostic value of coronary CTA, both for the presence and extent of coronary luminal stenoses and for the presence of non-obstructive coronary atherosclerotic plaque. A strong predictive value has been demonstrated, independent of traditional risk factors, concerning mortality and the occurrence of major CV events.[165–167,203,204] Importantly, event rates are very low in the absence of any plaque (0.22–0.28% per annualized death rate).[165] In patients with coronary plaque but without stenosis, the death rate is higher but remains below 0.5%, confirming the excellent prognosis conferred by the absence of coronary stenosis on CT scans. In contrast, patients with left main stenosis or proximal triple vessel disease have a univariate hazard ratio for all-cause mortality of 10.52, suggesting that annual mortality for coronary CTA-defined stenoses is similar to that found in ICA studies.[44,165] Mortality for single and dual-vessel disease is also in the range expected from ICA studies.[44,165]

Due to potential overestimation of obstructive coronary disease by coronary CTA,[105,168] it may be prudent to perform additional ischaemia testing before sending for ICA a high event risk patient who is not very symptomatic on the basis of anatomy visualised by coronary CTA alone (*Table 20*).

6.4.4.2 Invasive coronary angiography

Despite the recognized limitations of ICA to identify vulnerable plaques the extent, severity of luminal obstruction and location of coronary disease on coronary arteriography have been convincingly demonstrated to be important prognostic indicators in patients with angina (*Table 20*).[41,181,205]

Several prognostic indices have been used to relate severity of disease to the risk of subsequent cardiac events; the simplest and most widely used is the classification of disease into one-vessel, two-vessel, three-vessel, or left main (LM) stem CAD. In the CASS registry of medically treated patients, the 12-year survival rate of patients with normal coronary arteries was 91%, compared with 74% for those with one-vessel disease, 59% for those with two-vessel disease and 50% for those with three-vessel disease ($P < 0.001$).[183] Patients with severe stenosis of the LM coronary artery have a poor prognosis when treated medically. The presence of severe proximal left anterior descending (LAD) disease also significantly reduces the survival rate. The 5-year survival rate with three-vessel disease plus >95% proximal LAD stenosis was reported to be 59%, compared with a rate of 79% with three-vessel disease without LAD stenosis.[44] However, it should be appreciated that, in these 'older' studies, preventive therapy was not at the level of current recommendations regarding both lifestyle and drug therapy. Accordingly, absolute estimates of event risk derived from these studies probably overestimate the risk of future events. Annual mortality rates corresponding to certain angiographic scenarios can be found in the web addenda figure W3.

More information on event risk stratification using intravascular ultrasound or optical coherence tomography and the invasive measurement of the functional severity of coronary lesions can be found in the web addenda of this document.

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Table 20 Risk stratification by invasive or non-invasive coronary arteriography in patients with stable coronary artery disease

Recommendations	Class [a]	Level [b]
ICA (with FFR when necessary) is recommended for risk stratification in patients with severe stable angina (CCS 3) or with a clinical profile suggesting a high event risk, particularly if the symptoms are inadequately responding to medical treatment.	I	C
ICA (with FFR when necessary) is recommended for patients with mild or no symptoms with medical treatment in whom non-invasive risk stratification indicates a high event risk and revascularisation is considered for improvement of prognosis.	I	C
ICA (with FFR when necessary) should be considered for event risk stratification in patients with an inconclusive diagnosis on non-invasive testing, or conflicting results from different non-invasive modalities.	IIa	C
If coronary CTA is available for event risk stratification, possible overestimation of stenosis severity should be considered in segments with severe calcification, especially in patients at high intermediate PTP. Additional stress imaging may be necessary before referring a patient with few/no symptoms to ICA.	IIa	C

CCS = Canadian Cardiovascular Society; CTA = computed tomography angiography; FFR = fractional flow reserve; ICA = invasive coronary angiography; PTP = pre-test probability; SCAD = stable coronary artery disease.
[a] Class of recommendation.
[b] Level of evidence.

6.5 Diagnostic aspects in the asymptomatic individual without known coronary artery disease (see web addenda)

In an effort to lower the high burden of coronary deaths in asymptomatic adults, numerous measurements of risk factors and risk markers, as well as stress tests, are often performed as screening investigations. Details on the value of the various attempts to achieve this goal can be found in the new European Guidelines on prevention.[37] The key messages of these Guidelines with respect to testing in asymptomatic individuals without known CAD are summarized in the web addenda of this document. The recent American College of Cardiology Foundation/American Heart Association (ACCF/AHA) guidelines for assessment of CV risk in asymptomatic adults give recommendations that are almost identical to those of the new European Guidelines.[2,37] These recommendations were adapted for the purpose of these Guidelines (*Table 21*).

There are no data on how to manage asymptomatic patients who receive stress testing and have a pathologic test result, beyond the recommendations listed in these Guidelines. However, the principles of risk stratification, as described above for symptomatic patients, also apply to these individuals.[230] Thus, patients at low and intermediate risk should receive preventive treatment as outlined in the European Guidelines on cardiovascular disease prevention in clinical practice.[37] Only patients at high event risk, based on the result of a stress test performed without proper indication (for definitions

Table 21 Testing in asymptomatic patients at risk for stable coronary artery disease

Recommendations	Class [a]	Level [b]	Ref. [c]
In asymptomatic adults with hypertension or diabetes a resting ECG should be considered for CV risk assessment.	IIa	C	-
In asymptomatic adults at intermediate risk (see SCORE for definition of intermediate risk - www.heartscore.org) measurement of carotid intima-media thickness with screening for atherosclerotic plaques by carotid ultrasound, measurement of ankle-brachial index or measurement of coronary calcium using CT should be considered for CV risk assessment.	IIa	B	221-225
In asymptomatic adults with diabetes, 40 years of age and older, measurement of coronary calcium using CT may be considered for CV risk assessment.	IIb	B	226, 227
In asymptomatic adults without hypertension or diabetes a resting ECG may be considered.	IIb	C	-
In intermediate-risk asymptomatic adults (see SCORE for definition of intermediate risk - www.heartscore.org), (including sedentary adults considering starting a vigorous exercise programme), an exercise ECG may be considered for CV risk assessment particularly when attention is paid to non-ECG markers such as exercise capacity.	IIb	B	228, 229
In asymptomatic adults with diabetes or asymptomatic adults with a strong family history of CAD or when previous risk assessment testing suggests high risk of CAD, such as a coronary artery calcium score of 400 or greater stress imaging tests (MPI, stress echocardiography, perfusion CMR) may be considered for advanced CV risk assessment.	IIb	C	-
In low- or intermediate-risk (based on SCORE) asymptomatic adults stress imaging tests are not indicated for further CV risk assessment.	III	C	-

CAD = coronary artery disease; CMR = cardiac magnetic resonance; CT = computed tomography; CV = cardiovascular; MPI = myocardial perfusion imaging; SCORE = systematic coronary risk evaluation.
[a] Class of recommendation.
[b] Level of evidence.
[c] Reference(s) supporting levels of evidence.

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see *Table 17*), should be considered for ICA. It is important to remember that data demonstrating improved prognosis following appropriate management are still lacking.

Persons whose occupations impact on public safety (e.g. airline pilots, lorry or bus drivers) or who are professional or high-profile athletes not uncommonly undergo periodic exercise testing for assessment of exercise capacity and evaluation of possible heart disease,including CAD. Although there are insufficient data to justify this approach, these evaluations are done for medico-legal reasons in some cases. The threshold for adding imaging to standard exercise electrocardiography in such persons may properly be lower than in the average patient. Otherwise, the same considerations as discussed above for other asymptomatic persons apply for these individuals.

6.6 Management aspects in the patient with known coronary artery disease

The clinical course of patients with known SCAD may continue to be stable or be complicated by phases of instability, MI and heart failure. Revascularization(s) may become necessary in the course of the disease. Recommendations for the management of patients in these clinical situations are given in the respective guidelines.[1,89,172,231]

There are no randomized trials evaluating the impact on outcome of different strategies for the follow-up of patients with SCAD. In particular, there are currently no data suggesting that any form of follow-up stress testing improves outcome in asymptomatic patients.[232] However re-assessment of the prognosis, following an initial evaluation documenting a low event risk status (*Figure 3*), may be considered after the expiration of the period for which the test is valid and the patient's prognosis becomes less well established and potentially less favourable (*Table 22*). A period of 3 years has been suggested in previous guidelines,[91] although the mean validity period of a normal SPECT myocardial perfusion study is even longer in patients without known CAD (approximately 5.5 years)[233,234]. In contrast, the validity period in patients with known CAD is shorter and adversely modulated by clinical risk factors, such as age, female gender and the presence of diabetes.[233] Thus, clinical judgement is required for determining the need for repeated stress testing, which should be performed using the same stress and imaging techniques.[91]

By consensus, the following recommendations can be made:

Table 22 Re-assessment in patients with stable coronary artery disease

Recommendations	Class [a]	Level [b]
Follow-up visits are recommended every 4–6 months in the first year following institution of therapy for SCAD which may be extended to 1 year afterwards.Visits should be to the general practitioner who may refer to the cardiologist in case of uncertainty.These visits should include a careful history and biochemical testing as clinically appropriate.	I	C
An annual resting ECG is recommended and an additional ECG if a change in anginal status occurred or symptoms suggesting an arrhythmia appeared or medication has been changed which might alter electrical conduction.	I	C
An exercise ECG or stress imaging if appropriate is recommended in the presence of recurrent or new symptoms once instability has been ruled out.	I	C
Reassessment of the prognosis using stress testing may be considered in asymptomatic patients after the expiration of the period for which the previous test was felt to be valid ("warranty period").	IIb	C
Repetition of an exercise ECG may only be considered after at least 2 years following the last test (unless there is a change in clinical presentation).	IIb	C

ECG = electrocardiogram; SCAD = stable coronary artery disease.
[a] Class of recommendation.
[b] Level of evidence.

6.7 Special diagnostic considerations: angina with 'normal' coronary arteries (see web addenda)

Since the beginning of ICA it has been known that many patients, especially women, who undergo this procedure because of symptoms of chest pain or shortness of breath with exertion felt to be inappropriate by patient and/or physician, do not have significant obstructive CAD.[235,236] These patients often present with one of the following types of chest pain, each of which is associated with a different pathology:

(1) Angina with mostly typical features (although duration may be prolonged and relationship to exercise somewhat inconsistent), which is often associated with abnormal results of stress tests and often represents angina due to microvascular disease (microvascular angina).

(2) Pain, which has typical features of angina in terms of location and duration but occurs predominantly at rest (atypical angina), which may be due to coronary spasm (vasospastic angina).

(3) Pain that involves a small portion of the left hemithorax, lasts for several hours or even days, is not relieved by nitroglycerin and may be provoked by palpation (non-anginal pain, often musculoskeletal in origin).

For the clinicopathological correlation of symptoms with coronary anatomy, please consult the web addenda of this document. Patients with microvascular angina often have a typical constellation of classical atherosclerotic risk factors and represent a large group of patients who undergo a variety of non-invasive stress tests, and even repeated ICA, with the intention of revascularization. Microvascular disease may co-exist in patients with angiographically significant stenoses (≥70%). These patients probably belong to the group of approximately 20% of patients whose symptoms persist unchanged or have shown only minor amelioration after successful revascularization.[237,238]

In contrast, patients with vasospastic angina predominantly experience angina at rest, which may also lead to emergency coronary angiograms. The rationale for the angiogram is not to miss a potentially treatable occlusive or near-occlusive lesion in these patients, who

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may present as ST-elevation acute coronary syndrome (ACS), non-ST-elevation MI or unstable angina.

Of course, thoracic pain may also be due to gastro-oesophageal reflux disease, musculo-skeletal problem, aortic disease or pericardial disease. A detailed discussion of the management of this group with non-anginal pain is beyond the scope of these Guidelines.

6.7.1 Microvascular angina

6.7.1.1 Clinical picture (see web addenda)

Primary coronary microvascular disease should be suspected by exclusion in patients with sufficiently typical chest pain in whom, despite abnormalities of the ECG and/or stress test results indicative of myocardial ischaemia, coronary angiography fails to show fixed or dynamic obstructions in epicardial coronary arteries.[52] Microvascular disease may also occur in the setting of specific diseases,[239] such as hypertrophic cardiomyopathy or aortic stenosis, and this is defined as secondary coronary microvascular disease (which is not addressed in these Guidelines).

Arterial hypertension, either with or without associated ventricular hypertrophy, is frequently encountered in the population with chest pain and 'normal coronary arteries'. The consequence of coronary microvascular disease—which is still often called 'hypertensive heart disease' but is similarly encountered in patients with diabetes or a strong family history of vascular disease—is a reduced coronary flow reserve (CFR) and later interstitial and perivascular fibrosis, resulting in impaired diastolic dysfunction.[86] Even later in the course of the disease, epicardial plaques and stenoses may develop and eventually dominate the clinical picture.[86]

6.7.1.2 Pathogenesis and prognosis (see web addenda)

More details of the clinical presentation, the pathogenesis and prognosis of coronary microvascular disease are discussed in the web addenda of these Guidelines.

6.7.1.3 Diagnosis and management of coronary microvascular disease (see web addenda)

Diagnosis and management of patients with microvascular angina represent a complex challenge. The diagnosis may be made if a patient with exercise-induced angina has normal or non-obstructed coronary arteries by arteriography (coronary CTA or ICA), but objective signs of exercise-induced ischaemia (ST-depression on exercise ECG, ischaemic changes) by MPI. Usually no wall motion abnormalities can be induced during DSE (*Table 23*).[240] It is necessary to differentiate this pain from non-cardiac chest pain. Diffuse coronary artery spasm, pronounced in the distal epicardial coronary arteries and probably extending into the microvasculature, may be provoked by intracoronary injection of acetylcholine in a substantial proportion of patients with typical coronary microvascular disease.[241] The clinical presentation of patients with microvascular disease differs from those with purely vasospastic angina, since the former usually have exercise-related symptoms in addition to symptoms at rest.

Invasive and non-invasive methods of supporting the diagnosis of microvascular disease (and supporting also some of the recommendations below) are discussed in the web addenda of this document.

Table 23 Investigation in patients with suspected coronary microvascular disease

Recommendations	Class [a]	Level [b]
Exercise or dobutamine echocardiography should be considered in order to establish whether regional wall motion abnormalities occur in conjunction with angina and ST-changes.	IIa	C
Transthoracic doppler echocardiography of the LAD with measurement of diastolic coronary blood flow following intravenous adenosine and at rest may be considered for non invasive measurement of coronary flow reserve.	IIb	C
Intracoronary acetylcholine and adenosine with Doppler measurements may be considered during coronary arteriography, if the arteriogram is visually normal, to assess endothelium dependent and non-endothelium dependent coronary flow reserve, and detect microvascular/epicardial vasospasm.	IIb	C

FFR = fractional flow reserve; LAD = left anterior descending.
[a] Class of recommendation.
[b] Level of evidence.

6.7.2 Vasospastic angina

6.7.2.1 Clinical picture

Patients with vasospastic angina present with typically located anginal pain, which occurs at rest but does not—or occurs only occasionally—with exertion. Such pain typically occurs at night and in the early morning hours. If the chest pain is severe, this may lead to hospital admission. Nitrates usually relieve the pain within minutes. Angina at rest caused by spasm is often observed in patients with otherwise stable obstructive atherosclerosis, while spasm-induced effort angina can occasionally occur in patients with non-obstructive atherosclerosis.[242]

6.7.2.2 Pathogenesis and prognosis (see web addenda)

These aspects of vasospastic angina are discussed in the web addenda of this document.

6.7.2.3 Diagnosis of vasospastic angina

6.7.2.3.1 Electrocardiography

The ECG during vasospasm is classically described as showing ST-elevation. Angiographically, these patients usually show focal occlusive spasm (Prinzmetal's angina or variant angina)[243]. Most patients with coronary vasospasm, however, angiographically show distally pronounced diffuse subtotal vasospasm, which is usually associated with ST-depression. This form of spasm is usually associated with microvascular spasm and is found in patients presenting with microvascular and resting angina. In other patients, no ST-segment shift is seen during provoked vasospasm.[244,245] As attacks of vasospasm tend to resolve themselves quickly, 12-lead ECG documentation is often difficult. Repeated 24-h ECG monitoring may be able to capture ST-segment shifts associated with anginal symptoms in these patients.

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6.7.2.3.2 Coronary arteriography

Although the demonstration of ST-elevation at the time of angina and a normal coronary arteriogram make the diagnosis of variant angina highly likely, there is often uncertainty about the diagnosis in less well-documented or clinically less straightforward cases.

Spontaneous spasm during coronary arteriography is only occasionally observed in patients with symptoms suggestive of vasospastic angina. Hence, provocation tests are commonly used to demonstrate the presence and also the type of coronary vasospasm. Hyperventilation and the cold pressor test have only a rather limited sensitivity for the detection of coronary spasm. Thus, acetylcholine injections into the coronary artery are nowadays used in most centres for provocation of coronary spasm (*Table 24*). Acetylcholine is injected in incremental doses up to 200 μg, separated by intervals.[246] Intracoronary ergonovine provocation at incremental doses of up to 60 μg gives similar results.[246]

Coronary spasm may be focal or diffuse. Lumen reductions between 75–99% when compared with the diameter following nitroglycerin injection are defined as spasm in the literature,[247] but severe chest pain with ST-segment depression may also occur without epicardial spasm.[248] The latter phenomenon, which has been termed microvascular spasm, is often seen in patients with a history of microvascular angina. Lumen reductions <30% are commonly seen in non-spastic coronary segments and may represent the 'physiological' constrictor response to high-dose acetylcholine or to ergonovine provocation.

Acetylcholine or ergonovine provocation of coronary spasm is a safe test,[249,250] provided that the agent is infused selectively into the left coronary artery or the right coronary artery. Non-invasive intravenous ergonovine provocative testing has also been described, with echocardiographic or perfusion scintigraphy supplementing electrocardiographic monitoring, increasing the sensitivity and specificity of these tests.[251] However, as fatal complications may occur with *intravenous* injection of ergonovine, due to prolonged spasm involving multiple vessels,[252] the intracoronary route is preferred. Provocative testing with *intravenous* ergonovine is not recommended in patients without known coronary anatomy, nor in patients with high-grade obstructive lesions on coronary arteriography.

Table 24 Diagnostic tests in suspected vasospastic angina

Recommendations	Class [a]	Level [b]
An ECG is recommended during angina if possible.	I	C
Coronary arteriography is recommended in patients with characteristic episodic resting chest pain and ST-segment changes that resolve with nitrates and/or calcium antagonists to determine the extent of underlying coronary disease.	I	C
Ambulatory ST-segment monitoring should be considered to identify ST-deviation in the absence of an increased heart rate.	IIa	C
Intracoronary provocative testing should be considered to identify coronary spasm in patients with normal findings or non obstructive lesions on coronary arteriography and the clinical picture of coronary spasm to diagnose the site and mode of spasm.	IIa	C

ECG = electrocardiogram.
[a] Class of recommendation.
[b] Level of evidence.

7. Lifestyle and pharmacological management

7.1 Risk factors and ischaemia management

7.1.1 General management of stable coronary artery disease patients

The aim of the management of SCAD is to reduce symptoms and improve prognosis. The management of CAD patients encompasses lifestyle modification, control of CAD risk factors, evidence-based pharmacological therapy and patient education. Lifestyle recommendations are described in recent ESC guidelines.[37,62]

7.1.2 Lifestyle modifications and control of risk factors

7.1.2.1 Smoking

Smoking is a strong and independent risk factor for CVD and all smoking, including environmental smoking exposure, must be avoided in all patients with CVD.[253] The benefits of smoking cessation have been extensively reported,[254] and quitting smoking is potentially the most effective of all preventive measures, being associated with a reduction in mortality of 36% after MI.[255] Clinicians treating patients with CAD can take advantage of the unique situation and emphasize that the risk of future CAD events can be dramatically reduced by smoking cessation. Thus, smoking status should be assessed systematically (including passive smoking) and all smokers should be advised to quit and offered cessation assistance.[37] Quitting smoking is complex because smoking is both pharmacologically and psychologically highly addictive. Advice, encouragement and pharmacological aid consistently improve success rates. Nicotine replacement therapy is safe in patients with CAD and should routinely be offered.[256,257] Bupropion and varenicline have been found safe to use in patients with stable CAD in some studies,[258–260] although the safety of varenicline has recently been questioned in a meta-analysis,[261] being associated with a small but statistically significant increase in CVD.

*7.1.2.2 Diet (*Table 25*)*

A healthy diet reduces CVD risk. Cornerstones of a healthy diet are summarized below. Energy intake should be limited to the amount of energy needed to maintain (or obtain) a healthy weight—that is, a BMI <25 kg/m^2. In general, when following the rules for a healthy diet, no dietary supplements are needed. N-3 polyunsaturated fatty acid (PUFA) consumption, mainly from oily fish, is potentially associated with beneficial effects on cardiac risk factors, notably reduction in triglycerides, but not all randomized, controlled trials have shown reductions in CV events.[262–265] Thus current recommendations are to increase PUFA intake through fish consumption, rather than from supplements.[37] Recently, the largest study ever conducted with a so-called 'Mediterranean' diet, supplemented with extra-virgin olive

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Table 25 Recommended diet intakes

• Saturated fatty acids to account for <10% of total energy intake, through replacement by polyunsaturated fatty acids.
• Trans unsaturated fatty acids <1% of total energy intake.
• <5 g of salt per day.
• 30–45 g of fibre per day, from wholegrain products, fruits and vegetables.
• 200 g of fruit per day (2–3 servings).
• 200 g of vegetables per day (2–3 servings).
• Fish at least twice a week, one being oily fish.
• Consumption of alcoholic beverages should be limited to 2 glasses per day (20 g/day of alcohol) for men and 1 glass per day (10 g/day of alcohol) for non-pregnant women.

oil or nuts, reduced the incidence of major cardiovascular events in patients at high risk of CV events but without prior CV disease.[266]

7.1.2.3 *Physical activity*

Regular physical activity is associated with a decrease in CV morbidity and mortality in patients with established CAD and physical activity should be incorporated into daily activities. Aerobic exercise should be offered to patients with known CAD, usually as part of a structured cardiac rehabilitation program, with the need for an evaluation of both exercise capacity and exercise-associated risk. Patients with previous acute MI, CABG, percutaneous coronary intervention (PCI), stable angina pectoris or stable chronic heart failure should undergo moderate-to-vigorous intensity aerobic exercise training $\geq$3 times a week and for 30 min per session. Sedentary patients should be strongly encouraged to start light-intensity exercise programmes after adequate exercise-related risk stratification.[37] In patients with significant CAD who are not candidates for revascularization, exercise training may offer an alternative means of symptom alleviation and improved prognosis.

7.1.2.4 *Sexual activity*

Sexual activity is associated with an exercise workload of up to 6 METS (1 MET = approximately 3.5 mL oxygen consumption/kg/min) depending on the type of activity. Sympathetic activation is intrinsic to sexual arousal and heart rate and blood pressure (BP) response may be higher than expected from the level of exercise. Sexual activity may thus trigger ischaemia, and nitroglycerin prior to sexual intercourse may be helpful as in other physical activity.

Patients with mild angina, successful coronary revascularization and New York Heart Association (NYHA) functional Class I heart failure generally do not need specific evaluation before resuming sexual activity. Patients with more symptomatic heart disease, including moderate angina, may be guided by an exercise stress test as a means of assessing risk and reassuring the patient. Exercise training should be advocated to improve exercise capacity and reduce myocardial oxygen consumption during sexual activity.

Erectile dysfunction (ED) is associated with cardiac risk factors and is more prevalent in patients with CAD. The common denominator between erectile dysfunction and CAD is endothelial dysfunction and antihypertensive medication—in particular β-blockers and thiazides—increases the risk of erectile dysfunction.

Lifestyle and pharmacological intervention—including weight loss, exercise training, smoking cessation and statin treatment—ameliorate ED.[267] Pharmacological therapy with phosphodiesterase type 5 (PDE5) inhibitors (sildenafil, tadalafil and vardenafil) are effective, safe and well tolerated in men with stable CAD.[268] Low-risk patients, as defined above, can usually receive PDE5 inhibitors without cardiac work-up. However, use of nitric oxide donors, i.e. all of the preparations of nitroglycerin as well as isosorbide mononitrate and isosorbide dinitrate, are absolute contra-indications to the use of PDE5 inhibitors because of the risk of synergistic effects on vasodilation, causing hypotension and haemodynamic collapse. PDE5 inhibitors are not recommended in patients with low blood pressure, with severe heart failure (NYHA III–IV), refractory angina or recent CV events.[269,270] Patients must be informed about the potentially harmful interactions between PDE5 inhibitors and nitrates. If a patient on a PDE5 inhibitor develops chest pain, nitrates should not be administered in the first 24 hours (sildenafil, vardenafil) to 48 hours (tadalafil).

7.1.2.5 *Weight management*

Both overweight and obesity are associated with an increased risk of death in CAD. Weight reduction in overweight and obese people is recommended in order to achieve favourable effects on BP, dyslipidaemia and glucose metabolism.[37] The presence of sleep apnoea symptoms should be carefully assessed, especially in obese patients. Sleep apnoea has been associated with an increase in CV mortality and morbidity.[271]

7.1.2.6 *Lipid management*

Dyslipidemia should be managed according to lipid guidelines with pharmacological and lifestyle intervention.[62] Patients with established CAD are regarded as being at very high risk for cardiovascular events and statin treatment should be considered, irrespective of low density lipoprotein (LDL) cholesterol (LDL-C) levels. The goals of treatment are LDL-C below 1.8 mmol/L (<70 mg/dL) or >50% LDL-C reduction when target level cannot be reached. In the majority of patients this is achievable through statin monotherapy. Other interventions (e.g. fibrates, resins, nicotinic acid, ezetimibe) may lower LDL cholesterol but no benefit on clinical outcomes has been reported for these alternatives. Although elevated levels of triglycerides and low HDL cholesterol (HDL-C) are associated with increased CVD risk, clinical trial evidence is insufficient to specify treatment targets, which should be regarded as not indicated.

For patients undergoing PCI for SCAD, high dose atorvastatin has been shown to reduce the frequency of peri-procedural MI in both statin-naïve patients and patients receiving chronic statin therapy.[62,272] Thus reloading with high intensity statin before PCI may be considered.[62]

7.1.2.7 *Arterial Hypertension*

Particular attention should be given to control of elevated BP but thresholds for the definition of hypertension by 24-h ambulatory and home BP monitoring differ from those measured at office or clinic (see *Table 26*). Elevated BP is a major risk factor for CAD as well as heart failure, cerebrovascular disease and renal failure. There is sufficient evidence to recommend that systolic BP (SBP)

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Table 26 Blood pressure thresholds for definition of hypertension with different types of blood pressure measurement (adapted from Umpierrez *et al.* 2012 [273]).

	SBP (mmHg)	D BP (mmHg)
Office BP	140	90
Home BP	135	85
Ambulatory BP		
24-h	130	80
Daytime (or awake)	135	85
Nighttime (or asleep)	120	70

BP= blood pressure; DPB= diastolic blood pressure; SBP= systolic blood pressure.

be lowered to <140 mmHg and diastolic BP (DBP) to <90 mmHg in SCAD patients with hypertension. Based on current data, it may be prudent to recommend lowering SBP/DBP to values within the range 130–139/80–85 mmHg. BP targets in diabetes are recommended to be <140/85 mmHg (see below).[37,273]

7.1.2.8 Diabetes and other disorders (see also chapter 9 and web addenda)

Diabetes mellitus is a strong risk factor for CV complications, increases the risk of progression of coronary disease and should be managed carefully, with good control of glycated haemoglobin (HbA1c) to <7.0% (53 mmol/mol) generally and <6.5%–6.9% (48–52 mmol/mol) on an individual basis. Glucose control should be based on individual considerations, depending on the patient's characteristics including age, presence of complications and diabetes duration.

As for other disorders, attention to management of risk factors is recommended, including weight management, exercise recommendations and statin treatment with an LDL-C target of 1.8 mmol/L (<70 mg/dL) in diabetic patients with angiographically proven CAD.[62] The traditional treatment goal for BP in diabetes, i.e. below 130 mmHg, is not supported by outcome evidence in trials and has been difficult to achieve in the majority of patients. Thus, the BP target in patients with CAD and diabetes is to be <140/85 mmHg. An angiotensin converting enzyme (ACE) inhibitor or renin-angiotensin receptor blocker should always be included because of the renal protective effects.[37,274,275]

Patients with chronic kidney disease (CKD) are at high risk and particular care should be taken to address risk factors and achieve BP and lipid targets. Statins are generally well tolerated in CKD stages 1–2 (GFR >60–89 mL/min/1.73 m^2) whereas, in CKD stages 3–5, statins with minimal renal excretion should be chosen (atorvastatin, fluvastatin, pitavastatin, rosuvastatin).[62]

7.1.2.9 Psychosocial factors

Depression, anxiety and distress are common in patients with CAD. Patients should be assessed for psychosocial distress and appropriate care offered. Refer for psychotherapy, medication or collaborative care in the case of clinically significant symptoms of depression, anxiety and hostility. This approach can reduce symptoms and enhance quality of life, although evidence for a definite beneficial effect on cardiac endpoints is inconclusive.[37]

7.1.2.10 Cardiac rehabilitation

A comprehensive risk-reduction regimen, integrated into comprehensive cardiac rehabilitation, is recommended to patients with CAD.[37,276] Cardiac rehabilitation is commonly offered after MI or recent coronary intervention, but should be considered in all patients with CAD, including those with chronic angina. Exercise-based cardiac rehabilitation is effective in reducing total- and CV mortality and hospital admissions,[276] whereas effects on total MI or revascularization (CABG or PCI) are less clear, especially in the long term.[277,278]

Evidence also points towards beneficial effects on health-related quality of life (QoL). In selected sub-groups, centre-based cardiac rehabilitation may be substituted for home-based rehabilitation, which is non-inferior. Patient participation in cardiac rehabilitation remains far too low, particularly in women, the elderly and the socio-economically deprived, and could benefit from systematic referral.

7.1.2.11 Influenza vaccination

An annual influenza vaccination is recommended for patients with CAD, especially the elderly.[279,280]

7.1.2.12 Hormone replacement therapy

For decades, evidence from epidemiological and laboratory studies led us to believe that circulating oestrogens had a beneficial effect on the risk of CVD and that this could be transferred to the benefits of hormone replacement therapy (HRT). However, results from large randomized trials have not supported this; on the contrary, HRT increases the risk of CVD in women above the age of 60.[281]

The mechanisms are unclear and, if instituted at an earlier age (i.e. at the time of menopause) in women with intact vascular endothelium and few CV risk factors, the effect of HRT is still debated.[282] However, HRT is at present not recommended for primary or secondary prevention of CVD.

7.1.3 Pharmacological management of stable coronary artery disease patients

7.1.3.1 Aims of treatment

The two aims of the pharmacological management of stable CAD patients are to obtain relief of symptoms and to prevent CV events.

Relief of anginal symptoms: rapidly acting formulations of nitroglycerin are able to provide immediate relief of the angina symptoms once the episode has started or when the symptom is likely to occur (immediate treatment or prevention of angina). Anti-ischaemic drugs—but also lifestyle changes, regular exercise training, patient education and revascularization—all have a role to play in minimizing or eradicating symptoms over the long term (long-term prevention).

To prevent the occurrence of CV events: efforts to prevent MI and death in coronary disease focus primarily on reducing the incidence of acute thrombotic events and the development of ventricular dysfunction. These aims are achieved by pharmacological or lifestyle interventions which: (i) reduce plaque progression; (ii) stabilize plaque, by reducing inflammation and (iii) prevent thrombosis, should plaque rupture or erosion occur. In patients with severe lesions in coronary arteries supplying a large area of jeopardized myocardium, a combined pharmacological and revascularization strategy

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offers additional opportunities for improving prognosis by improving heart perfusion or providing alternative perfusion routes.

7.1.3.2 Drugs

Evidence supporting the optimal medical therapy (OMT) for SCAD has been reviewed and detailed elsewhere,[283] and is summarized below. *Table 27* indicates the main side-effects, contra-indications and major drug–drug interactions for each drug class. *Table 28* presents the recommendations for drug therapy.

7.1.3.3 Anti-ischaemic drugs

7.1.3.3.1 Nitrates. Nitrates offer coronary arteriolar and venous vasodilatation, which are the basis of symptomatic relief of effort angina, acting by their active component nitric oxide (NO) and by the reduction of preload.

Short-acting nitrates for acute effort angina. Sublingual nitroglycerin is the standard initial therapy for effort angina. When angina starts, the patient should rest sitting (standing promotes syncope, lying down enhances venous return and heart work) and take sublingual nitroglycerin (0.3–0.6 mg) every 5 min until the pain goes or a maximum of 1.2 mg has been taken within 15 min. Nitroglycerin spray acts more rapidly. Nitroglycerin can be used prophylactically when angina can be expected, such as activity after a meal, emotional stress, sexual activity and in colder weather.[283]

Isosorbide dinitrate (5 mg sublingually) helps to abort anginal attacks for about 1 h. Because the dinitrate requires hepatic conversion to the mononitrate, the onset of anti-anginal action (within 3–4 min) is slower than with nitroglycerin. After oral ingestion, haemodynamic and anti-anginal effects persist for several hours, conferring longer protection against angina than sublingual nitroglycerin.[284]

Long-acting nitrates for angina prophylaxis. Long-acting nitrates are not continuously effective if regularly taken over a prolonged period without a nitrate-free or nitrate-low interval of about 8–10 hours (tolerance). Worsening of endothelial dysfunction is a potential complication of long-acting nitrates, hence the common practice of the routine use of long-acting nitrates as first line therapy for patients with effort angina needs re-evaluation.[283]

Isosorbide dinitrate (oral preparation) is frequently given for the prophylaxis of angina. In a crucial placebo-controlled study, exercise duration improved significantly for 6–8 h after single oral doses of 15–120mg isosorbide dinitrate, but for only 2 h when the same doses were given repetitively four times daily, despite much higher plasma isosorbide dinitrate concentrations during sustained than during acute therapy.[284] With the extended-release formulation of isosorbide dinitrate, eccentric twice-daily dosing, with 40 mg in the morning, repeated 7 hours later, was not superior to placebo in a large multicentre study.[284] Thus prolonged therapy with isosorbide dinitrate is not evidence-based.

Mononitrates have similar dosage and effects to those of isosorbide dinitrate. Nitrate tolerance—likewise a potential problem—can be prevented by changes in dosing and timing of administration, as well as by using slow-release preparations.[285,286] Thus only twice-daily rapid-release preparations or very high doses of slow-release mononitrate—also twice daily—give sustained anti-anginal benefit.

Transdermal nitroglycerin patches fail to cover 24 h during prolonged use. A discontinuous administration at 12 h intervals allows on and off effects to start within minutes and last 3–5 h. There are no efficacy data for second or third doses during chronic administration.

Nitrate side-effects. Hypotension is the most serious, and headache the most common side-effect of nitrates. Headaches (aspirin may relieve these) may facilitate loss of compliance, yet often pass over.

Failure of therapy. Apart from non-compliance, treatment failure includes nitric oxide resistance and nitrate tolerance.

Nitrate drug interactions. Many are pharmacodynamic, including potentiation of vasodilator effects with calcium channel blockers (CCBs). Note that serious hypotension can occur with the selective PDE5 inhibitors (sildenafil and others) for erectile dysfunction or for the treatment of pulmonary hypertension. Sildenafil decreases the BP by about 8.4/5.5 mmHg and by much more with nitrates. In the case of inadvertent PDE5–nitrate combinations, emergency α-adrenergic agonists or even norepinephrine may be needed. Nitrates should not be given with α-adrenergic blockers. In men with prostatic problems, taking tamsulosin ($\alpha 1_A$ and $\alpha 1_D$ blocker), nitrates can be given.

7.1.3.3.2 β-blockers. β-blockers act directly on the heart to reduce heart rate, contractility, atrioventricular (AV) conduction and ectopic activity. Additionally, they may increase perfusion of ischaemic areas by prolonging the diastole and increasing vascular resistance in non-ischaemic areas. In post-MI patients, β-blockers achieved a 30% risk reduction for CV death and MI.[287] Thus β-blockers may also be protective in patients with SCAD, but without supportive evidence from placebo-controlled clinical trials. However, a recent retrospective analysis of the REACH registry suggested that, in patients with either CAD risk factors only, known prior MI, or known CAD without MI, the use of β-blockers was not associated with a lower risk of cardiovascular events.[288] Although propensity score matching was used for the analysis, the demonstration lacks the strength of a randomized evaluation. Among other limitations, most of the β-blocker trials in post-MI patients were performed before the implementation of other secondary prevention therapies, such as statins and ACE inhibitors, leaving uncertainty regarding their efficacy when added to modern therapeutic strategies. β-Blockers are clearly effective in controlling exercise-induced angina, improving exercise capacity and limiting both symptomatic as well as asymptomatic ischaemic episodes. Regarding angina control, β-blockers and CCBs are similar.[289–292] β-Blockers can be combined with dihydropyridines (DHPs) to control angina.[293–297] Combination therapy of β-blockers with verapamil and diltiazem should be avoided because of the risk of bradycardia or AV block (*Table 27*).

The most widely used β-blockers in Europe are those with predominant β_1-blockade, such as metoprolol,[298] bisoprolol, atenolol or nevibolol. Carvedilol, a non-selective β-α1blocker, is also often used. All of these reduce cardiac events in patients with heart failure.[299–302] In summary, there is evidence for prognostic benefits from the use of β-blockers in post-MI patients, or in heart failure. Extrapolation from these data suggests that β-blockers may be the first-line anti-anginal therapy in stable CAD patients without contra-indications. Nevibolol and bisoprolol are partly secreted by the kidney, whereas carvedilol and metoprolol are metabolized by the liver, hence being safer in patients with renal compromise.

7.1.3.3.3 Calcium channel blockers. Calcium antagonists (i.e. CCBs) act chiefly by vasodilation and reduction of the peripheral vascular resistance. CCBs are a heterogeneous group of drugs that can chemically be classified into the DHPs and the non-DHPs, their common pharmacological property being selective inhibition of L-channel opening in vascular smooth muscle and in the myocardium.

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Table 27 Major side-effects, contra-indications, drug–drug interactions (DDI) and precautions of anti-ischaemic drugs. (List is not exhaustive: refer to summary of products characteristics for details.)

Drug class	Side effects [a]	Contraindications	DDI	Precautions
Short-acting and long-acting nitrates[329]	• Headache • Flushing • Hypotension • Syncope and postural hypotension • Reflex tachycardia • Methaemoglobinaemia	• Hypertrophic obstructive cardiomyopathy	• PDE5 inhibitors (sildenafil or similar agents) • α-adrenergic blockers • CCBs	-
ß-blockers[291, 293, 302,b]	• Fatigue, depression[304] • Bradycardia • Heart block • Bronchospasm • Peripheral vasoconstriction • Postural hypotension • Impotence • Hypoglycaemia/mask hypoglycaemia signs	• Low heart rate or heart conduction disorder • Cardiogenic shock • Asthma • COPD caution; may use cardioselective ß-blockers if fully treated by inhaled steroids and long-acting ß-agonists[330] • Severe peripheral vascular disease • Decompensated heart failure • Vasospastic angina	• Heart-rate lowering CCB • Sinus-node or AV conduction depressors	• Diabetics • COPD[330]
CCBs: heart-rate lowering[303, 304, 331]	• Bradycardia • Heart conduction defect • Low ejection fraction • Constipation • Gingival hyperplasia	• Low heart rate or heart rhythm disorder • Sick sinus syndrome • Congestive heart failure • Low BP	• Cardiodepressant (ß-blockers, flecainide) • CYP3A4 substrates	-
CCBs: Dihydropyridines[27, 305, 331]	• Headache • Ankle swelling • Fatigue • Flushing • Reflex tachycardia	• Cardiogenic shock • Severe aortic stenosis • Obstructive cardiomyopathy	• CYP3A4 substrates	-
Ivabradine[307]	• Visual disturbances • Headache, dizziness • Bradycardia • Atrial fibrillation • Heart block	• Low heart rate or heart rhythm disorder • Allergy • Severe hepatic disease	• QTc prolonging drugs • Macrolide antibiotics • Anti-HIV • Anti-fungal	• Age >75 years • Severe renal failure
Nicorandil[177]	• Headache • Flushing • Dizziness, weakness • Nausea • Hypotension • Oral, anal, gastrointestinal ulceration	• Cardiogenic shock • Heart failure • Low blood pressure	• PDE5 inhibitors (Sildenafil or similar agents)	-
Trimetazidine[315, 316]	• Gastric discomfort • Nausea • Headache • Movement disorders	• Allergy • Parkinson disease • Tremors and movement disorders • Severe renal impairment	• None reported	• Moderate renal impairment • Elderly
Ranolazine[317,218, 318]	• Dizziness • Constipation • Nausea • QT prolongation	• Liver cirrhosis	• CYP450 substrates (digoxin, simvastatin, cyclosporine) • QTc prolonging drugs	-
Allopurinol[323]	• Rash • Gastric discomfort	• Hypersensitivity	* Mercaptopurine / Azathioprine	• Severe renal failure

AV = atrioventricular; CCBs = calcium channel blockers; CHF = congestive heart failure; COPD = chronic obstructive pulmonary disease; DDI= Drug-Drug Interactions; HIV = Human Immunodeficiency Virus; PDE5 = phosphodiesterase type 5.

[a] Very frequent or frequent; may vary according to specific drugs within the therapeutic class.

[b] Atenolol, metoprolol CR, bisoprolol, carvedilol.

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Table 28 Pharmacological treatments in stable coronary artery disease patients

Indication	Class [a]	Level [b]	Ref. [c]
General considerations			
Optimal medical treatment indicates at least one drug for angina/ischaemia relief plus drugs for event prevention.	I	C	-
It is recommended to educate patients about the disease, risk factors and treatment strategy.	I	C	-
It is indicated to review the patient's response soon after starting therapy.	I	C	-
Angina/ischaemia[d] relief			
Short-acting nitrates are recommended.	I	B	3, 329
First-line treatment is indicated with ß-blockers and/or calcium channel blockers to control heart rate and symptoms.	I	A	3, 331
For second-line treatment it is recommended to add long-acting nitrates or ivabradine or nicorandil or ranolazine, according to heart rate, blood pressure and tolerance.	IIa	B	177, 307, 3, 199, 284, 286, 308, 319-321, 328, 364
For second-line treatment, trimetazidine may be considered.	IIb	B	313, 315
According to comorbidities/tolerance it is indicated to use second-line therapies as first-line treatment in selected patients.	I	C	-
In asymptomatic patients with large areas of ischaemia (>10%) ß-blockers should be considered.	IIa	C	-
In patients with vasospastic angina, calcium channel blockers and nitrates should be considered and beta-blockers avoided.	IIa	B	3, 365
Event prevention			
Low-dose aspirin daily is recommended in all SCAD patients.	I	A	333, 334, 366
Clopidogrel is indicated as an alternative in case of aspirin intolerance.	I	B	335
Statins are recommended in all SCAD patients.	I	A	62
It is recommended to use ACE inhibitors (or ARBs) if presence of other conditions (e.g. heart failure, hypertension or diabetes).	I	A	348, 349, 351, 352

ACE = angiotensin converting enzyme; SCAD = stable coronary artery disease.
[a] Class of recommendation.
[b] Level of evidence.
[c] Reference(s) supporting levels of evidence.
[d] No demonstration of benefit on prognosis

Distinctions between the DHPs and non-DHPs are reflected in different binding sites on the calcium channel pores and in the greater vascular selectivity of the DHP agents (amlodipine, nifedipine, felodipine).

The non-DHPs, by virtue of nodal inhibition, tend to reduce the heart rate (heart rate-lowering agents, verapamil and diltiazem) and explain the anti-anginal properties.

- **Non-dihydropyridine (heart rate-lowering calcium channel blocker s)**

Verapamil. Among CCBs, verapamil has a large range of approved indications, including all varieties of angina (effort, vasospastic, unstable), supraventricular tachycardias and hypertension.

Indirect evidence suggests good safety but with risks of heart block, bradycardia and heart failure. Compared with metoprolol, the anti-anti-anginal activity was similar.[298] Compared with atenonol in hypertension with CAD, verapamil gave less new diabetes, fewer anginal attacks,[303] and less psychological depression.[304] β-Blockade combined with verapamil is not advised (due to risk of heart block): instead, use DHP-β-blockade.

Diltiazem. Diltiazem, with its low side-effect profile, has advantages, compared with verapamil, in the treatment of effort angina.[295] Like verapamil, it acts by peripheral vasodilation, relief of exercise-induced coronary constriction, a modest negative inotropic effect and sinus node inhibition. There are no outcome studies comparing diltiazem and verapamil. As with verapamil, combination with β-blockade, as well as the use in patients with CAD and left ventricular dysfunction, is not advised.

- **Dihydropyridines**

Long-acting nifedipine. This agent is a powerful arterial vasodilator with few serious side-effects. Long-acting nifedipine is especially well-tested in hypertensive anginal patients when added to β-blockade.[27] In ACTION, a large placebo-controlled trial long-acting nifedipine in SCAD proved to be safe and reduced the need for coronary angiography and cardiovascular interventions.[27] Contra-indications to nifedipine are few (severe aortic stenosis, obstructive cardiomyopathy, or heart failure) and careful combination with β-blockade is usually feasible and desirable. Vasodilatory side-effects include headache and ankle oedema.

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Amlodipine. The very long half-life of amlodipine and its good tolerability make it an effective once-a-day anti-anginal and antihypertensive agent, setting it apart from agents that are taken either twice or three times daily. Side-effects are few; mainly ankle oedema. In patients with CAD and normal blood pressure, amlodipine reduced CV events in a 24-month trial.[305] Exercise-induced ischaemia is more effectively reduced by amlodipine than by the β-blocker atenolol and the combination is even better.[306]

However, the CCB–β-blocker combination is often underused, even in some studies reporting 'optimally treated' stable effort angina.

Others. Felodipine, lacidipine and lercanidipine share the standard properties of other long-acting DHPs.

7.1.3.3.4 Ivabradine. Ivabradine is a heart rate-lowering agent selectively inhibiting the sinus node *I*(f) pacemaking current, thereby decreasing the myocardial oxygen demand without effect on inotropism or BP.[307] It was approved by the European Medicines Agency (EMA) for therapy of chronic stable angina in patients intolerant to—or inadequately controlled by—β-blockers and whose heart rate exceeded 60 b.p.m. (in sinus rhythm).[220,307] Ivabradine was as effective as atenolol or amlodipine in patients with SCAD; adding ivabradine 7.5 mg twice daily to atenolol therapy gave better control of heart rate and anginal symptoms.[307–309] In 1507 patients with prior angina enrolled in the Morbidity-Mortality Evaluation of the I_f Inhibitor Ivabradine in Patients With Coronary Artery Disease and Left Ventricular Dysfunction (BEAUTIFUL) trial, ivabradine reduced the composite primary endpoint of CV death, hospitalization with MI and HF, and reduced hospitalization for MI. The effect was predominant in patients with a heart rate ≥70 bpm.[310] Ivabradine is thus an effective anti-anginal agent, alone or in combination with β-blockers.

7.1.3.3.5 Nicorandil. Nicorandil is a nitrate derivative of nicotinamide that can be used for the prevention and long-term treatment of angina,[177] and may be added after β-blockers and CCBs. It is EMA- but not FDA approved. Nicorandil dilates epicardial coronary arteries and stimulates ATP-sensitive potassium channels (KATP) in vascular smooth muscle. In the prospective Impact Of Nicorandil in Angina (IONA) study, over a mean of 1.6 years in 5126 patients with SCAD, CV events were reduced by 14% (relative risk 0.86; $P = 0.027$). However, symptom relief was not reported.[177] Long-term use of oral nicorandil may stabilize coronary plaque in patients with stable angina.[311] Occasional side-effects include oral, intestinal and perianal ulceration.

7.1.3.3.6 Trimetazidine. Trimetazidine is an anti-ischaemic metabolic modulator,[312] with similar anti-anginal efficacy to propranolol in doses of 20 mg thrice daily. The heart rate and rate × pressure product at rest and at peak exercise remained unchanged in the trimetazidine group, thus showing a non-mechanical anti-ischaemic action.[313,314]

Trimetazidine (35 mg twice daily) added to beta-blockade (atenolol) improved effort-induced myocardial ischaemia, as reviewed by the EMA in June 2012,[315] and remains contra-indicated in Parkinson's disease and motion disorders [such as tremor (shaking), muscle rigidity and walking disorders and restless leg syndrome]. In diabetic persons, trimetazidine improved HbA1c and glycaemia, while increasing forearm glucose uptake.[316] Trimetazidine has not been evaluated in large outcome studies in SCAD patients.

7.1.3.3.7 Ranolazine. Ranolazine is a selective inhibitor of late sodium current with anti-ischaemic and metabolic properties.[317,318] Doses of 500–2000 mg daily reduced angina and increased exercise capacity without changes in heart rate or BP.[318] The EMA approved ranolazine in 2009 for add-on treatment in stable angina in patients inadequately controlled by—or intolerant to—first-line agents (beta-blockers and/or calcium antagonists).[310] In the 6560 patients of the Metabolic Efficiency with Ranolazine for Less Ischemia in Non-ST-Elevation Acute Coronary Syndromes: Thrombolysis In Myocardial Infarction (MERLIN-TIMI 36) trial presenting with recent non-ST-elevation ACS (NSTE-ACS),[319] ranolazine therapy showed no overall benefit. In patients with prior chronic angina enrolled in the MERLIN trial, ranolazine reduced recurrent ischaemia [hazard ratio (HR) 0.78; $P = 0.002$].[320,321] In those studied after the coronary event, ranolazine reduced the incidence of newly increased HbA1c by 32%.[320] In the recent TERISA study (Type 2 Diabetes Evaluation of Ranolazine in Subjects With Chronic Stable Angina), ranolazine reduced episodes of stable angina in 949 diabetes patients already receiving one or two anti-anginal drugs and led to less use of sublingual nitroglycerin, and the benefits appeared more prominent in patients with higher rather than lower HbA_{1c} levels. These results suggest that this drug can be added to other well-established anti-anginal drugs, in particular in patients with higher HbA_{1c} levels, who may also more often rely on medical management.[322]

Ranolazine plasma levels increase with cytochrome P3A (CYP3A) inhibitors (diltiazem, verapamil, macrolide antibiotics, grapefruit juice). Ranolazine clearance is reduced by renal and hepatic impairment.[317] Ranolazine increases QTc, and should therefore be used carefully in patients with QT prolongation or on QT-prolonging drugs.[317]

7.1.3.3.8 Allopurinol. Allopurinol, an inhibitor of xanthine oxidase that reduces uric acid in persons with gout, is also anti-anginal. There is limited clinical evidence but, in a randomized crossover study of 65 patients with SCAD, allopurinol 600 mg/day increased times to ST-segment depression and to chest pain.[323] In renal impairment, such high doses may have toxic side-effects. In optimally treated SCAD patients, allopurinol reduced vascular oxidative stress,[206] while in heart failure patients it conserved ATP.[324]

7.1.3.3.9 Molsidomine. This direct NO donor has anti-ischaemic effects similar to those of isosorbide dinitrate.[325] The long-acting once-daily 16 mg formulation is as effective as 8 mg twice daily.[325]

7.1.3.4 Patients with low blood pressure

Anti-anginal drugs should be started at very low doses, with preferential use of drugs with no- or limited impact on BP, such as ivabradine (in patients with sinus rhythm), ranolazine or trimetazidine.

7.1.3.5 Patients with low heart rate

Several studies have shown that increased resting heart rate is a strong independent risk factor for adverse outcome in patients with SCAD. There is a linear relationship between resting heart rate and major cardiovascular events, with a persistent decrease in CV risk with lower heart rate.[43,326–328] A clinical benefit has been demonstrated of heart rate reduction using various drugs. Although lowering the heart rate <60 b.p.m. is an important goal in the treatment of SCAD, patients presenting with low heart rate should be treated differently. Heart rate lowering drugs (β-blockers, ivabradine, heart rate lowering CCBs) should be avoided or used with caution and, if needed, started at very low doses. Anti-anginal drugs without heart lowering effects should preferably be given.

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7.2 Event prevention

7.2.1 Antiplatelet agents

Antiplatelet agents decrease platelet aggregation and may prevent formation of coronary thrombus. Due to a favourable ratio between benefit and risk in patients with stable CAD and its low cost, low-dose aspirin is the drug of choice in most cases and clopidogrel may be considered for some patients. The use of antiplatelet agents is associated with a higher bleeding risk.

7.2.1.1 Low-dose aspirin

Aspirin remains the cornerstone of pharmacological prevention of arterial thrombosis. It acts via irreversible inhibition of platelet cyclooxygenase-1 (COX-1) and thus thromboxane production, which is normally complete with chronic dosing $\geq$75 mg/day. Contrary to the antiplatelet effects, the gastrointestinal side-effects of aspirin increase at higher doses. The optimal risk–benefit ratio appears to be achieved with an aspirin dosage of 75–150 mg/day.[332–334]

7.2.1.2 P2Y12 inhibitors

P2Y12 inhibitors, including thienopyridines, act as antagonists of the platelet adenosine diphosphate (ADP) receptor $P2Y_{12}$, thereby inhibiting platelet aggregation. The major study supporting the use of thienopyridine in stable coronary patients is the Clopidogrel vs. Aspirin in Patients at Risk of Ischaemic Events (CAPRIE) trial, which showed an overall benefit of clopidogrel as compared with aspirin (with also a favourable safety profile) in preventing CV events in three categories of patients with previous MI, previous stroke or peripheral vascular disease (PVD).[335] The clopidogrel benefit was driven by the peripheral vascular disease (PVD) sub-group and the dose of aspirin with which it was compared (325 mg/day) may not be the safest dose. Clopidogrel should thus be proposed as a second-line treatment, especially for aspirin-intolerant CVD patients. Prasugrel and ticagrelor are new $P2Y_{12}$ antagonists that achieve greater platelet inhibition, compared with clopidogrel.[336,337] Prasugrel and ticagrelor are both associated with a significant reduction of CV outcomes as compared with clopidogrel in ACS patients,[338,339] but no clinical studies have evaluated the benefit of these drugs in SCAD patients. After unstable angina or myocardial infarction without ST-segment elevation when patients are stabilized and medically managed, there are no data supporting a beneficial effect of intensified platelet inhibition.[340]

7.2.1.3 Combination of antiplatelet agents

Dual antiplatelet therapy combining aspirin and a thienopyridine is the standard of care for patients with ACS, including after the acute phase, when the patients are stabilized, or in SCAD patients who have undergone elective PCI.[1,338,339,341,342] However, in the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) study,[343] Dual antiplatelet therapy did not confer benefit in patients with stable vascular disease or at risk of atherothrombotic events, although a significant benefit was observed in a *post-hoc* analysis of patients with documented atherothrombotic disease, and in particular in coronary patients with a prior history of MI.[344] Combined antiplatelet therapy was also recently tested with an antagonist of protease activated receptor type 1 (PAR-1).[341] The primary efficacy endpoint—a composite of CV death, MI or stroke—was significantly reduced with vorapaxar in addition to standard antiplatelet therapy in patients with stable atherosclerosis, and this benefit was particularly evident in the post-MI group of patients.[345] However, it increased the risk of moderate or severe bleeding, including intracranial haemorrhage. Altogether, on the basis of these *post-hoc* analyses, combined antiplatelet therapy may be beneficial only in selected patients at high risk of ischaemic events, but cannot be recommended systematically in SCAD patients.

7.2.1.4 Poor response to antiplatelet agents

There is a wide variation in response to antiplatelet therapy and a great interest has recently emerged in the use of functional and/or genetic assays to guide such treatment. High platelet reactivity on aspirin and/or clopidogrel treatment results from multiple factors, including non-compliance, accelerated platelet turnover, drug interactions, patient characteristics (such as age, gender, diabetes) and single nucleotide polymorphisms [*cytochrome P450 2C19 (CYP2C19*2), ATP-binding cassette sub-family B member 1(ABCB1)* for clopidogrel). The influence of genetic variants on the response to antiplatelet agents, especially clopidogrel, has been well established in patients with ACS and planned PCI, but not in patients with stable CAD.[346] However, there is currently no recommendation to perform genetic testing in patients with stable CAD. Platelet function testing in SCAD patients undergoing PCI is not recommended as a routine (see chapter 8).[347]

7.2.2 Lipid-lowering agents (see lipid management, above)

Patients with documented CAD are regarded as being at very high risk and should be treated with statins, in line with recommendations in the ESC/European Atherosclerosis Society Guidelines for the management of dyslipidaemia.[62] The treatment target is LDL-C $<$1.8 mmol/L and/or $>$50% reduction if the target level cannot be reached.

7.2.3 Renin-angiotensin-aldosterone system blockers

Angiotensin converting enzyme inhibitors reduce total mortality, MI, stroke and heart failure among specific subgroups of patients, including those with heart failure,[348–350] previous vascular disease alone,[351–353] or high-risk diabetes.[354] Hence, it is appropriate to consider ACE inhibitors for the treatment of patients with SCAD, especially with co-existing hypertension, LVEF $\leq$40%, diabetes or CKD, unless contra-indicated.

However, not all clinical trials have demonstrated that the ACE inhibitors reduce all-cause mortality, CV mortality, non-fatal MI, stroke and heart failure in patients with atherosclerosis and preserved LV function.[351,352,355] In SCAD patients with hypertension, a combination therapy consisting of an ACE inhibitor and a DHP CCB, such as perindopril/amlodipine in the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) trial and benazepril/amlodipine in the Avoiding Cardiovascular Events Through Combination Therapy in Patients Living With Systolic Hypertension (ACCOMPLISH) trial, is preferred.[356,357] In contrast, adding an angiotensin II receptor antagonist (ARB) to an ACE inhibitor was associated with more adverse events, without an increase in benefit.[358,359]

Hence, ARB treatment may be an alternative therapy for patients with SCAD when ACE inhibition is indicated but not tolerated. There

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are, however, no clinical outcome studies showing a beneficial effect of ARB in SCAD.

Aldosterone blockade with spironolactone or eplerenone is recommended for use in post-MI patients without significant renal dysfunction or hyperkalaemia, who are already receiving therapeutic doses of an ACE inhibitor and a β-blocker, have an LVEF ≤40% and have either diabetes or heart failure.[360]

7.3 Other drugs

7.3.1 Analgesics

The use of selective cyclooxygenase-2 (COX-2) inhibitors and traditional non-selective non-steroidal anti-inflammatory drugs (NSAIDs) has been associated with an increased risk for CV events in recent clinical trials in arthritis and cancer prevention and are not recommended.[361–363] In patients at increased CV risk in need of pain relief, it is therefore recommended to commence with acetaminophen or aspirin at the lowest efficacious dose, especially for short-term needs.

If adequate pain relief requires the use of NSAIDs, these agents should be used in the lowest effective doses and for the shortest possible duration. In patients with atherosclerotic vascular disease—and in SCAD in particular—NSAID treatment should, when this is indicated for other reasons, be combined with low-dose aspirin to ensure effective platelet inhibition.

7.4 Strategy

Figure 4 summarizes the medical management of SCAD patients. This common strategy might be adjusted according to patient comorbidities, contra-indications, personal preference and drug costs. The medical management consists of a combination of *at least* a drug for angina relief plus drugs to improve prognosis, as well as use of sublingual nitroglycerin for chest pain management. It is recommended that either a β-blocker or a CCB to a short-acting nitrate be added as first-line treatment to control heart rate and symptoms. If the symptoms are not controlled, it is advised to switch to the other option (CCB or β-blocker) or to combine a β-blocker and a DHP CCB. The combination of a heart-lowering CCB with a β-blocker is not advised. Other anti-anginal drugs might be used as a second-line treatment when symptoms are not satisfactorily controlled. In selected patients with intolerance or contra-indications to both β-blockers and CCBs, second-line drugs can be used as a first-line treatment. The event prevention is optimally achieved by the prescription of antiplatelet agents and statins. In selected patients, the use of ACE inhibitors or ARBs can be considered.

7.5 Treatment of particular forms of SCAD

7.5.1 Microvascular angina

All patients with microvascular angina should achieve optimal coronary risk factor control. Symptomatic treatment is empirical because of the limited knowledge of its causes. Furthermore, the results of available therapeutic trials cannot be accepted as conclusive because of variable patient selection, small sample size, inadequate design and lack of demonstration of clinical improvement of microvascular disease.

Traditional anti-ischaemic drugs are the first step in medical treatment.[52] Short-acting nitrates can be used to treat anginal attacks, but often they are only partially effective. β-Blockers seem a rational approach because the dominant symptom is effort-related angina; they were indeed found to improve symptoms in several studies and should constitute the first choice of therapy, particularly in patients

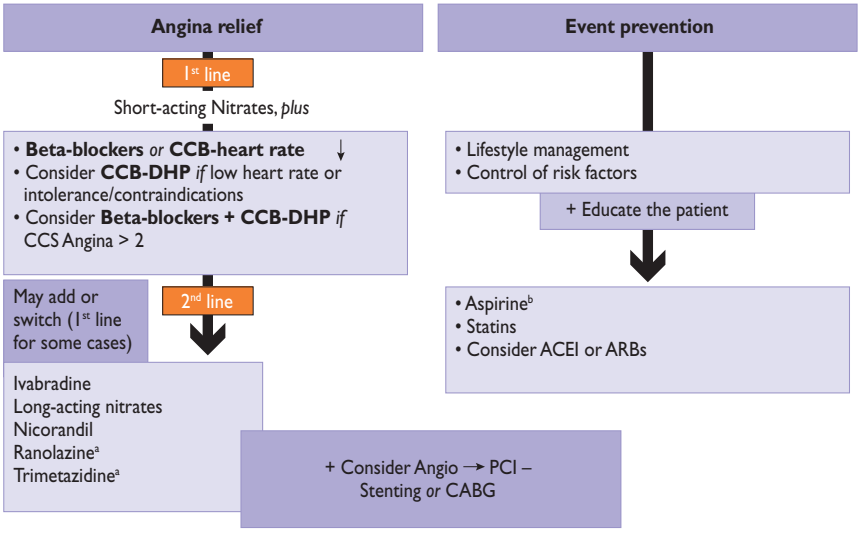

Figure 4 Medical management of patients with stable coronary artery disease. ACEI = angiotensin converting enzyme inhibitor; CABG = coronary artery bypass graft; CCB = calcium channel blockers; CCS = Canadian Cardiovascular Society; DHP = dihydropyridine; PCI = percutaneous coronary intervention.
[a]Data for diabetics.
[b]if intolerance, consider clopidogrel

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with evidence of increased adrenergic activity (e.g. high heart rate at rest or during low-workload exercise).

Calcium antagonists and long-acting nitrates have shown variable results in clinical trials and are more helpful when used in addition to β-blockers in the case of insufficient control of symptoms. Calcium antagonist, however, can be first-line therapy in patients with a significant variable threshold of effort angina.[367] In patients with persisting symptoms despite optimal anti-ischaemic drug therapy, several other treatments have been proposed. ACE inhibitors (and possibly ARBs) may improve microvascular function by counteracting the vasoconstrictor effects of angiotensin II; they have improved symptoms and exercise results in small trials and can be helpful, particularly in patients with hypertension or diabetes mellitus. α-Adrenergic antagonists may decrease sympathetic-mediated vasoconstriction and may be considered in individual patients, although clinical benefits have usually been disappointing. Improvement of exercise capacity has been observed in a small trial with nicorandil.[368] Improvement of anginal symptoms, probably mediated primarily by improvement of endothelial function, has been reported with statins and with oestrogen replacement treatment.[369,370] In patients with angina refractory to various combinations of the previous medications, other forms of treatment can be proposed. Xanthine derivatives (aminophylline, bamiphylline) can be added to anti-ischaemic treatment to reduce angina by adenosine receptor blockade; adenosine is indeed a major mediator of cardiac ischaemic pain (see *Table 29*). New anti-ischaemic drugs such as ranolazine or ivabradine have shown good effects in some patients with microvascular angina. Finally, in case of refractory angina, additional interventions may be discussed **(see section 9 on refractory angina)**.

In patients with microvascular angina, the susceptibility of symptoms to medical treatment is extremely variable and experimentation of different drug combinations, is needed before establishing satisfactory symptom control.

Table 29 Treatment in patients with microvascular angina

Recommendations	Class [a]	Level [b]	Ref. [c]
It is recommended that all patients receive secondary prevention medications including aspirin and statins.	I	B	371
ß-blockers are recommended as a first line treatment.	I	B	372
Calcium antagonists are recommended if ß-blockers do not achieve sufficient symptomatic benefit or are not tolerated.	I	B	367
ACE inhibitors or nicorandil may be considered in patients with refractory symptoms.	IIb	B	368
Xanthine derivatives or non-pharmacological treatments such as neurostimulatory techniques may be considered in patients with symptoms refractory to the above listed drugs.	IIb	B	373–375

ACE = angiotensin converting enzyme.
[a] Class of recommendation.
[b] Level of evidence.
[c] Reference(s) supporting levels of evidence.

7.5.2 Treatment of vasospastic angina

All patients with vasospastic angina should achieve optimal coronary risk factor control, in particular through smoking cessation and aspirin. A drug-related cause (e.g. cocaine or amphetamines) should be systemically researched and managed if detected. Chronic preventive treatment of vasospastic angina is mainly based on the use of CCBs.[376] Average doses of these drugs (240–360 mg/day of verapamil or diltiazem, 40–60 mg/day of nifedipine) usually prevent spasm in about 90% of patients. Long-acting nitrates can be added in some patients to improve the efficacy of treatment and should be scheduled to cover the period of the day in which ischaemic episodes most frequently occur, in order to prevent nitrate tolerance. β-Blockers should be avoided, as they might favour spasm by leaving α-mediated vasoconstriction unopposed by β-mediated vasodilation.

In about 10% of cases, coronary artery spasm is refractory to standard vasodilator therapy, although refractoriness is usually limited to brief periods in most patients. Very high doses of calcium antagonists and nitrates usually prevent transient ischaemic episodes in these critical periods. In the very rare patients in whom even this treatment is insufficient, the addition of anti-adrenergic drugs like guanethidine or clonidine might be helpful.[377] PCI with stent implantation at the site of spasm (even in the absence of significant stenosis),[378] as well as chemical or surgical sympathectomy,[379] have also been reported but are not recommended. Because of the high prevalence of silent ischaemic episodes and possible arrhythmias, 24-hour ambulatory ECG monitoring can be used to verify the treatment efficiency.

Implantation of an automatic cardioverter defibrillator or of a pacemaker is indicated in patients with ischaemia-related life-threatening tachyarrhythmias or bradyarrhythmias, respectively, when coronary spasm presents a poor or uncertain response to medical therapy.

8. Revascularization

8.1 Percutaneous coronary intervention

Advances in techniques, equipment, stents and adjuvant therapy have established PCI as a routine and safe procedure in patients with SCAD and suitable coronary anatomy. The mortality risk associated with the procedure in SCAD is <0.5%.[380–382] The efficacy of PCI in SCAD in comparison to medical therapy and CABG has been the subject of extensive evaluation.

8.1.1 Type of stent and dual antiplatelet therapy

Bare metal stents (BMS) are associated with a 20–30% rate of recurrence of angiographic stenosis within 6–9 months after implantation. Drug-eluting stents (DES) reduce the incidence of angiographic restenosis and ischaemia-driven repeat revascularization. For the first

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Table 30 Stenting and peri-procedural antiplatelet strategies in stable coronary artery disease patients

Recommendations	Class [a]	Level [b]	Ref. [c]
DES is recommended in SCAD patients undergoing stenting if there is no contraindication to prolonged DAPT.	I	A	172
Aspirin is recommended for elective stenting.	I	B	172
Clopidogrel is recommended for elective stenting.	I	A	172
Prasugrel or ticagrelor should be considered in patients with stent thrombosis on clopidogrel without treatment interruption.	IIa	C	-
GP IIbIIIa antagonists should be considered for bailout situation only.	IIa	C	172
Platelet function testing or genetic testing may be considered in specific or high risk situations (e.g. prior history of stent thrombosis; compliance issue; suspicion of resistance; high bleeding risk) if results may change the treatment strategy.	IIb	C	-
Prasugrel or ticagrelor may be considered in specific high risk situations of elective stenting (e.g. left main stenting; high risk of stent thrombosis; diabetes).	IIb	C	-
Pretreatment with clopidogrel (when coronary anatomy is not known) is not recommended.	III	A	386, 388, 249, 387
Routine platelet function testing (clopidogrel and aspirin) to adjust antiplatelet therapy before or after elective stenting is not recommended.	III	A	347, 398
Prasugrel or ticagrelor is not recommended in low risk elective stenting.	III	C	-

DATP = Dual antiplatelet therapy; SCAD = stable coronary artery disease.
[a] Class of recommendation.
[b] Level of evidence.
[c] Reference(s) supporting levels of evidence.

generation of DES, this benefit has been extensively demonstrated in spite of a slightly higher incidence of late and very late stent thrombosis,[383] related to delayed endothelialization, which requires longer dual antiplatelet therapy (DAPT) to prevent stent thrombosis. First-generation sirolimus-eluting stents (SES) and paclitaxel-eluting stents (PES) have been extensively compared in head-to-head randomized controlled trials. Angiographic results were better with SES and translated into significant differences in terms of repeat revascularization.[384] The most recent or 'second- generation' DES (with thinner struts and biodegradable or more biocompatible polymers) showed superior clinical outcomes for both efficacy and safety when compared with first-generation DES.[385] Second-generation DES—preferring those tested in large all-comers trials and compared with other DES with proven outcome—are therefore the recommended option in SCAD patients with no contra-indication to DAPT (see *Table 30*).

A recent meta-analysis confirmed that clopidogrel pretreatment in stable patients undergoing elective PCI does not reduce mortality or major adverse cardiac events (MACE), as compared with clopidogrel administration in the catheterization laboratory.[386] On the basis of several randomized trials and this meta-analysis—and contrary to a diffuse common practice—SCAD patients who undergo diagnostic coronary angiography with the possibility of undergoing *ad-hoc* PCI (revascularization within the same procedure) should not be treated with clopidogrel before the coronary anatomy is known.[249,386–388] The bleeding risk of routine DAPT, administered before catheterization in patients who do not require stenting (no significant CAD or CAD requiring CABG surgery), is not balanced by a detectable benefit in terms of ischaemic events in those undergoing PCI. Despite the overwhelming advantages shown in ACS patients—and especially diabetic patients—in the absence of randomized clinical trials, the use of prasugrel or ticagrelor cannot be recommended in SCAD patients undergoing elective PCI. An off-label use of these drugs is, however, common practice in some high-risk patients, especially in cases of documented stent thrombosis. After stenting, premature discontinuation of antiplatelet therapy is a major risk factor for stent thrombosis and should be avoided.[389,390]

Current guidelines recommended 6–12 months of DAPT after first-generation stents.[172] New-generation DES have been associated with lower rates of stent thrombosis,[391,392] and recent data from registries and randomized controlled trials suggested that a shorter duration of DAPT might be sufficient in stable coronary patients.[393–396] Considering the risk–benefit ratio of DAPT beyond 6 months—and while waiting for more information from the ongoing studies exploring various durations of treatment including more than a year—we endorsed the current ESC recommendation of 6–12 months of DAPT in SCAD patients undergoing PCI revascularization with a latest-generation DES (see section 9.5 for more details and for recommendations).[172] Shorter durations (1–3 months) are reasonable in patients with high bleeding risk or undergoing undeferrable surgery or on concomitant anticoagulant treatment for which the use of clopidogrel only has shown significant advantages in a single small-scale trial (What is the Optimal antiplatElet and anticoagulant therapy in patients with oral anticoagulation and coronary StenTing (WOEST)).[397]

8.1.2 Intracoronary assessment of stenosis severity (fractional flow reserve, intravascular ultrasound and optical coherence tomography) (see web addenda)

When non-invasive stress imaging is contra-indicated, non-diagnostic, or unavailable, the measurement of FFR during adenosine

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Table 31 Use of fractional flow reserve, intravascular ultrasound, and optical coherence tomography in SCAD

Recommendations	Class [a]	Level [b]	Ref. [c]
FFR is recommended to identify hemodynamically relevant coronary lesion(s) when evidence of ischaemia is not available.	I	A	399, 401, 405
Revascularization of stenoses with FFR <0.80 is recommended in patients with angina symptoms or a positive stress test.	I	B	400
IVUS or OCT may be considered to characterize lesions.	IIb	B	404, 406
IVUS or OCT may be considered to improve stent deployment.	IIb	B	288, 404
Revascularization of an angiographically intermediate stenosis without related ischaemia or without FFR <0.80 is not recommended.	III	B	399, 405

FFR = fractional flow reserve; IVUS = intravascular ultrasound; OCT = optical coherence tomography; SCAD = stable coronary artery disease.
[a] Class of recommendation.
[b] Level of evidence.
[c] Reference(s) supporting levels of evidence.

infusion is particularly helpful in identify haemodynamically or functionally significant stenosis, inducing ischaemia, justifying revascularization (see *Table 31*). In patients with FFR >0.80, studies in the BMS era have demonstrated that medical treatment provides better outcomes than immediate revascularization.[110,172,399] Accordingly, a patient with a stenosis and an FFR >0.80 (two measurements or during adenosine infusion) should not be revascularized. The recent Fractional Flow Reserve vs. Angiography for Multivessel Evaluation (FAME-2) study confirmed that SCAD patients with stenoses having FFR ≤0.80 gain a benefit from PCI revascularization in addition to OMT, a benefit driven only by the reduced need for urgent revascularization (the study was stopped prematurely by the DSMB for that reason). Patients without ischaemia have excellent outcomes on medical therapy alone.[400] Although the study suffers from significant limitations (the open nature of the trial may have affected the decision on 'urgent' revascularization; low-risk population), FFR can guide PCI in a clinically-effective way.

Fractional flow reserve, although in general not useful in very high grade lesions (angiographically >90%), which practically always have an FFR ≤0.8, may help the decision on when to revascularize in many uncertain clinical conditions. One such condition is 'multivessel disease', which occurs in a very heterogeneous population. In these patients, FFR measurement may change the strategy of revascularization (PCI vs. CABG) and the extent of revascularization according to the functional assessment of stenoses in critical coronary locations. Another critical situation for revascularization is LM stenosis, a lesion site that is of major prognostic importance and often determines the type of treatment. A recent single-centre study showed that angiography is not always reliable in the determination of the severity of LM stenoses and that deferred revascularization, if FFR >0.80, may be a safe approach.[401]

Another situation relevant to these Guidelines, where FFR may be useful, is in 'post-ACS' patients. Once the culprit lesion has been treated, the patient can be considered as a stable or stabilized CAD patient. Non-invasive stress testing/imaging immediately after the acute phase may be impossible, contra-indicated or hazardous. Non-culprit stenoses in patients with recent ACS can be evaluated by FFR, either during the index procedure or in a staged procedure.[399,402]

The use of intravascular ultrasound (IVUS) has been broadly investigated in SCAD with many different subsets of lesions (see *Table 31*). Unlike FFR, IVUS is an imaging diagnostic tool and does not provide assessment of the functional severity of a stenosis. Previously accepted cut-off limits of 3.5 or 4.0 mm^2 for major epicardial artery stenosis and 6.0 mm^2 for left main stenosis[403] have been shown to be unreliable and poorly correlated with FFR, with somewhat better results when the absolute IVUS measurements are corrected for the reference vessel size. Once the indication to treatment is established, when more information is needed, IVUS is far superior to FFR because it provides an anatomical characterization of the lesion in terms of vessel size and plaque composition and can control stent expansion and strut apposition. More recently, optical coherence tomography (OCT) has been developed as a new intracoronary imaging tool with superior resolution (<10 μm) able to offer detailed assessment of superficial components including measurements of the thickness of the fibrous cap of lipidic plaques.[404] The usefulness of OCT in SCAD patients with vulnerable plaques has not been well established,[404] and certainly treatment of non-functionally critical lesions based only on the presence of elements of instability is not recommended. The facilitated technique of image acquisition allows optimization of stent expansion and apposition, and long-term assessment of stent healing.[404]

8.2 Coronary artery bypass surgery

8.2.1 Arterial vs. venous grafts

For the last 25 years the principle technique underpinning CABG has been the use of an internal mammary artery (IMA) to the LAD coronary artery with supplemental vein grafts as required. This followed a seminal publication from the Cleveland Clinic in 1986, showing that an IMA to the LAD improved survival and reduced the subsequent incidence of MI, recurrent angina and the need for repeat revascularization.[407]

Since then, several angiographic studies have confirmed the superior patency of both IMA grafts in comparison to vein grafts both early and late after CABG.[408,409] Most importantly, this superior graft patency appears to translate into a survival benefit. In 2001 a systematic review comparing single (SIMA) and bilateral (BIMA) IMA grafting reported a significant survival benefit with BIMA grafts with a hazard ratio for death of 0.81.[410] Recent studies have reported that a survival

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benefit of BIMA grafts extends to the second and third decades of follow-up,[411,412] and especially in patients with diabetes.[169]

Previous concerns that the use of BIMA grafting may increase early postoperative mortality and/or morbidity have been dispelled by the Arterial Revascularization Trial (ART) which, in one of the largest trials ever conducted in cardiac surgery, randomized 3102 patients to SIMA or BIMA, with supplemental grafts as necessary.[413] Whilst the primary outcome of this trial is 10-year survival, an interim analysis of safety at 1 year showed similar mortality of around 2% in both groups, with no difference in the incidence of MI, death or stroke but a slight increase in the incidence of sternal wound reconstruction in the BIMA group (1.9 vs. 0.6%).[413] The data are currently being analysed to determine the key patient and operating factors that predispose to sternal dehiscence.

The radial artery has also been proposed as a second arterial graft, rather than a second IMA graft. In two randomized trials, the radial artery patency at 1 year was variously reported to be 'superior' and 'equivalent' to that of vein grafts.[414,415] In an additional small, randomized trial the 5-year patency of the radial artery was significantly superior to that of vein grafts when placed to the circumflex coronary system.[416,417]

Nevertheless, despite angiographic and clinical evidence of the potential superiority of arterial grafts, the reality is that the vast majority of bypass grafts—with the exception of the IMA to the LAD—are performed with saphenous vein grafts. Best current evidence suggests that the patency rate of saphenous vein grafts is slightly lower in off-pump surgery and when harvested using endoscopic, rather than open techniques.[418,419]

8.2.2 On-pump vs. off-pump surgery (see web addenda)

Off-pump surgery was initially proposed almost three decades ago.[420] Numerous randomized trials and meta-analyses have shown no significant beneficial effect on mortality,[421,422] but there have been reductions in stroke, transfusion, re-operation for peri-operative bleeding and postoperative complications, possibly at the cost of an excess of repeat revascularization with off-pump CABG. The two largest randomized trials, the Veterans Affairs (VA) Randomized On/Off Bypass (ROOBY) ($n = 2203$)[419] and The CABG Off or On Pump Revascularization Study (CORONARY) ($n = 4752$)[421] both reported no difference in the primary composite endpoint at 30 days. ROOBY reported a poorer outcome (death or complication) in the off-pump composite endpoint at one year (9.9 vs. 7.4%) while CORONARY has still to report at the time of writing. In contrast to the randomized trials, several large propensity-matched registries,[423–425] which generally include higher-risk patients, have reported a reduction in mortality in patients undergoing off-pump CABG, although off-pump surgery is still performed in a minority of centres.

8.3 Revascularization vs. medical therapy

8.3.1 General rules for revascularization (see web addenda)

The decision to revascularize a patient should be based on the presence of significant obstructive coronary artery stenosis, the amount of related ischaemia and the expected benefit to prognosis and/or symptoms (*Figure 5*). There are many clinical, anatomical, technical and environmental factors that may be discussed before the benefit of revascularization can be anticipated (*Table 32*, *Figure 5*). The vast number of possible combinations makes absolute recommendations difficult to mandate in every situation. In this regard, for a given patient in a given hospital, clinical judgement with consensual rather than individual decision-making, with a Heart Team discussion, should prevail, although this has to be individualized since, in many patients, the preferred approach is often quite clear-cut.

When technically feasible, with an acceptable level of risk and a good life expectancy, revascularization is indicated in chronic angina refractory to OMT. It can also be considered as first-line treatment in the situations discussed below.

8.3.1.1 Post-myocardial infarction

The Swiss Interventional Study on Silent Ischemia Type II (SWISSI II) trial, involving 201 patients with a recent ST-segment elevation MI or non-ST segment elevation MI, investigated whether revascularization with PCI was better than drug therapy in stable patients with silent myocardial ischaemia (see description below).

During a lengthy 10-year follow-up period, the primary endpoint, which was survival free of cardiac death, non-fatal MI or revascularization, was significantly better in the PCI group.

PCI also significantly reduced the rates of cardiac death and all-cause mortality or MI. In addition, objective evidence of ischaemia was reduced in the revascularization group.[431]

The Danish trial in Acute Myocardial Infarction (DANAMI) compared a deferred invasive strategy of PCI or CABG with a conservative strategy in 503 patients with inducible myocardial ischaemia, who had received thrombolysis for a first MI. Stress testing was performed at discharge and in patients randomized to the invasive strategy; angiography was performed within two weeks of stress testing. Patients with unstable angina were excluded.

Angina plus ischaemia was present in 25%, angina alone in 16% and 57% had silent ischaemia on stress testing.[432] At 2.5 years follow-up, the invasive strategy was associated with a reduction in the incidence of re-infarction and less frequent angina. This was noted in patients with both symptomatic and asymptomatic ischaemia.[433]

In contrast, the Occluded Artery Trial (OAT), following a strategy of routine PCI 3 to 28 days after acute MI, found no discernible benefit in terms of death, re-infarction, or heart failure at 4-year follow-up among asymptomatic or minimally symptomatic patients with occlusion of the infarct-related artery.[434] The findings of the OAT study, however, should not be interpreted as applying to all patients experiencing ST-elevation MI, but just to those with a late occluded artery and no- or minimal angina. Two smaller studies [The Open Artery Trial (TOAT) and Desobstruction Coronaire en Post-Infarctus (DECOPI)] dealt with similar situations of stable patients after a Q-wave MI, without residual ischaemia and a persistent total occlusion of the infarct-related artery, and these studies did not show any clinical benefit of stenting over medical therapy.[435,436]

Post-lytic revascularization studies. Old trials (not discussed here) comparing an invasive- with a conservative approach after fibrinolytic therapy did not show any differences in patient outcomes, but these studies antedated the use of stenting and modern antiplatelet therapies.[437–439] In contrast, more recent randomized studies, comparing systematic early PCI with a conservative ischaemia guided strategy, have demonstrated favourable trends with early PCI and a significant reduction of death or MI in a meta-analysis.[440,441]

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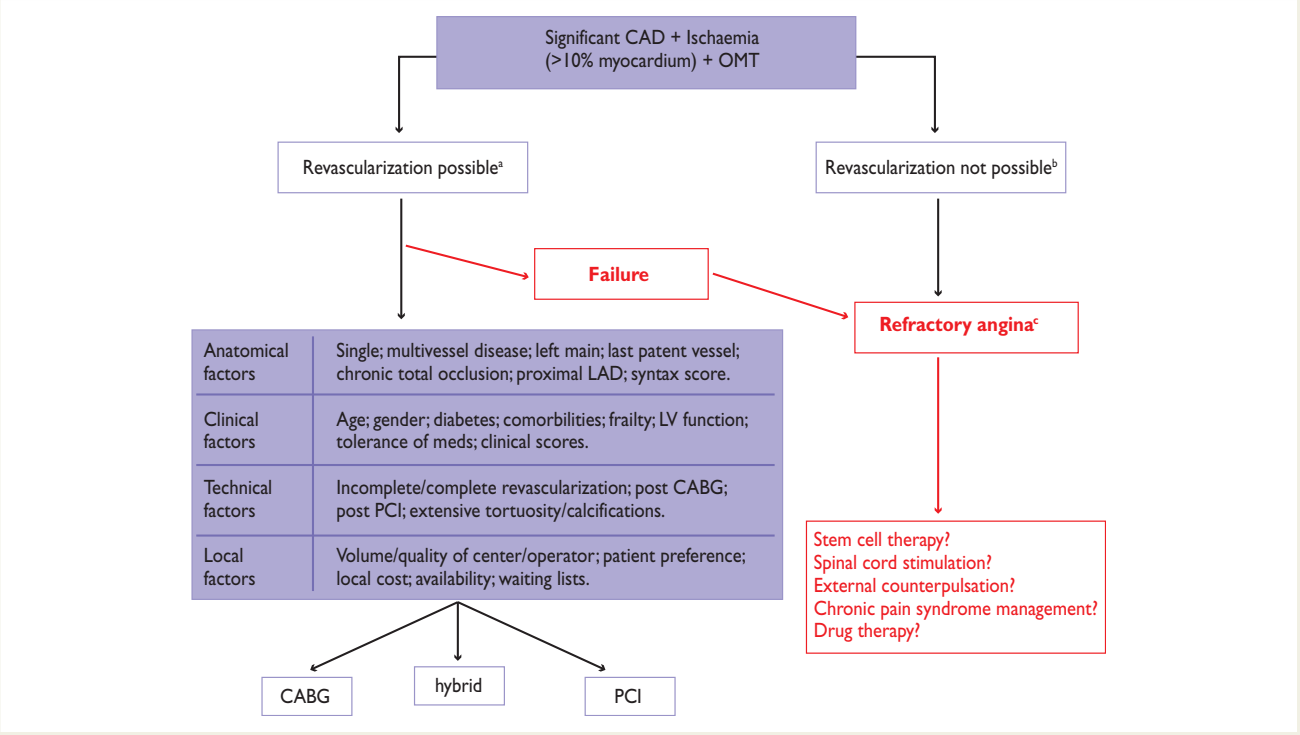

Figure 5 Global strategy of intervention in stable coronary artery disease (SCAD) patients with demonstrated ischaemia. CABG = coronary artery bypass graft; CAD= coronary artery disease; LAD = left anterior descending; LV = left ventricular; OMT = optimal medical treatment; PCI = percutaneous coronary intervention.
[a]Indication of revascularization for prognosis or symptoms (see *Table* 32).
[b]Not suitable for revascularization due to anatomy or clinical conditions.
[c]See section 9.

8.3.1.2 Left ventricular dysfunction

In general, revascularization improves survival in 'sicker' patients, especially in the presence of LV dysfunction.[442–447] From the early days of coronary angiography, it has been well recognized that LV dysfunction is one of the most powerful indicators of an adverse prognosis.[448] As techniques of revascularization improved, LV dysfunction has become a prime target—as opposed to a contra-indication—for coronary revascularization. Several older studies, including a meta-analysis, suggested that survival was improved by CABG over medical therapy in patients with mild-to-moderate systolic dysfunction.[445,449–452] The CASS randomized trial of bypass surgery vs. medical therapy demonstrated no overall differences in survival, except in the subset of patients with an ejection fraction (EF) of 0.35–0.49, in association with triple vessel disease.[453] The more contemporary Surgical Treatment for Ischemic Heart Failure (STICH) trial of subjects with more severe impairment of LV function (EF <0.35) demonstrated no survival difference at 5 years between CABG and OMT,[430] although CV mortality was reduced, as were hospitalization rates for major CV causes, in the CABG group. Moreover, if the data are analysed by treatment received and as per protocol, due to the large number of crossovers to both therapies, the differences in all-cause mortality reached statistical significance in favour of the CABG group; in this respect the trial can be considered to have demonstrated a modestly positive result in favour of surgery, with potentially important clinical implications. The subset analysed by viability testing is inconclusive.[429]

8.3.1.3 Multivessel disease and/or large ischaemic territory

Observational studies from the CASS registry and the meta-analysis of seven randomized trials—comprising a total of 2649 patients—of CABG vs. medical therapy suggested a survival advantage of surgery in patients with three-vessel disease (or LM disease), but no difference in patients with one- or two-vessel disease, except in patients with involvement of the proximal LAD plus one other major coronary artery.[445,454–458] In addition, these studies demonstrated a greater efficacy from CABG over medical therapy in respect of symptom relief, bearing in mind the caveat that, in these trials, the methods of medical therapy and secondary prevention were obsolete by today's standards. In the more contemporary Medical, Angioplasty, or Surgery Study (MASS II) trial of CABG, PCI and medical therapy, patients treated with CABG enjoyed a better survival and lower rates of subsequent MI and need for additional revascularization procedures over a follow-up period of 10 years.[459] The importance of the severity of symptoms was emphasized by two studies from the CASS registry, which demonstrated that, in patients with mild angina pectoris and triple vessel disease, survival advantage was confined to those with mild-to-moderate LV dysfunction. On the other hand, among patients with severe angina, survival was

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Table 32 Use of stable coronary artery disease patients on optical medical therapy (adapted from ESC/EACTS 2010 Guidelines)[172]

Indication [a]	To improve prognosis:		To improve symptoms persistent on OMT:		
	Class [d]	Level [e]	Class [d]	Level [e]	Ref. [f]
A Heart Team approach to revascularization is recommended in patients with unprotected left main, 2–3 vessel disease, diabetes or comorbidities.	I	C	I	C	266, 426–428
Left main >50% diameter stenosis[b].	I	A	I	A	172
Any proximal LAD >50% diameter stenosis[b].	I	A	I	A	172
2–3 vessel disease with impaired LV function / CHF.	I	B	IIa	B	172
Single remaining vessel (>50% diameter stenosis[b]).	I	C	I	A	172
Proven large area of ischaemia (>10% LV[c])	I	B	I	B	172
Any significant stenosis with limiting symptoms or symptoms non responsive/intolerant to OMT.	NA	NA	I	A	172
Dyspnoea/cardiac heart failure with >10% ischaemia/viability[c] supplied by stenosis >50%.	IIb	B[429, 430]	IIa	B	172
No limiting symptoms with OMT in vessel other than left main or proximal LAD or single remaining vessel or vessel subtending area of ischaemia <10% of myocardium or with FFR ≥0.80.	III	A	III	C	23, 25, 172, 400

References attached to these recommendations can be found in Table 8 of the original ESC guidelines for myocardial revascularization.[172]
CCS = Canadian Cardiovascular Society; CHF: congestive heart failure; FFR = fractional fow reserve; LAD = left anterior descending; LV = left ventricle; NA: not available; OMT = optimal medical treatment; SCAD = stable coronary artery disease.
[a] In asymptomatic patients, the decision will be guided by the extent of ischaemia on stress testing.
[b] With documented ischaemia or FFR < 0.80 for angiographic diameter stenoses 50–90%.
[c] As assessed by non-invasive test (SPECT, MRI, stress echocardiography).
[d] Class of recommendation.
[e] Level of evidence.
[f] Reference(s) supporting levels of evidence.

improved irrespective of LV function. In addition, the greater the number of proximal stenosis, the greater the surgical benefit.[456,460] Observational studies also support a survival advantage for CABG in patients with double-vessel disease in the presence of severe or extensive ischaemia or severe angina.[197,461–464] The concept of a revascularization benefit in patients with extended ischaemia is currently being tested in the ongoing International Study of Comparative Health Effectiveness with Medical and Invasive Approaches (ISCHEMIA).[197,214,465]

8.3.1.4 Left main coronary artery disease

The survival advantages for bypass surgery in patients with 50% or greater stenosis of the LM coronary artery was established by the striking differences noted in the Veterans Administration Cooperative Study in a subgroup of 113 patients,[466,467] and confirmed in a subsequent meta-analysis,[468] and in studies from the CASS registry [469,470] The data now need to be re-interpreted in the light of more recent data evaluating the functional severity of LM stenoses and the possibility that revascularization can be safely deferred if FFR >0.80.[401]

Irrespective, LM CAD (stenosis 50% or greater) continues to be a Class 1 indication for revascularization.[172,471] No further randomized, controlled trials of bypass surgery or PCI vs. medical therapy are likely to be undertaken in patients with LM CAD.

8.3.2 Revascularization in lower-risk populations

8.3.2.1 The randomized studies (see web addenda)

The older randomized studies that investigated revascularization vs. OMT are selectively reviewed in the web addenda.[26,41,461,472,473,459,474–477] The three most recent studies are also the largest and most informative studies for this comparison of revascularization with OMT.

The Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial (n = 2287) compared PCI + OMT with OMT only, in patients with SCAD or ischaemia and coronary lesions suitable for PCI. The target study population for the COURAGE trial were patients with chronic angina pectoris Canadian Cardiovascular Society (CCS) Class I–III), stable post-MI patients and asymptomatic patients with objective evidence of myocardial ischaemia. All patients had angiographically defined CAD, with at least one vessel meeting AHA/American College of Cardiology (ACC) Class I or II indications for PCI. Patients with a prior CABG were accepted. Patients with stenosis >80% in one or more vessels, subtending a large area of myocardium, could be enrolled even in the absence of objective ischaemia. The primary endpoint of all-cause death or non-fatal MI did not differ between the two groups during a mean follow-up of 4.6 years.[23,478] However, in patients who were invasively treated, freedom from angina was significantly better up to 3 years of follow-up. In a sub-study, patients with >10% ischaemia on stress myocardial perfusion scintigraphy

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had a higher rate of death or MI. More PCI + OMT patients exhibited significant ischaemia reduction (33 vs. 19%; $P = 0.0004$). Patients with ischaemia reduction had lower unadjusted risk for death or MI, particularly if baseline ischaemia was moderate to severe.[214]

The Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (BARI-2D) trial ($n = 2368$) evaluated whether PCI or CABG (choice left to the discretion of the treating physician), combined with OMT, would be better than OMT alone in patients with SCAD and type 2 diabetes mellitus.[25] The target study population were patients with a diagnosis of type 2 diabetes and angiographically documented CAD for which revascularization was not required for prompt control of severe or unstable angina. Patients with stenosis >70% presenting with angina symptoms were eligible for randomization, even without documented ischaemia. In contrast, approximately 30% of patients were asymptomatic with a positive stress test. The primary endpoint of all-cause mortality at 5 years follow-up did not differ between the two treatment strategies, nor did rates of MI or stroke. The patients with most severe disease were selected for CABG rather than PCI and were a higher-risk group that drew a greater benefit from early revascularization (reduction of MI compared with OMT).

In the Fractional Flow Reserve vs. Angiography for Multivessel Evaluation (FAME-2) trial, 888 SCAD patients with functionally significant stenosis (FFR ≤0.80) were randomly assigned to FFR-guided PCI plus OMT, or to OMT alone.[400] The target study population were patients who had at least one functionally significant stenosis and, on average, large areas of ischaemic myocardium (mean FFR value of 0.68) while the low-risk patients with non-ischaemic FFR values were not randomized but followed in a separate registry. The study was stopped prematurely by the Data Safety Monitoring Board, due to a highly significant reduction in hospital re-admission and urgent revascularization in the FFR ≤0.80-PCI group, compared with the FFR ≤0.80-OMT group. There was no difference in rates of death or MI between the two strategies. In patients without ischaemia (registry), the outcome appeared to be favourable with OMT only.

Altogether, seven major (*n* of 200 or more) randomized trials of revascularization vs. medical therapy in chronic SCAD have been published over the past 10 years (*Table 33*). Typically, populations of these studies were selected after an angiogram, had demonstrated at least one significant stenosis of an epicardial coronary artery in patients with typical or suspected angina—with or without documented myocardial ischaemia—with, in general, good LV function, no comorbidities and excluding patients at high angiographic risk, patients with LM coronary disease, CABG, multivessel disease, or lesions deemed to be treated with revascularization without further discussion for OMT only.

The results of these studies comparing myocardial revascularization with OMT have been somewhat consistent in confirming that, except for better symptom relief and lesser frequency of urgent revascularization, there is no advantage of revascularization over OMT alone to reduce mortality in angiographically selected patients

Table 33 Characteristics of the seven most recent randomized trials

	TIME[475]	MASS II[479]	SWISSI II[431]	COURAGE[23]	BARI–2D[25]	JSAP[477]	FAME–2[400]
Recruitment (years)	1996–2000	1995–2000	1991–97	1999–2004	2001–2005	2002–2004	2010–2012
Study size (n)	301	611	201	2287	2368	384	888
Mean age (years)	80	60	55	61	62	64	64
Angina CCS	II–IV	II–III	0	0–III	0–II	0–II	I–IV
Stress ischaemia (% of patients)	69	NA	100	NA	NA	NA	100
Prior MI (% of patients)	47	44	100	39	38	15	37
Mean LVEF (%)	52	67	57	62	NA	65	16% with EF<0.50
Angiographic selection	No	Yes	Yes	Yes	Yes	Yes	Yes
Mandatory documented ischaemia	No	No	Yes	No	No	No	Yes
Revascularization	PCI *or* CABG	PCI *or* CABG	PCI	PCI	PCI *or* CABG	PCI	PCI
Primary Endpoint (PEP)	Angina	Death/MI/ refractory angina	Death/MI/ revascularization	Death/MI	Death	Death/ACS	Death/MI/ Urgent revascularization
Revascularization better on PEP	Yes	No at 1 year Yes at 5 yrs (CABG)	Yes	No	No	Yes	Yes

CABG = coronary artery bypass graft; CCS = Canadian Cardiovascular Society; LVEF = left ventricular ejection fraction; MI = myocardial infarction; PCI = percutaneous coronary intervention.

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presenting with SCAD, acknowledging the possibility of crossover from medical therapy to intervention during follow-up. Although interventional and surgical techniques have improved in the past two decades, medical therapy has also improved over the same period.

As a result, OMT may substantially improve long-term outcomes of patients treated conservatively but also of patients undergoing revascularization, reducing the impact of revascularization itself on survival in non-ACS patients.

8.3.2.2 Limitations of the randomized studies (see web addenda)

All of these studies have their limitations, which may limit their general applicability. These limitations are discussed in the additional web addenda. In brief:

- Some patient subsets that are commonly encountered in clinical practice were under-represented and the amount of evidence may appear insufficient, or even contradictory to other studies.
- Patients were considered for inclusion only after coronary angiography was performed: therefore conclusions from these trials cannot be extended to patients with unknown coronary anatomy.
- Crossover rates from OMT to revascularization were high and much higher than initially expected, suggesting that revascularization was merely deferred in 33–42% of patients randomized to a conservative approach.
- Documented ischaemia was not mandatory for enrolment in COURAGE or in BARI 2D. Many patients with severe ischaemia—and, as such, considered to be at higher risk—were not randomized in the study.
- The rapid evolution of revascularization techniques (e.g. DES for PCI and arterial grafts for CABG) and antiplatelet, anticoagulant, lipid-lowering and anti-ischaemic drugs render many of the studies obsolete by contemporary standards or difficult to interpret (e.g. stents used were mostly BMS).
- OMT was particularly well carried out in these trials (not reflecting current practice), which emphasizes the need to educate physicians in clinical practice about the necessity and the scope of OMT.
- COURAGE and BARI 2D failed to meet the statistical endpoint of superiority and, as such, were neutral trials demonstrating that an initial approach of intervention was neutral upon death or MI.
- Several meta-analyses of randomized studies have shown divergent results on hard outcomes, as have registries with propensity analyses.

8.3.2.3 Overall interpretation

In low-risk, stable CAD patients, after an ischaemic documentation and a careful clinical and angiographic selection, the strategy of initial OMT is safe and should be the default approach. When a period of OMT has not been adequately conducted, cardiologists and surgeons should be more conservative when making a decision over revascularization, especially in case of high-risk comorbidities, difficult anatomies, mildly symptomatic patients or in patients without extensive provocable ischaemia. The trials have shown that, despite frequent crossovers to revascularization, the majority of patients remain on OMT alone for the duration of the trial.

When initial OMT has failed and patients remain symptomatic, or when the ischaemic risk appears important, the various options need to be discussed (OMT reinforcement or revascularization). The advantages, limitations and advice from the Heart Team must be fully presented in the discussion with the patient.

The early hazards of revascularization are well known: early peri-procedural MI, stent thrombosis or late restenosis (much reduced now by second-generation DES) after PCI, peri-operative MI, stroke, cognitive dysfunction, surgical wound infection, prolonged hospital stay and rehabilitation after CABG. Potential advantages of an initial revascularization strategy (PCI or CABG) include better relief of symptoms and no significant excess of mortality, fewer drugs, fewer hospital visits and less revascularization within the first year with globally improved QoL. The advantage of revascularization over OMT on symptom relief is, however, blunted over time. OMT is safer in the short term, and as safe as revascularization for mortality up to 5 years in patients meeting the low-risk inclusion criteria of these trials. However, OMT requires larger doses and numbers of medications that may have a direct impact on adherence to treatment, side-effects, drug interactions, QoL and long-term cost to the patient and third party payers.

8.3.2.4 Ongoing studies for management of stable coronary artery disease patients with demonstrated ischaemia

Several studies have suggested that patients with more extensive ischaemia benefit from revascularization—and that this benefit could translate into a long-term survival benefit if ischaemia is severe and reduction of ischaemia is significant. This hypothesis has been poorly investigated prospectively, although the positive randomized trials 'Asymptomatic Cardiac Ischaemia Pilot' (ACIP) and SWISSI II—with subset analyses of the CABG population in BARI 2D, plus the results of PCI in FAME 2—strongly suggest that ischaemia plays a key role in the benefit afforded by revascularization.[25,431,461,480]

The hypothesis of deciding upon an invasive approach *prior* to angiography and not after (as in COURAGE and BARI 2D)—on the basis of documented clinically meaningful ischaemia during stress testing or haemodynamic assessment of stenoses identified at the time of angiography—certainly needs re-evaluation. This hypothesis is currently being evaluated in randomized trials: in the ongoing ISCHEMIA trial, patients are randomized—before coronary angiography—to a conservative OMT strategy or to an invasive strategy when they have documented myocardial ischaemia, the primary endpoint being death or MI.

8.4 Percutaneous coronary intervention vs. coronary artery bypass graft (see web addenda)

8.4.1 Recent data and recommendations

The relative indications for PCI and CABG in SCAD patients have been clearly defined by the recent recommendations.[172,217,481,482] There has been an increasing recognition of the value of the Heart Team in reaching consensus over if, when, and how to revascularize patients. *Figures 6* and *7* show suggested algorithms to help simplify the decision-making process and to possibly avoid the need for systematic discussion of every patient with locally agreed protocols (refer to specific ESC Guidelines on myocardial revascularization for class and LOE concerning the respective indications of PCI and CABG).[172] The Guidelines emphasize the importance of

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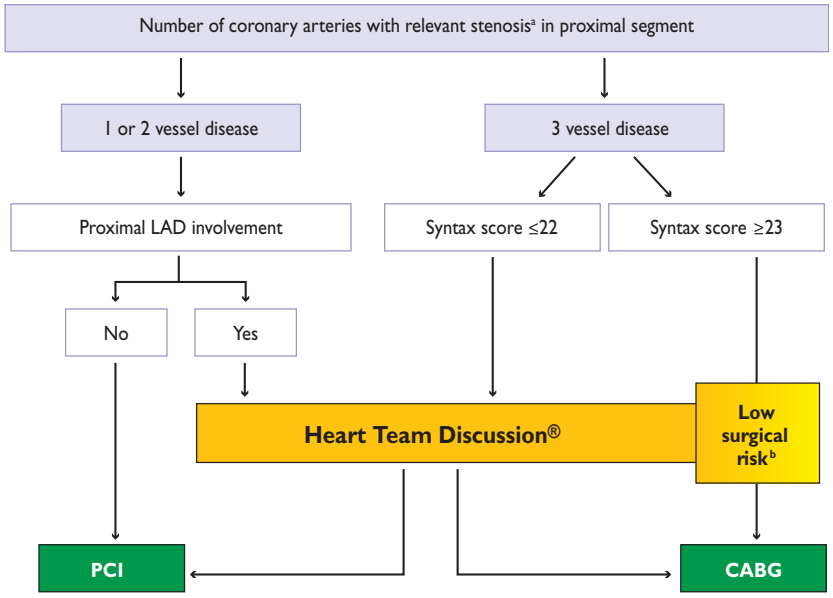

Figure 6 Percutaneous coronary intervention (PCI) or coronary artery bypass graft surgery (CABG) in stable coronary artery disease without left main coronary artery involvement. CABG = coronary artery bypass graft; LAD = left anterior descending; PCI = percutaneous coronary intervention.
[a]>50% stenosis and proof of ischaemia, >90% stenosis in two angiographic views, or FFR = 0.80.
[b]CABG is the preferred option in most patients unless patients co-morbidities or specificities deserve discussion by the heart team. According to local practice (time constraints, workload) direct transfer to CABG may be allowed in these low risk patients, when formal discussion in a multidisciplinary team is not required (adapted from ESC/EACTS Guidelines on Myocardial Revascularization 2010).

OMT in all patients and for both procedures, and the pivotal role of the heart team in most decisions over revascularization in patient with multivessel or left main disease. This is particularly true for patients with three-vessel disease when they present with a syntax score ≥22 or when complete revascularization is not achievable by one technique of revascularization, or when they have diabetes. For these patients, CABG should most often be the preferred option.

In SYNergy between percutaneous coronary intervention with TAXus and cardiac surgery (SYNTAX), 1800 patients with three-vessel or left main coronary artery disease were randomized to undergo CABG or PCI. Publication of the 5-year results of the SYNTAX trial have confirmed the initial findings, with a higher rate of major adverse cardiac or cerebrovascular events at 12 months in the PCI group, in large part because of an increased rate of repeat revascularization.[427,483,484] At 5 years, all-cause death was 13.9% with PCI, against 11.4% with CABG ($P = 0.10$) and cardiac death was 9.0 vs. 5.3% ($P = 0.003$) in favour of CABG. MACE was significantly reduced with CABG also.[484]

Interestingly, this benefit was driven by the upper two tertiles of the SYNTAX score; although PCI and CABG performed as well on all endpoints for SYNTAX scores of 22 or less, there was a clear benefit with CABG at 5 years, especially in patients with scores of 33 or more. In patients with intermediate or high SYNTAX scores, MACE was significantly increased with PCI (intermediate score, 25.8% of the CABG group vs. 36.0% of the PCI group; $P = 0.008$; high score, 26.8 vs. 44.0%; $P < 0.0001$).

These findings are consistent with the survival benefit of CABG reported in several large propensity-matched registries comparing outcome of PCI and CABG.[485–487] Indeed, in a recently published study of 7235 pairs of patients, matched for numerous baseline characteristics, the overall 8-year survival rates were 78.0% for CABG and 71.2% for stenting (HR 0.68; 95% CI 0.64–0.74; $P < 0.001$). For anatomic groups, the HRs ranged from 0.53 ($P < 0.001$) for patients with three-vessel disease involving the proximal LAD to 0.78 ($P = 0.05$) for patients with two-vessel disease but no disease in the LAD artery. A lower risk of death after CABG was observed in all subgroups stratified by a number of baseline risk factors.[487] Most recently, the Asymptomatic atrial fibrillation and Stroke Evaluation in pacemaker patients and the atrial fibrillation Reduction atrial pacing Trial (ASSERT) reported survival in 86 244 CABG and 103 549 PCI propensity-matched patients with two- or three-vessel CAD. At 4-year follow-up there was increased mortality with PCI, compared with CABG. Despite statistical adjustment, this huge registry cannot eliminate confounding variables and the fact that sicker patients may have been assigned to PCI.[488]

In SYNTAX, the results for 705 patients with LMS disease differ from the remaining patients with three-vessel CAD. For these patients, there was no overall difference between CABG and PCI in terms of death (8.4% CABG vs. 7.3% PCI; $P = 0.64$) or MI (4.1 vs. 6.9%; $P = 0.14$) but a higher incidence of stroke with CABG (4 vs. 1.2%; $P = 0.02$). The advantage of CABG was reduced repeat revascularization at 12% vs. 20% for stents ($P = 0.004$).

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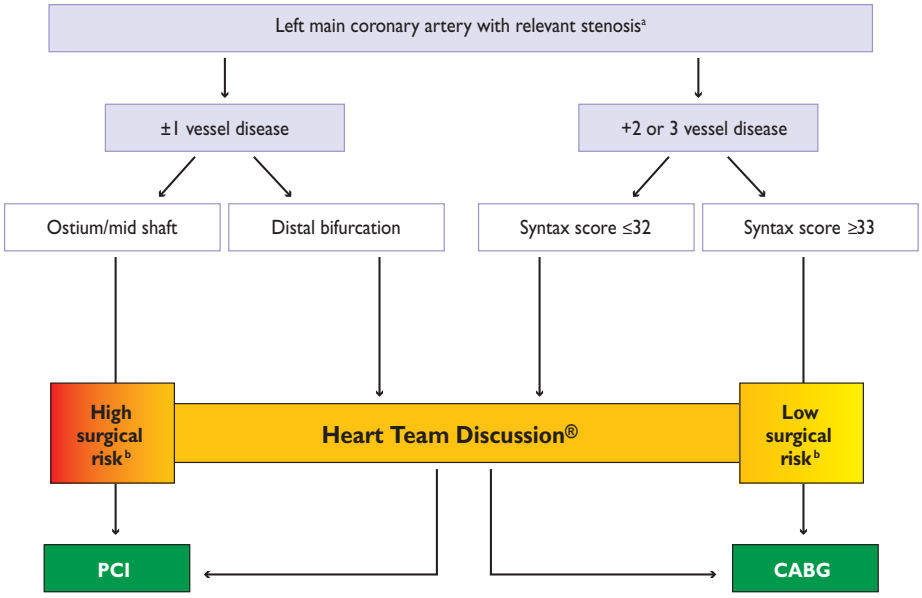

Figure 7 Percutaneous coronary intervention (PCI) or coronary artery bypass graft surgery (CABG) in stable coronary artery disease with left main coronary artery involvement. CABG = coronary artery bypass graft; PCI = percutaneous coronary intervention.
[a]>50% stenosis and proof of ischaemia, >70% stenosis in two angiographic views, or fractional fow reserve = 0.80.
[b]Preferred option in general. According to local practice (time constraints, workload) direct decision may be taken without formal multidisciplinary discussion, but preferably with locally agreed protocols (adapted from ESC/EACTS Guidelines on Myocardial Revascularization 2010).

'Premier of Randomized Comparison of Bypass Surgery vs. Angioplasty Using Sirolimus-Eluting Stent in Patients with Left Main Coronary Artery Disease' (PRECOMBAT), another randomized trial of 600 patients with left main stem (LMS) disease, reported a composite endpoint of death, cerebrovascular accident and MI as 4.7% for CABG and 4.4% for PCI.[489] Furthermore, the incidence of stroke was substantially lower than in SYNTAX and similar for PCI (0.4%) and CABG (0.7%). It should be acknowledged that Left Main SYNTAX was a subgroup analysis and PRECOMBAT was not powered to detect a difference in hard clinical endpoint. Accordingly, further large randomized controlled trials are needed to establish the optimal mode of LM revascularization with this degree of complexity [e.g. the Evaluation of XIENCE PRIME or XIENCE V vs. Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization (EXCEL)].

Meanwhile, angiographic characteristics of the LM disease are key in selection between PCI and CABG (calcifications, ostial/mid/distal, LM size, distal lesions, etc.) and, for at least lower severity of LMS disease, PCI produces at least equivalent—if not superior—outcomes to CABG.

The Design of the Future Revascularization Evaluation in patients with Diabetes mellitus: Optimal management of Multivessel disease (FREEDOM) trial (see chapter 9.2 on diabetes for details)—which demonstrated a significant reduction on the primary ischaemic outcome at 5 years in patients treated with CABG vs. PCI—taking into consideration previous trials, suggests that there is a significant mortality benefit from bypass surgery vs. PCI in diabetic patients with multivessel disease when both options of revascularization are technically feasible,[426] albeit at the price of an increased risk of non-fatal stroke.

The role of hybrid coronary revascularization (*Figure 5*) combining Left Internal Mammary Artery (LIMA)-to-LAD artery grafting and PCI of at least one non-LAD artery is evolving and is an option in patients with multivessel disease and technical issues over one of the two techniques of revascularization, comorbidities, prior history of revascularization with limitations in graft conduits or access for PCI (e.g. occlusion). It allows complete revascularization with the advantages of both modes of revascularization. No randomized study, and only small series of patients have so far been published, precluding any firm recommendation.

8.4.2 Target populations of the randomized studies (see web addenda)

Over the last two decades there have been approximately 20 trials of PCI vs. CABG, which have consistently reported no overall difference in survival between the two interventional techniques, possibly related to the low risk of the populations studied.[490]

In contrast, several propensity-matched registries have consistently demonstrated a survival benefit of CABG after intervention, accompanied by a marked reduction in the need for repeat intervention, although it may still be susceptible to confounding factors.[485–487]

8.5 Scores and decisions (see web addenda)

8.5.1 Scores (see web addenda)

Interventional and surgical scores have been developed to evaluate the risk of the different revascularization strategies.[428,491] Although

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we lack prospective validation of these scores in randomized studies comparing CABG to PCI, the recommendations—and now the practice—are heavily based on these scores as tools for decision-making in individual patients.

8.5.2 Appropriate utilization of revascularization (see web addenda)

Appropriateness criteria are based upon expert consensus as to when a procedure is appropriate.[492] This is, however, an important and complex area of concern as the cost of imaging and revascularization comes under increasing but appropriate scrutiny.

9. Special groups or considerations

9.1 Women (see web addenda)

Coronary artery disease develops 5–10 years later in women than in men. Recent studies indicate that the decline in mortality from CAD does not extend to younger women, in whom it has remained constant.[493] CVD guidelines in general are based on research conducted primarily in men, the mean percentage of women enrolled in clinical trials since 2006 being 30%.[494] CVD risk factors in women and men are the same, although their distribution differs over time and between regions. Stable angina is the most common initial presentation of CAD in women.[495] There is a widespread understanding that women with CAD present with symptoms that are different from those in men. Some of this is due to women presenting at older ages and symptoms becoming less specific with advancing age. Several studies have indicated gender-related differences in the care of both acute and chronic CAD, in part related to differences in presentation and pathophysiology. Compared with men, women have higher rates of procedural complication, including mortality, stroke and vascular complications. Women also have higher complication rates following CABG but, although the numbers of women included in trials are limited, results do not indicate gender-related differences in outcome.[496,497] Nonetheless, it may be prudent to adopt a more conservative approach in undertaking PCI and CABG in women.

Probably the most important difference between CAD in men and women is that women, presenting with MI and angina twice as often as men, have no significant obstructive CAD.[23,480] (see section 6.7.1 on microvascular angina).[498] However, the notion that these women have 'normal' coronary arteries should be reconsidered in light of the IVUS sub-study within the Women's Ischemia Syndrome Evaluation (WISE) showing that, among a sample of 100 such women, ~80% had definite coronary atherosclerosis that was concealed by positive remodelling.[499] Until sufficient trial-based evidence is available, women with chest pain and no obstructive coronary disease should be screened for CVD risk factors and treated according to risk stratification, as described in CVD prevention Guidelines,[37] supplemented by individualized symptomatic treatment for angina (see sections 7.5.1 and 7.5.2 on treatment of microvascular and vasospastic angina). At present HRT is not recommended for primary or secondary prevention of CVD.

9.2 Patients with diabetes (see web addenda)

Mortality due to CVD is increased three-fold in diabetic men and two- to five-fold in diabetic women, compared with age- and sex-matched non-diabetic persons. A target HbA1c $<7\%$ (<53 mmol/mol) and target blood pressure $<140/85$ mmHg are recommended in recent European Guidelines on CVD prevention. The high prevalence of significant CAD and prohibitively high cardiovascular mortality may suggest the usefulness of routine screening extended to asymptomatic patients. In the absence of outcome trials confirming a clinical benefit, this strategy is not recommended. Coronary artery revascularization of diabetics remains a challenge. The decision to use either PCI or CABG as preferred mode of revascularization should be based on anatomical factors, together with clinical factors and other logistical or local factors (see chapter 8 and *Figure 6*). As a rule, PCI is recommended in diabetic patient with single-vessel disease. Conversely, given the results of the FREEDOM trial, CABG is recommended in diabetic patients with multivessel disease after discussion in a Heart Team meeting.

9.3 Patients with chronic kidney disease (see web addenda)

Chronic kidney disease is a risk factor for—and strongly associated with—CAD and has a major impact on outcomes and therapeutic decisions. The use of drugs and iodinated contrast agents is exposes patients to more complications. This is also a group of patients poorly explored in clinical trials, with limited strong evidence based medicine.

9.4 Elderly patients (see web addenda)

This population is specific in many ways:

(1) Higher prevalence of comorbidities.
(2) Population is usually undertreated and under-represented in clinical trials.
(3) Difficult diagnosis due to atypical symptoms and difficulties in performing stress testing.
(4) Patients are more often referred to PCI than CABG but age should not be the sole criterion for the choice of type of revascularization.
(5) Higher risk of complications during and after coronary revascularization.

9.5 The patient after revascularization (see web addenda)

Therapy and secondary prevention should be initiated during hospitalization, when patients are highly motivated. Follow-up strategies should focus on the assessment of the patient's symptoms, functional status and secondary prevention, and not only on the detection of restenosis or graft occlusion. Recommendations are given below in *Table 34*.

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Table 34 Follow-up of revascularized stable coronary artery disease patients

Recommendations	Class [a]	Level [b]	Ref. [c]
General measures			
It is recommended that all revascularized patients receive a secondary prevention and be scheduled for follow-up visit.	I	A	500
It is recommended to instruct patients before discharge about return to work and reuptake of full activities. Patients have to be advised to seek immediate medical contact if symptoms (re-) occur.	I	C	-
Antiplatelet therapy			
SAPT, usually aspirin, is recommended indefinitely.	I	A	172, 333, 501-503
DAPT is indicated after BMS for at least 1 month.	I	A	501, 502, 504, 505
DAPT is indicated for 6 to 12 months after 2nd generation DES.	I	B	
DAPT may be used for more than 1 year in patients at high ischaemic risk (e.g. stent thrombosis, recurrent ACS on DAPT, post MI/diffuse CAD) and low bleeding risk.	IIb	B	334, 504, 505
DAPT for 1 to 3 months may be used in patients at high bleeding risk or with undeferrable surgery or concomitant anticoagulant treatment.	IIb	C	-
Imaging management			
In symptomatic patients, stress imaging (stress echocardiography, MRI or MPS) is indicated rather than stress ECG.	I	C	-
In patients with low risk ischaemic findings (<5% of the myocardium) at stress imaging, optimal medical therapy is recommended.	I	C	-
In patients with high risk ischaemic findings (>10% of myocardium) at stress imaging, coronary angiography is recommended.	I	C	-
Late (6 months) stress imaging test after revascularization may be considered to detect patients with restenosis after stenting or graft occlusion irrespective of symptoms[d].	IIb	C	-
After high risk PCIs (e.g. LM disease) late (3-12 months) control angiography may be considered, irrespective of symptoms.	IIb	C	-
Systematic control angiography, early or late after PCI, is not recommended.	III	C	-

ACS = acute coronary syndrome; BMS = bare metal stents; CABG = coronary artery bypass graft surgery; DAPT = dual antiplatelet therapy; DES = drug eluting stents; ECG = electrocardiogram; LM = left main; MPS = myocardial perfusion scintigraphy; MRI = magnetic resonance imaging; PCI = percutaneous coronary intervention; SAPT = single antiplatelet therapy.

[a] Class of recommendation.

[b] Level of evidence.

[c] Reference(s) supporting levels of evidence.

[d] Specific patient subsets indicated for early stress testing:

– patients with safety critical professions (e.g. pilots, drivers, divers) and competitive athletes.

– patients who would like to engage in activities for, which high oxygen consumption is required.

9.6 Repeat revascularization of the patient with prior coronary artery bypass graft revascularization (see web addenda)

Repeat revascularization in the patient who has undergone prior CABG poses a clinical challenge.[506–508] Considerations in determining the preferred modality of revascularization include the age of patients, co-morbidities and diffuseness of coronary disease, as well as the potential for damage to patent grafts, intraluminal embolization in saphenous vein grafts, lack of suitable arterial and venous conduits and instability of a graft-independent circulation. PCI may be preferred in patients with discrete lesions in grafts and preserved LV function or accessible native vessel disease. Repeat bypass surgery may be preferred when the vessels are unsuitable for PCI and when there are good distal vessel targets for bypass graft placement.

The use of distal embolic protection devices is recommended in saphenous vein graft interventions. Any revascularization strategy needs to be accompanied by optimizing medical therapy with anti-anginal drugs and risk factor reduction.

9.7 Chronic total occlusions (see web addenda)

Chronic total occlusions (CTO) are identified in 15–30% of all patients referred for coronary angiography. A worse prognosis has been attached to chronic total occlusions. Revascularization needs to be discussed in patients with symptoms of occlusion or large ischaemic areas. Percutaneous coronary intervention (PCI) of CTOs is technically challenging and requires familiarity with advanced techniques and specialized equipment. Surgical treatment, with the implantation of a distal bypass graft, is also a valid option for discussion.

9.8 Refractory angina (see web addenda)

The term 'refractory angina' is defined as "a chronic condition caused by clinically established reversible myocardial ischaemia in the presence of CAD, which cannot be adequately controlled by a combination of medical therapy, angioplasty or coronary artery bypass graft". For this patient group, a number of treatment options has

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Table 35 Treatment options in refractory angina

Recommendations	Class [a]	Level [b]	Ref. [c]
EECP should be considered for symptom relief in patients with invalidating angina refractory to optimal medical and revascularization strategies.	IIa	B	509, 510
TENS may be considered to ameliorate symptoms of invalidating angina refractory to optimal medical and revascularization strategies.	IIb	C	-
SCS may be considered to ameliorate symptoms and quality of life in patients with invalidating angina refractory to optimal medical and revascularization strategies.	IIb	B	511, 512, 513
TMR is not indicated in patients with invalidating angina refractory to optimal medical and revascularization strategies.	III	A	514

EECP = enhanced external counterpulsation; TENS = transcutaneous electrical nerve stimulation; TMR = transmyocardial revascularization; SC = spinal cord stimulation.
[a] Class of recommendation.
[b] Level of evidence.
[c] Reference(s) supporting levels of evidence.

emerged, including some new pharmacological options (see section 7.1.3.2 on drugs) and non-pharmacological treatments (see *Table 35*).

Among non-pharmacological treatments, enhanced external counterpulsation therapy and neurostimulatory techniques have shown that they can ameliorate symptoms and improve quality of life, although convincing evidence regarding reduction in both ischaemia burden and mortality is still lacking. Conversely, transmyocardial or percutaneous myocardial revascularization have been abandoned because they are ineffective.

9.9 Primary care (see web addenda)

Primary care physicians have an important role in the identification and management of patients with SCAD. In particular:

- identifying those patients presenting with symptoms of possible SCAD that requires further evaluation and investigation
- identifying those at increased risk of developing SCAD and ensuring that modifiable risk factors are actively managed, with lifestyle and therapeutic interventions, in order to reduce their future risk
- ensuring that those with SCAD are aware of the benefits, both in respect of symptom control and prognosis, of optimal medical therapy and, in appropriate cases, the benefits of percutaneous intervention or surgery
- establishing a systematic approach to the follow-up of patients with SCAD, at appropriate intervals, for the primary care physician to re-appraise the patient's clinical symptoms, medication and risk factors.

9.10 Gaps in evidence (see web addenda)

These guidelines suffer from limitations inherent in the evidence available, uncertainties on the best imaging modalities, on what is the best modern pharmacologic approach and on what is the real benefit from myocardial revascularization.

The CME text '2013 ESC Guidelines on the management of stable coronary artery disease' is accredited by the European Board for Accreditation in Cardiology (EBAC). EBAC works according to the quality standards of the European Accreditation Council for Continuing Medical Education (EACCME), which is an institution of the European Union of Medical Specialists (UEMS). In compliance with EBAC/EACCME Guidelines, all authors participating in this programme have disclosed any potential conflicts of interest that might cause a bias in the article. The Organizing Committee is responsible for ensuring that all potential conflicts of interest relevant to the programme are declared to the participants prior to the CME activities.

CME questions for this article are available at: European Heart Journal http://www.oxforde-learning.com/eurheartj and European Society of Cardiology http://www.escardio.org/guidelines.

References

1. Hamm CW, Bassand JP, Agewall S, Bax J, Boersma E, Bueno H, Caso P, Dudek D, Gielen S, Huber K, Ohman M, Petrie MC, Sonntag F, Uva MS, Storey RF, Wijns W, Zahger D, Bax JJ, Auricchio A, Baumgartner H, Ceconi C, Dean V, Deaton C, Fagard R, Funck-Brentano C, Hasdai D, Hoes A, Knuuti J, Kolh P, McDonagh T, Moulin C, Poldermans D, Popescu BA, Reiner Z, Sechtem U, Sirnes PA, Torbicki A, Vahanian A, Windecker S, Achenbach S, Badimon L, Bertrand M, Botker HE, Collet JP, Crea F, Danchin N, Falk E, Goudevenos J, Gulba D, Hambrecht R, Herrmann J, Kastrati A, Kjeldsen K, Kristensen SD, Lancellotti P, Mehilli J, Merkely B, Montalescot G, Neumann FJ, Neyses L, Perk J, Roffi M, Romeo F, Ruda M, Swahn E, Valgimigli M, Vrints CJ, Widimsky P. ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: The Task Force for the management of acute coronary syndromes (ACS) in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J* 2011;**32**:2999–3054.
2. Greenland P, Alpert JS, Beller GA, Benjamin EJ, Budoff MJ, Fayad ZA, Foster E, Hlatky MA, Hodgson JM, Kushner FG, Lauer MS, Shaw LJ, Smith SC Jr., Taylor AJ, Weintraub WS, Wenger NK, Jacobs AK, Anderson JL, Albert N, Buller CE, Creager MA, Ettinger SM, Guyton RA, Halperin JL, Hochman JS, Nishimura R, Ohman EM, Page RL, Stevenson WG, Tarkington LG, Yancy CW. 2010 ACCF/AHA guideline for assessment of cardiovascular risk in asymptomatic adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2010;**56**:e50–e103.
3. Fox K, Garcia MA, Ardissino D, Buszman P, Camici PG, Crea F, Daly C, De Backer G, Hjemdahl P, Lopez-Sendon J, Marco J, Morais J, Pepper J, Sechtem U, Simoons M, Thygesen K, Priori SG, Blanc JJ, Budaj A, Camm J, Dean V, Deckers J, Dickstein K, Lekakis J, McGregor K, Metra M, Morais J, Osterspey A, Tamargo J, Zamorano JL. Guidelines on the management of stable angina pectoris: executive summary: The Task Force on the Management of Stable Angina Pectoris of the European Society of Cardiology. *Eur Heart J* 2006;**27**:1341–1381.
4. Gibbons RJ, Chatterjee K, Daley J, Douglas JS, Fihn SD, Gardin JM, Grunwald MA, Levy D, Lytle BW, O'Rourke RA, Schafer WP, Williams SV, Ritchie JL, Cheitlin MD, Eagle KA, Gardner TJ, Garson A Jr. Russell RO, Ryan TJ, Smith SC Jr. ACC/AHA/ACP-ASIM guidelines for the management of patients with chronic stable angina: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Management of Patients With Chronic Stable Angina). *J Am Coll Cardiol* 1999;**33**:2092–2197.

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5. Campeau L. The Canadian Cardiovascular Society grading of angina pectoris revisited 30 years later. *Can J Cardiol* 2002;**18**:371–379.
6. Anderson JL, Adams CD, Antman EM, Bridges CR, Califf RM, Casey DE Jr., Chavey WE 2nd, Fesmire FM, Hochman JS, Levin TN, Lincoff AM, Peterson ED, Theroux P, Wenger NK, Wright RS, Smith SC Jr., Jacobs AK, Halperin JL, Hunt SA, Krumholz HM, Kushner FG, Lytle BW, Nishimura R, Ornato JP, Page RL, Riegel B. ACC/AHA 2007 guidelines for the management of patients with unstable angina/non-ST-Elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines for the Management of Patients With Unstable Angina/Non-ST-Elevation Myocardial Infarction) developed in collaboration with the American College of Emergency Physicians, the Society for Cardiovascular Angiography and Interventions, and the Society of Thoracic Surgeons endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation and the Society for Academic Emergency Medicine. *J Am Coll Cardiol* 2007;**50**:e1–e157.
7. Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD. Third universal definition of myocardial infarction. *Eur Heart J* 2012;**33**:2551–2567.
8. Ndrepepa G, Braun S, Mehilli J, Birkmeier KA, Byrne RA, Ott I, Hosl K, Schulz S, Fusaro M, Pache J, Hausleiter J, Laugwitz KL, Massberg S, Seyfarth M, Schomig A, Kastrati A. Prognostic value of sensitive troponin T in patients with stable and unstable angina and undetectable conventional troponin. *Am Heart J* 2011;**161**:68–75.
9. Omland T, de Lemos JA, Sabatine MS, Christophi CA, Rice MM, Jablonski KA, Tjora S, Domanski MJ, Gersh BJ, Rouleau JL, Pfeffer MA, Braunwald E. A sensitive cardiac troponin T assay in stable coronary artery disease. *N Eng J Med* 2009;**361**:2538–2547.
10. Crea F. Chronic ischaemic heart disease. In. *ESC textbook of cardiology*. Oxford: Oxford University Press; 2010.
11. Crea F, Pupita G, Galassi AR, el-Tamimi H, Kaski JC, Davies G, Maseri A. Role of adenosine in pathogenesis of anginal pain. *Circulation* 1990;**81**:164–172.
12. Rose GA, Blackburn H. Cardiovascular survey methods. *Monogr Ser World Health Organ* 1968;**56**:1–188.
13. National Institutes of Health NH, Lung, and Blood Institute. *Morbidity & Mortality: 2012 Chart Book on Cardiovascular, Lung, and Blood Diseases*. Bethesda, MD: National Heart, Lung, and Blood Institute; 2012.
14. Reis SE, Holubkov R, Conrad Smith AJ, Kelsey SF, Sharaf BL, Reichek N, Rogers WJ, Merz CN, Sopko G, Pepine CJ. Coronary microvascular dysfunction is highly prevalent in women with chest pain in the absence of coronary artery disease: results from the NHLBI WISE study. *Am Heart J* 2001;**141**:735–741.
15. Han SH, Bae JH, Holmes DR Jr., Lennon RJ, Eeckhout E, Barsness GW, Rihal CS, Lerman A. Sex differences in atheroma burden and endothelial function in patients with early coronary atherosclerosis. *Eur Heart J* 2008;**29**:1359–1369.
16. Hemingway H, McCallum A, Shipley M, Manderbacka K, Martikainen P, Keskimaki I. Incidence and prognostic implications of stable angina pectoris among women and men. *JAMA* 2006;**295**:1404–1411.
17. Ducimetiere P, Ruidavets JB, Montaye M, Haas B, Yarnell J. Five-year incidence of angina pectoris and other forms of coronary heart disease in healthy men aged 50–59 in France and Northern Ireland: the Prospective Epidemiological Study of Myocardial Infarction (PRIME) Study. *Int J Epidemiol* 2001;**30**:1057–1062.
18. Roger VL, Go AS, Lloyd-Jones DM, Benjamin EJ, Berry JD, Borden WB, Bravata DM, Dai S, Ford ES, Fox CS, Fullerton HJ, Gillespie C, Hailpern SM, Heit JA, Howard VJ, Kissela BM, Kittner SJ, Lackland DT, Lichtman JH, Lisabeth LD, Makuc DM, Marcus GM, Marelli A, Matchar DB, Moy CS, Mozaffarian D, Mussolino ME, Nichol G, Paynter NP, Soliman EZ, Sorlie PD, Sotoodehnia N, Turan TN, Virani SS, Wong ND, Woo D, Turner MB. Heart disease and stroke statistics: 2012 update: a report from the american heart association. *Circulation* 2012;**125**:e2–e220.
19. Ong P, Athanasiadis A, Borgulya G, Mahrholdt H, Kaski JC, Sechtem U. High prevalence of a pathological response to acetylcholine testing in patients with stable angina pectoris and unobstructed coronary arteries. The ACOVA Study (Abnormal COronary VAsomotion in patients with stable angina and unobstructed coronary arteries). *J Am Coll Cardiol* 2012;**59**:655–662.
20. Kitta Y, Obata JE, Nakamura T, Hirano M, Kodama Y, Fujioka D, Saito Y, Kawabata K, Sano K, Kobayashi T, Yano T, Nakamura K, Kugiyama K. Persistent impairment of endothelial vasomotor function has a negative impact on outcome in patients with coronary artery disease. *J Am Coll Cardiol* 2009;**53**:323–330.
21. Gulati M, Cooper-DeHoff RM, McClure C, Johnson BD, Shaw LJ, Handberg EM, Zineh I, Kelsey SF, Arnsdorf MF, Black HR, Pepine CJ, Merz CN. Adverse cardiovascular outcomes in women with nonobstructive coronary artery disease: a report from the Women's Ischemia Syndrome Evaluation Study and the St James Women Take Heart Project. *Arch Intern Med* 2009;**169**843–850.
22. Jespersen L, Hvelplund A, Abildstrom SZ, Pedersen F, Galatius S, Madsen JK, Jorgensen E, Kelbaek H, Prescott E. Stable angina pectoris with no obstructive coronary artery disease is associated with increased risks of major adverse cardiovascular events. *Eur Heart J* 2012;**33**:734–744.
23. Boden WE, O'Rourke RA, Teo KK, Hartigan PM, Maron DJ, Kostuk WJ, Knudtson M, Dada M, Casperson P, Harris CL, Chaitman BR, Shaw L, Gosselin G, Nawaz S, Title LM, Gau G, Blaustein AS, Booth DC, Bates ER, Spertus JA, Berman DS, Mancini GB, Weintraub WS. Optimal medical therapy with or without PCI for stable coronary disease. *N Eng J Med* 2007;**356**:1503–1516.
24. Chung SC, Hlatky MA, Faxon D, Ramanathan K, Adler D, Mooradian A, Rihal C, Stone RA, Bromberger JT, Kelsey SF, Brooks MM. The effect of age on clinical outcomes and health status BARI 2D (Bypass Angioplasty Revascularization Investigation in Type 2 Diabetes). *J Am Coll Cardiol* 2011;**58**:810–819.
25. Frye RL, August P, Brooks MM, Hardison RM, Kelsey SF, MacGregor JM, Orchard TJ, Chaitman BR, Genuth SM, Goldberg SH, Hlatky MA, Jones TL, Molitch ME, Nesto RW, Sako EY, Sobel BE. A randomized trial of therapies for type 2 diabetes and coronary artery disease. *N Eng J Med* 2009;**360**:2503–2515.
26. Henderson RA, Pocock SJ, Clayton TC, Knight R, Fox KA, Julian DG, Chamberlain DA. Seven-year outcome in the RITA-2 trial: coronary angioplasty versus medical therapy. *J Am Coll Cardiol* 2003;**42**:1161–1170.
27. Poole-Wilson PA, Lubsen J, Kirwan BA, van Dalen FJ, Wagener G, Danchin N, Just H, Fox KA, Pocock SJ, Clayton TC, Motro M, Parker JD, Bourassa MG, Dart AM, Hildebrandt P, Hjalmarson A, Kragten JA, Molhoek GP, Otterstad JE, Seabra-Gomes R, Soler-Soler J, Weber S. Effect of long-acting nifedipine on mortality and cardiovascular morbidity in patients with stable angina requiring treatment (ACTION trial): randomised controlled trial. *Lancet* 2004;**364**:849–857.
28. Steg PG, Greenlaw N, Tardif JC, Tendera M, Ford I, Kaab S, Abergel H, Fox KM, Ferrari R. Women and men with stable coronary artery disease have similar clinical outcomes: insights from the international prospective CLARIFY registry. *Eur Heart J* 2012;**33**:2831–2840.
29. Daly CA, De Stavola B, Sendon JL, Tavazzi L, Boersma E, Clemens F, Danchin N, Delahaye F, Gitt A, Julian D, Mulcahy D, Ruzyllo W, Thygesen K, Verheugt F, Fox KM. Predicting prognosis in stable angina: results from the Euro heart survey of stable angina: prospective observational study. *BMJ* 2006;**332**:262–267.
30. Steg PG, Bhatt DL, Wilson PW, D'Agostino R Sr., Ohman EM, Rother J, Liau CS, Hirsch AT, Mas JL, Ikeda Y, Pencina MJ, Goto S. One-year cardiovascular event rates in outpatients with atherothrombosis. *JAMA* 2007;**297**:1197–1206.
31. Bayturan O, Kapadia S, Nicholls SJ, Tuzcu EM, Shao M, Uno K, Shreevatsa A, Lavoie AJ, Wolski K, Schoenhagen P, Nissen SE. Clinical predictors of plaque progression despite very low levels of low-density lipoprotein cholesterol. *J Am Coll Cardiol* 2010;**55**:2736–2742.
32. Chhatriwalla AK, Nicholls SJ, Wang TH, Wolski K, Sipahi I, Crowe T, Schoenhagen P, Kapadia S, Tuzcu EM, Nissen SE. Low levels of low-density lipoprotein cholesterol and blood pressure and progression of coronary atherosclerosis. *J Am Coll Cardiol* 2009;**53**:1110–1115.
33. Kronmal RA, McClelland RL, Detrano R, Shea S, Lima JA, Cushman M, Bild DE, Burke GL. Risk factors for the progression of coronary artery calcification in asymptomatic subjects: results from the Multi-Ethnic Study of Atherosclerosis (MESA). *Circulation* 2007;**115**:2722–2730.
34. Nicholls SJ, Hsu A, Wolski K, Hu B, Bayturan O, Lavoie A, Uno K, Tuzcu EM, Nissen SE. Intravascular ultrasound-derived measures of coronary atherosclerotic plaque burden and clinical outcome. *J Am Coll Cardiol* 2010;**55**:2399–2407.
35. Pekkanen J, Linn S, Heiss G, Suchindran CM, Leon A, Rifkind BM, Tyroler HA. Ten-year mortality from cardiovascular disease in relation to cholesterol level among men with and without preexisting cardiovascular disease. *N Eng J Med* 1990;**322**:1700–1707.
36. Bayturan O, Tuzcu EM, Uno K, Lavoie AJ, Hu T, Shreevatsa A, Wolski K, Schoenhagen P, Kapadia S, Nissen SE, Nicholls SJ. Comparison of rates of progression of coronary atherosclerosis in patients with diabetes mellitus versus those with the metabolic syndrome. *Am J Cardiol* 2010;**105**:1735–1739.
37. Perk J, De Backer G, Gohlke H, Graham I, Reiner Z, Verschuren M, Albus C, Benlian P, Boysen G, Cifkova R, Deaton C, Ebrahim S, Fisher M, Germano G, Hobbs R, Hoes A, Karadeniz S, Mezzani A, Prescott E, Ryden L, Scherer M, Syvanne M, Scholte Op Reimer WJ, Vrints C, Wood D, Zamorano JL, Zannad F, Cooney MT, Bax J, Baumgartner H, Ceconi C, Dean V, Fagard R, Funck-Brentano C, Hasdai D, Kirchhof P, Knuuti J, Kolh P, McDonagh T, Moulin C, Popescu BA, Sechtem U, Sirnes PA, Tendera M, Torbicki A, Vahanian A, Windecker S, Aboyans V, Ezquerra EA, Baigent C, Brotons C, Burell G, Ceriello A, De Sutter J, Deckers J, Del Prato S, Diener HC, Fitzsimons D, Fras Z, Hambrecht R, Jankowski P, Keil U, Kirby M, Larsen ML, Mancia G, Manolis AJ, McMurray J, Pajak A, Parkhomenko A, Rallidis L, Rigo F, Rocha E, Ruilope LM, van der Velde E, Vanuzzo D, Viigimaa M, Volpe M, Wiklund O, Wolpert C. European Guidelines on cardiovascular disease prevention in clinical practice (version 2012): The Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts) * Developed with the special contribution of the European Association

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for Cardiovascular Prevention & Rehabilitation (EACPR). *Eur Heart J* 2012;**33**:1635–1701.
38. Frey P, Waters DD, DeMicco DA, Breazna A, Samuels L, Pipe A, Wun CC, Benowitz NL. Impact of smoking on cardiovascular events in patients with coronary disease receiving contemporary medical therapy (from the Treating to New Targets [TNT] and the Incremental Decrease in End Points Through Aggressive Lipid Lowering [IDEAL] trials). *Am J Cardiol* 2011;**107**:145–150.
39. Otaki Y, Gransar H, Berman DS, Cheng VY, Dey D, Lin FY, Achenbach S, Al-Mallah M, Budoff MJ, Cademartiri F, Callister TQ, Chang HJ, Chinnaiyan K, Chow BJ, Delago A, Hadamitzky M, Hausleiter J, Kaufmann P, Maffei E, Raff G, Shaw LJ, Villines TC, Dunning A, Min JK. Impact of family history of coronary artery disease in young individuals (from the CONFIRM registry). *Am J Cardiol* 2013;**111**:1081–1086.
40. Nicholls SJ, Ballantyne CM, Barter PJ, Chapman MJ, Erbel RM, Libby P, Raichlen JS, Uno K, Borgman M, Wolski K, Nissen SE. Effect of two intensive statin regimens on progression of coronary disease. *N Eng J Med* 2011;**365**:2078–2087.
41. Mock MB, Ringqvist I, Fisher LD, Davis KB, Chaitman BR, Kouchoukos NT, Kaiser GC, Alderman E, Ryan TJ, Russell RO Jr., Mullin S, Fray D, Killip T 3rd. Survival of medically treated patients in the coronary artery surgery study (CASS) registry. *Circulation* 1982;**66**:562–568.
42. Harris PJ, Harrell FE Jr., Lee KL, Behar VS, Rosati RA. Survival in medically treated coronary artery disease. *Circulation* 1979;**60**:1259–1269.
43. Diaz A, Bourassa MG, Guertin MC, Tardif JC. Long-term prognostic value of resting heart rate in patients with suspected or proven coronary artery disease. *Eur Heart J* 2005;**26**:967–974.
44. Califf RM, Armstrong PW, Carver JR, D'Agostino RB, Strauss WE. 27th Bethesda Conference: matching the intensity of risk factor management with the hazard for coronary disease events. Task Force 5. Stratification of patients into high, medium and low risk subgroups for purposes of risk factor management. *J Am Coll Cardiol* 1996;**27**:1007–1019.
45. Califf RM, Mark DB, Harrell FE Jr., Hlatky MA, Lee KL, Rosati RA, Pryor DB. Importance of clinical measures of ischemia in the prognosis of patients with documented coronary artery disease. *J Am Coll Cardiol* 1988;**11**:20–26.
46. Ladwig KH, Roll G, Breithardt G, Budde T, Borggrefe M. Post-infarction depression and incomplete recovery 6 months after acute myocardial infarction. *Lancet* 1994;**343**:20–23.
47. Frasure-Smith N, Lesperance F, Talajic M. Depression following myocardial infarction. Impact on 6-month survival. *JAMA* 1993;**270**:1819–1825.
48. Amsterdam EA, Kirk JD, Bluemke DA, Diercks D, Farkouh ME, Garvey JL, Kontos MC, McCord J, Miller TD, Morise A, Newby LK, Ruberg FL, Scordo KA, Thompson PD. Testing of low-risk patients presenting to the emergency department with chest pain: a scientific statement from the American Heart Association. *Circulation* 2010;**122**:1756–1776.
49. Lockie TP, Rolandi MC, Guilcher A, Perera D, De Silva K, Williams R, Asrress KN, Patel K, Plein S, Chowienczyk P, Siebes M, Redwood SR, Marber MS. Synergistic adaptations to exercise in the systemic and coronary circulations that underlie the warm-up angina phenomenon. *Circulation* 2012;**126**:2565–2574.
50. Diamond GA. A clinically relevant classification of chest discomfort. *J Am Coll Cardiol* 1983;**1**:574–575.
51. Lanza GA, Sestito A, Sgueglia GA, Infusino F, Manolfi M, Crea F, Maseri A. Current clinical features, diagnostic assessment and prognostic determinants of patients with variant angina. *Int J Cardiol* 2007;**118**:41–47.
52. Lanza GA, Crea F. Primary coronary microvascular dysfunction: clinical presentation, pathophysiology, and management. *Circulation* 2010;**121**:2317–2325.
53. Campeau L. Letter: Grading of angina pectoris. *Circulation* 1976;**54**:522–523.
54. Boesner S, Haasenritter J, Becker A, Karatolios K, Vaucher P, Gencer B, Herzig L, Heinzel-Gutenbrunner M, Schaefer JR, Abu Hani M, Keller H, Sonnichsen AC, Baum E, Donner-Banzhoff N. Ruling out coronary artery disease in primary care: development and validation of a simple prediction rule. *CMAJ* 2010;**182**:1295–1300.
55. Boesner S, Becker A, Abu Hani M, Keller H, Sonnichsen AC, Haasenritter J, Karatolios K, Schaefer JR, Baum E, Donner-Banzhoff N. Accuracy of symptoms and signs for coronary heart disease assessed in primary care. *Br J Gen Pract* 2010;**60**:e246–e257.
56. Madjid M, Fatemi O. Components of the complete blood count as risk predictors for coronary heart disease: in-depth review and update. *Tex Heart Inst J* 2013;**40**:17–29.
57. Ryden L. ESC Guideline diabetes 2013. *Eur Heart J* 2013.
58. Bartnik M, Ryden L, Malmberg K, Ohrvik J, Pyorala K, Standl E, Ferrari R, Simoons M, Soler-Soler J, Euro Heart Survey I. Oral glucose tolerance test is needed for appropriate classification of glucose regulation in patients with coronary artery disease: a report from the Euro Heart Survey on Diabetes and the Heart. *Heart* 2007;**93**:72–77.
59. Lenzen M, Ryden L, Ohrvik J, Bartnik M, Malmberg K, Scholte Op Reimer W, Simoons ML. Diabetes known or newly detected, but not impaired glucose regulation, has a negative influence on 1-year outcome in patients with coronary artery disease: a report from the Euro Heart Survey on diabetes and the heart. *Eur Heart J* 2006;**27**:2969–2974.
60. Selvin E, Steffes MW, Zhu H, Matsushita K, Wagenknecht L, Pankow J, Coresh J, Brancati FL. Glycated hemoglobin, diabetes, and cardiovascular risk in nondiabetic adults. *N Eng J Med* 2010;**362**:800–811.
61. Gerstein HC, Islam S, Anand S, Almahmeed W, Damasceno A, Dans A, Lang CC, Luna MA, McQueen M, Rangarajan S, Rosengren A, Wang X, Yusuf S. Dysglycaemia and the risk of acute myocardial infarction in multiple ethnic groups: an analysis of 15,780 patients from the INTERHEART study. *Diabetologia* 2010;**53**:2509–2517.
62. Reiner Z, Catapano AL, De Backer G, Graham I, Taskinen MR, Wiklund O, Agewall S, Alegria E, Chapman MJ, Durrington P, Erdine S, Halcox J, Hobbs R, Kjekshus J, Filardi PP, Riccardi G, Storey RF, Wood D, Bax J, Vahanian A, Auricchio A, Baumgartner H, Ceconi C, Dean V, Deaton C, Fagard R, Filippatos G, Funck-Brentano C, Hasdai D, Hoes A, Kearney P, Knuuti J, Kolh P, McDonagh T, Moulin C, Poldermans D, Popescu BA, Sechtem U, Sirnes PA, Tendera M, Torbicki A, Vardas P, Widimsky P, Windecker S, Berkenboom G, De Graaf J, Descamps O, Gotcheva N, Griffith K, Guida GF, Gulec S, Henkin Y, Huber K, Kesaniemi YA, Lekakis J, Manolis AJ, Marques-Vidal P, Masana L, McMurray J, Mendes M, Pagava Z, Pedersen T, Prescott E, Rato Q, Rosano G, Sans S, Stalenhoef A, Tokgozoglu L, Viigimaa M, Wittekoek ME, Zamorano JL. ESC/EAS Guidelines for the management of dyslipidaemias: the Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS). *Eur Heart J* 2011;**32**:1769–1818.
63. Sedlis SP, Jurkovitz CT, Hartigan PM, Goldfarb DS, Lorin JD, Dada M, Maron DJ, Spertus JA, Mancini GB, Teo KK, O'Rourke RA, Boden WE, Weintraub WS. Optimal medical therapy with or without percutaneous coronary intervention for patients with stable coronary artery disease and chronic kidney disease. *Am J Cardiol* 2009;**104**:1647–1653.
64. Reddan DN, Szczech LA, Tuttle RH, Shaw LK, Jones RH, Schwab SJ, Smith MS, Califf RM, Mark DB, Owen WF Jr. Chronic kidney disease, mortality, and treatment strategies among patients with clinically significant coronary artery disease. *J Am Soc Nephrol* 2003;**14**:2373–2380.
65. Di Angelantonio E, Chowdhury R, Sarwar N, Aspelund T, Danesh J, Gudnason V. Chronic kidney disease and risk of major cardiovascular disease and non-vascular mortality: prospective population based cohort study. *BMJ* 2010;**341**:c4986.
66. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron* 1976;**16**:31–41.
67. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. *Ann Intern Med* 1999;**130**:461–470.
68. Inker LA, Schmid CH, Tighiouart H, Eckfeldt JH, Feldman HI, Greene T, Kusek JW, Manzi J, Van Lente F, Zhang YL, Coresh J, Levey AS, Investigators C-E. Estimating glomerular filtration rate from serum creatinine and cystatin C. *N Eng J Med* 2012;**367**:20–29.
69. Hemingway H, Philipson P, Chen R, Fitzpatrick NK, Damant J, Shipley M, Abrams KR, Moreno S, McAllister KS, Palmer S, Kaski JC, Timmis AD, Hingorani AD. Evaluating the quality of research into a single prognostic biomarker: a systematic review and meta-analysis of 83 studies of C-reactive protein in stable coronary artery disease. *PLoS Med* 2010;**7**:e1000286.
70. Sabatine MS, Morrow DA, de Lemos JA, Omland T, Sloan S, Jarolim P, Solomon SD, Pfeffer MA, Braunwald E. Evaluation of multiple biomarkers of cardiovascular stress for risk prediction and guiding medical therapy in patients with stable coronary disease. *Circulation* 2012;**125**:233–240.
71. Sutaria S, Philipson P, Fitzpatrick NK, Abrams K, Moreno SG, Timmis A, Hingorani AD, Hemingway H. Translational phases of evidence in a prognostic biomarker: a systematic review and meta-analysis of natriuretic peptides and the prognosis of stable coronary disease. *Heart* 2012;**98**:615–622.
72. Humphries SE, Drenos F, Ken-Dror G, Talmud PJ. Coronary heart disease risk prediction in the era of genome-wide association studies: current status and what the future holds. *Circulation* 2010;**121**:2235–2248.
73. Reichlin T, Hochholzer W, Bassetti S, Steuer S, Stelzig C, Hartwiger S, Biedert S, Schaub N, Buerge C, Potocki M, Noveanu M, Breidthardt T, Twerenbold R, Winkler K, Bingisser R, Mueller C. Early diagnosis of myocardial infarction with sensitive cardiac troponin assays. *N Eng J Med* 2009;**361**:858–867.
74. Keller T, Zeller T, Peetz D, Tzikas S, Roth A, Czyz E, Bickel C, Baldus S, Warnholtz A, Frohlich M, Sinning CR, Eleftheriadis MS, Wild PS, Schnabel RB, Lubos E, Jachmann N, Genth-Zotz S, Post F, Nicaud V, Tiret L, Lackner KJ, Munzel TF, Blankenberg S. Sensitive troponin I assay in early diagnosis of acute myocardial infarction. *N Eng J Med* 2009;**361**:868–877.
75. da Silveira AD, Ribeiro RA, Rossini AP, Stella SF, Ritta HA, Stein R, Polanczyk CA. Association of anemia with clinical outcomes in stable coronary artery disease. *Coron Artery Dis* 2008;**19**:21–26.

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76. Schwarz PE, Li J, Lindstrom J, Tuomilehto J. Tools for predicting the risk of type 2 diabetes in daily practice. *Horm Metab Res* 2009;**41**:86–97.
77. Di Angelantonio E, Danesh J, Eiriksdottir G, Gudnason V. Renal function and risk of coronary heart disease in general populations: new prospective study and systematic review. *PLoS Med* 2007;**4**:e270.
78. Androulakis A, Aznaouridis KA, Aggeli CJ, Roussakis GN, Michaelides AP, Kartalis AN, Stougiannos PN, Dilaveris PE, Misovoulos PI, Stefanadis CI, Kallikazaros IE. Transient ST-segment depression during paroxysms of atrial fibrillation in otherwise normal individuals: relation with underlying coronary artery disease. *J Am Coll Cardiol* 2007;**50**:1909–1911.
79. Daly C, Norrie J, Murdoch DL, Ford I, Dargie HJ, Fox K. The value of routine non-invasive tests to predict clinical outcome in stable angina. *Eur Heart J* 2003;**24**: 532–540.
80. Douglas PS, Garcia MJ, Haines DE, Lai WW, Manning WJ, Patel AR, Picard MH, Polk DM, Ragosta M, Ward RP, Weiner RB. ACCF/ASE/AHA/ASNC/HFSA/HRS/SCAI/SCCM/SCCT/SCMR 2011 Appropriate Use Criteria for Echocardiography. A Report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, American Society of Echocardiography, American Heart Association, American Society of Nuclear Cardiology, Heart Failure Society of America, Heart Rhythm Society, Society for Cardiovascular Angiography and Interventions, Society of Critical Care Medicine, Society of Cardiovascular Computed Tomography, and Society for Cardiovascular Magnetic Resonance Endorsed by the American College of Chest Physicians. *J Am Coll Cardiol* 2011;**57**:1126–1166.
81. Korcarz CE, Hirsch AT, Bruce C, DeCara JM, Mohler ER, Pogue B, Postley J, Tzou WS, Stein JH. Carotid intima-media thickness testing by non-sonographer clinicians: the office practice assessment of carotid atherosclerosis study. *J Am Soc Echocardiogr* 2008;**21**:117–122.
82. Stein JH, Korcarz CE, Hurst RT, Lonn E, Kendall CB, Mohler ER, Najjar SS, Rembold CM, Post WS, American Society of Echocardiography Carotid Intima-Media Thickness Task F. Use of carotid ultrasound to identify subclinical vascular disease and evaluate cardiovascular disease risk: a consensus statement from the American Society of Echocardiography Carotid Intima-Media Thickness Task Force. Endorsed by the Society for Vascular Medicine. *J Am Soc Echocardiogr* 2008;**21**:93–111.
83. Plichart M, Celermajer DS, Zureik M, Helmer C, Jouven X, Ritchie K, Tzourio C, Ducimetiere P, Empana JP. Carotid intima-media thickness in plaque-free site, carotid plaques and coronary heart disease risk prediction in older adults. The Three-City Study. *Atherosclerosis* 2011;**219**:917–924.
84. O'Mahony MS, Sim MF, Ho SF, Steward JA, Buchalter M, Burr M. Diastolic heart failure in older people. *Age Ageing* 2003;**32**:519–524.
85. Aroesty JM, McKay RG, Heller GV, Royal HD, Als AV, Grossman W. Simultaneous assessment of left ventricular systolic and diastolic dysfunction during pacing-induced ischemia. *Circulation* 1985;**71**:889–900.
86. Shaw LJ, Bugiardini R, Merz CN. Women and ischemic heart disease: evolving knowledge. *J Am Coll Cardiol* 2009;**54**:1561–1575.
87. Hendel RC, Patel MR, Kramer CM, Poon M, Carr JC, Gerstad NA, Gillam LD, Hodgson JM, Kim RJ, Lesser JR, Martin ET, Messer JV, Redberg RF, Rubin GD, Rumsfeld JS, Taylor AJ, Weigold WG, Woodard PK, Brindis RG, Douglas PS, Peterson ED, Wolk MJ, Allen JM. ACCF/ACR/SCCT/SCMR/ASNC/NASCI/SCAI/SIR 2006 appropriateness criteria for cardiac computed tomography and cardiac magnetic resonance imaging: a report of the American College of Cardiology Foundation Quality Strategic Directions Committee Appropriateness Criteria Working Group, American College of Radiology, Society of Cardiovascular Computed Tomography, Society for Cardiovascular Magnetic Resonance, American Society of Nuclear Cardiology, North American Society for Cardiac Imaging, Society for Cardiovascular Angiography and Interventions, and Society of Interventional Radiology. *J Am Coll Cardiol* 2006;**48**:1475–1497.
88. Cohn PF, Fox KM, Daly C. Silent myocardial ischemia. *Circulation* 2003;**108**: 1263–1277.
89. McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Bohm M, Dickstein K, Falk V, Filippatos G, Fonseca C, Gomez-Sanchez MA, Jaarsma T, Kober L, Lip GY, Maggioni AP, Parkhomenko A, Pieske BM, Popescu BA, Ronnevik PK, Rutten FH, Schwitter J, Seferovic P, Stepinska J, Trindade PT, Voors AA, Zannad F, Zeiher A, Bax JJ, Baumgartner H, Ceconi C, Dean V, Deaton C, Fagard R, Funck-Brentano C, Hasdai D, Hoes A, Kirchhof P, Knuuti J, Kolh P, McDonagh T, Moulin C, Reiner Z, Sechtem U, Sirnes PA, Tendera M, Torbicki A, Vahanian A, Windecker S, Bonet LA, Avraamides P, Ben Lamin HA, Brignole M, Coca A, Cowburn P, Dargie H, Elliott P, Flachskampf FA, Guida GF, Hardman S, Iung B, Merkely B, Mueller C, Nanas JN, Nielsen OW, Orn S, Parissis JT, Ponikowski P. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. *Eur Heart J* 2012;**33**:1787–1847.
90. Diamond GA, Forrester JS. Analysis of probability as an aid in the clinical diagnosis of coronary-artery disease. *N Eng J Med* 1979;**300**:1350–1358.
91. Gibbons RJ, Abrams J, Chatterjee K, Daley J, Deedwania PC, Douglas JS, Ferguson TB Jr., Fihn SD, Fraker TD Jr., Gardin JM, O'Rourke RA, Pasternak RC, Williams SV, Alpert JS, Antman EM, Hiratzka LF, Fuster V, Faxon DP, Gregoratos G, Jacobs AK, Smith SC Jr. ACC/AHA 2002 guideline update for the management of patients with chronic stable angina: summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on the Management of Patients With Chronic Stable Angina). *Circulation* 2003;**107**:149–158.
92. Diamond GA, Kaul S. Gone fishing!: on the "real-world" accuracy of computed tomographic coronary angiography: Comment on the "Ontario multidetector computed tomographic coronary angiography study". *Arch Intern Med* 2011;**171**: 1029–1031.
93. Mark DB, Hlatky MA, Harrell FE Jr., Lee KL, Califf RM, Pryor DB. Exercise treadmill score for predicting prognosis in coronary artery disease. *Ann Intern Med* 1987;**106**: 793–800.
94. Froelicher VF, Lehmann KG, Thomas R, Goldman S, Morrison D, Edson R, Lavori P, Myers J, Dennis C, Shabetai R, Do D, Froning J. The electrocardiographic exercise test in a population with reduced workup bias: diagnostic performance, computerized interpretation, and multivariable prediction. Veterans Affairs Cooperative Study in Health Services #016 (QUEXTA) Study Group. Quantitative Exercise Testing and Angiography. *Ann Intern Med* 1998;**128**:965–974.
95. Morise AP, Diamond GA. Comparison of the sensitivity and specificity of exercise electrocardiography in biased and unbiased populations of men and women. *Am Heart J* 1995;**130**:741–747.
96. Heijenbrok-Kal MH, Fleischmann KE, Hunink MG. Stress echocardiography, stress single-photon-emission computed tomography and electron beam computed tomography for the assessment of coronary artery disease: a meta-analysis of diagnostic performance. *Am Heart J* 2007;**154**:415–423.
97. Mc Ardle BA, Dowsley TF, deKemp RA, Wells GA, Beanlands RS. Does rubidium-82 PET have superior accuracy to SPECT perfusion imaging for the diagnosis of obstructive coronary disease?: A systematic review and meta-analysis. *J Am Coll Cardiol* 2012;**60**:1828–1837.
98. de Jong MC, Genders TS, van Geuns RJ, Moelker A, Hunink MG. Diagnostic performance of stress myocardial perfusion imaging for coronary artery disease: a systematic review and meta-analysis. Eur Radiol 2012;**22**:1881–1895.
99. Higgins JP, Williams G, Nagel JS, Higgins JA. Left bundle-branch block artifact on single photon emission computed tomography with technetium Tc 99m (Tc-99m) agents: mechanisms and a method to decrease false-positive interpretations. *Am Heart J* 2006;**152**:619–626.
100. Nandalur KR, Dwamena BA, Choudhri AF, Nandalur MR, Carlos RC. Diagnostic performance of stress cardiac magnetic resonance imaging in the detection of coronary artery disease: a meta-analysis. *J Am Coll Cardiol* 2007;**50**:1343–1353.
101. Hamon M, Fau G, Nee G, Ehtisham J, Morello R. Meta-analysis of the diagnostic performance of stress perfusion cardiovascular magnetic resonance for detection of coronary artery disease. *J Cardiovasc Magn Reson* 2010;**12**:29.
102. Schwitter J, Wacker CM, Wilke N, Al-Saadi N, Sauer E, Huettle K, Schonberg SO, Luchner A, Strohm O, Ahlstrom H, Dill T, Hoebel N, Simor T. MR-IMPACT II: Magnetic Resonance Imaging for Myocardial Perfusion Assessment in Coronary artery disease Trial: perfusion-cardiac magnetic resonance vs. single-photon emission computed tomography for the detection of coronary artery disease: a comparative multicentre, multivendor trial. *Eur Heart J* 2012; **34**(10):775–81
103. Budoff MJ, Dowe D, Jollis JG, Gitter M, Sutherland J, Halamert E, Scherer M, Bellinger R, Martin A, Benton R, Delago A, Min JK. Diagnostic performance of 64-multidetector row coronary computed tomographic angiography for evaluation of coronary artery stenosis in individuals without known coronary artery disease: results from the prospective multicenter ACCURACY (Assessment by Coronary Computed Tomographic Angiography of Individuals Undergoing Invasive Coronary Angiography) trial. *J Am Coll Cardiol* 2008;**52**:1724–1732.
104. Miller JM, Rochitte CE, Dewey M, Arbab-Zadeh A, Niinuma H, Gottlieb I, Paul N, Clouse ME, Shapiro EP, Hoe J, Lardo AC, Bush DE, de Roos A, Cox C, Brinker J, Lima JA. Diagnostic performance of coronary angiography by 64-row CT. *N Eng J Med* 2008;**359**:2324–2336.
105. Meijboom WB, Meijs MF, Schuijf JD, Cramer MJ, Mollet NR, van Mieghem CA, Nieman K, van Werkhoven JM, Pundziute G, Weustink AC, de Vos AM, Pugliese F, Rensing B, Jukema JW, Bax JJ, Prokop M, Doevendans PA, Hunink MG, Krestin GP, de Feyter PJ. Diagnostic accuracy of 64-slice computed tomography coronary angiography: a prospective, multicenter, multivendor study. *J Am Coll Cardiol* 2008;**52**:2135–2144.
106. Jaarsma C, Leiner T, Bekkers SC, Crijns HJ, Wildberger JE, Nagel E, Nelemans PJ, Schalla S. Diagnostic performance of noninvasive myocardial perfusion imaging using single-photon emission computed tomography, cardiac magnetic resonance, and positron emission tomography imaging for the detection of obstructive coronary artery disease: a meta-analysis. *J Am Coll Cardiol* 2012;**59**:1719–1728.

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107. National Institute for Health and Clinical Excellence. (2010) *Chest pain of recent onset*. (Clinical guideline 95.). **http://guidance.nice.org.uk/CG95., http://www.nice.org.uk/guidance/CG95 (7 August 2013)**.
108. Genders TS, Steyerberg EW, Alkadhi H, Leschka S, Desbiolles L, Nieman K, Galema TW, Meijboom WB, Mollet NR, de Feyter PJ, Cademartiri F, Maffei E, Dewey M, Zimmermann E, Laule M, Pugliese F, Barbagallo R, Sinitsyn V, Bogaert J, Goetschalckx K, Schoepf UJ, Rowe GW, Schuijf JD, Bax JJ, de Graaf FR, Knuuti J, Kajander S, van Mieghem CA, Meijs MF, Cramer MJ, Gopalan D, Feuchtner G, Friedrich G, Krestin GP, Hunink MG. A clinical prediction rule for the diagnosis of coronary artery disease: validation, updating, and extension. *Eur Heart J* 2011;**32**:1316–1330.
109. Miller TD, Roger VL, Hodge DO, Gibbons RJ. A simple clinical score accurately predicts outcome in a community-based population undergoing stress testing. *Am J Med* 2005;**118**:866–872.
110. Tonino PA, De Bruyne B, Pijls NH, Siebert U, Ikeno F, van' t Veer M, Klauss V, Manoharan G, Engstrom T, Oldroyd KG, Ver Lee PN, MacCarthy PA, Fearon WF. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. *N Eng J Med* 2009;**360**:213–224.
111. Abbara S, Arbab-Zadeh A, Callister TQ, Desai MY, Mamuya W, Thomson L, Weigold WG. SCCT guidelines for performance of coronary computed tomographic angiography: a report of the Society of Cardiovascular Computed Tomography Guidelines Committee. *J Cardiovasc Comput Tomogr* 2009;**3**:190–204.
112. Genders TS, Meijboom WB, Meijs MF, Schuijf JD, Mollet NR, Weustink AC, Pugliese F, Bax JJ, Cramer MJ, Krestin GP, de Feyter PJ, Hunink MG. CT coronary angiography in patients suspected of having coronary artery disease: decision making from various perspectives in the face of uncertainty. *Radiology* 2009;**253**:734–744.
113. Belardinelli R, Lacalaprice F, Carle F, Minnucci A, Cianci G, Perna G, D'Eusanio G. Exercise-induced myocardial ischaemia detected by cardiopulmonary exercise testing. *Eur Heart J* 2003;**24**:1304–1313.
114. Pradhan R, Chaudhary A, Donato AA. Predictive accuracy of ST depression during rapid atrial fibrillation on the presence of obstructive coronary artery disease. *Am J Emerg Med* 2012;**30**:1042–1047.
115. Shaw LJ, Mieres JH, Hendel RH, Boden WE, Gulati M, Veledar E, Hachamovitch R, Arrighi JA, Merz CN, Gibbons RJ, Wenger NK, Heller GV. Comparative effectiveness of exercise electrocardiography with or without myocardial perfusion single photon emission computed tomography in women with suspected coronary artery disease: results from the What Is the Optimal Method for Ischemia Evaluation in Women (WOMEN) trial. *Circulation* 2011;**124**:1239–1249.
116. Gianrossi R, Detrano R, Mulvihill D, Lehmann K, Dubach P, Colombo A, McArthur D, Froelicher V. Exercise-induced ST depression in the diagnosis of coronary artery disease. A meta-analysis. *Circulation* 1989;**80**:87–98.
117. Fleischmann KE, Hunink MG, Kuntz KM, Douglas PS. Exercise echocardiography or exercise SPECT imaging? A meta-analysis of diagnostic test performance. *JAMA* 1998;**280**:913–920.
118. Chelliah R, Anantharam B, Burden L, Alhajiri A, Senior R. Independent and incremental value of stress echocardiography over clinical and stress electrocardiographic parameters for the prediction of hard cardiac events in new-onset suspected angina with no history of coronary artery disease. *Eur J Echocardiogr* 2010;**11**:875–882.
119. Marwick TH, Shaw L, Case C, Vasey C, Thomas JD. Clinical and economic impact of exercise electrocardiography and exercise echocardiography in clinical practice. *Eur Heart J* 2003;**24**:1153–1163.
120. Mattera JA, Arain SA, Sinusas AJ, Finta L, Wackers FJ. Exercise testing with myocardial perfusion imaging in patients with normal baseline electrocardiograms: cost savings with a stepwise diagnostic strategy. *J Nucl Cardiol* 1998;**5**:498–506.
121. Sicari R, Nihoyannopoulos P, Evangelista A, Kasprzak J, Lancellotti P, Poldermans D, Voigt JU, Zamorano JL. Stress echocardiography expert consensus statement: European Association of Echocardiography (EAE) (a registered branch of the ESC). *Eur J Echocardiogr* 2008;**9**(415–437.
122. Senior R, Becher H, Monaghan M, Agati L, Zamorano J, Vanoverschelde JL, Nihoyannopoulos P. Contrast echocardiography: evidence-based recommendations by European Association of Echocardiography. *Eur J Echocardiogr* 2009;**10**:194–212.
123. Senior R, Moreo A, Gaibazzi N, Agati L, Tiemann K, Shivalkar B, von Bardeleben S, Galiuto L, Lardoux H, Trocino G, Carrio I, Le Guludec D, Sambuceti G, Becher H, Colonna P, Cate FT, Bramucci E, Cohen A, Bezante G, Aggeli C, Kasprzak JD. Comparison of Sulfur Hexafluoride Microbubble (SonoVue)-Enhanced Myocardial Echocardiography to gated Single Photon Emission Computerized Tomography for the Detection of Significant Coronary Artery Disease: A Large European Multicentre Study. *J Am Coll Cardiol* 2013; **pii**: S0735–1097(13)02262-6. doi: 10.1016/j.jacc.2013.04.082. [Epub ahead of print]
124. Plana JC, Mikati IA, Dokainish H, Lakkis N, Abukhalil J, Davis R, Hetzell BC, Zoghbi WA. A randomized cross-over study for evaluation of the effect of image optimization with contrast on the diagnostic accuracy of dobutamine echocardiography in coronary artery disease The OPTIMIZE Trial. *JACC Cardiovasc Imaging* 2008;**1**:145–152.
125. Voigt JU, Exner B, Schmiedehausen K, Huchzermeyer C, Reulbach U, Nixdorff U, Platsch G, Kuwert T, Daniel WG, Flachskampf FA. Strain-rate imaging during dobutamine stress echocardiography provides objective evidence of inducible ischemia. *Circulation* 2003;**107**:2120–2126.
126. Imbert L, Poussier S, Franken PR, Songy B, Verger A, Morel O, Wolf D, Noel A, Karcher G, Marie PY. Compared performance of high-sensitivity cameras dedicated to myocardial perfusion SPECT: a comprehensive analysis of phantom and human images. *J Nucl Med* 2012;**53**:1897–1903.
127. Ritchie JL, Bateman TM, Bonow RO, Crawford MH, Gibbons RJ, Hall RJ, O'Rourke RA, Parisi AF, Verani MS. Guidelines for clinical use of cardiac radionuclide imaging. Report of the American College of Cardiology/American Heart Association Task Force on Assessment of Diagnostic and Therapeutic Cardiovascular Procedures (Committee on Radionuclide Imaging), developed in collaboration with the American Society of Nuclear Cardiology. *J Am Coll Cardiol* 1995;**25**:521–547.
128. Al Jaroudi W, Iskandrian AE. Regadenoson: a new myocardial stress agent. *J Am Coll Cardiol* 2009;**54**:1123–1130.
129. Bateman TM, Heller GV, McGhie AI, Friedman JD, Case JA, Bryngelson JR, Hertenstein GK, Moutray KL, Reid K, Cullom SJ. Diagnostic accuracy of rest/stress ECG-gated Rb-82 myocardial perfusion PET: comparison with ECG-gated Tc-99m sestamibi SPECT. *J Nucl Cardiol* 2006;**13**:24–33.
130. Di Carli MF, Hachamovitch R. New technology for noninvasive evaluation of coronary artery disease. *Circulation* 2007;**115**:1464–1480.
131. Kajander S, Joutsiniemi E, Saraste M, Pietila M, Ukkonen H, Saraste A, Sipila HT, Teras M, Maki M, Airaksinen J, Hartiala J, Knuuti J. Cardiac positron emission tomography/computed tomography imaging accurately detects anatomically and functionally significant coronary artery disease. *Circulation* 2010;**122**:603–613.
132. Nagel E, Lehmkuhl HB, Bocksch W, Klein C, Vogel U, Frantz E, Ellmer A, Dreysse S, Fleck E. Noninvasive diagnosis of ischemia-induced wall motion abnormalities with the use of high-dose dobutamine stress MRI: comparison with dobutamine stress echocardiography. *Circulation* 1999;**99**:763–770.
133. Wahl A, Paetsch I, Gollesch A, Roethemeyer S, Foell D, Gebker R, Langreck H, Klein C, Fleck E, Nagel E. Safety and feasibility of high-dose dobutamine-atropine stress cardiovascular magnetic resonance for diagnosis of myocardial ischaemia: experience in 1000 consecutive cases. *Eur Heart J* 2004;**25**:1230–1236.
134. Secknus MA, Marwick TH. Evolution of dobutamine echocardiography protocols and indications: safety and side effects in 3,011 studies over 5 years. *J Am Coll Cardiol* 1997;**29**:1234–1240.
135. Hundley WG, Hamilton CA, Thomas MS, Herrington DM, Salido TB, Kitzman DW, Little WC, Link KM. Utility of fast cine magnetic resonance imaging and display for the detection of myocardial ischemia in patients not well suited for second harmonic stress echocardiography. *Circulation* 1999;**100**:1697–1702.
136. Greenwood JP, Maredia N, Younger JF, Brown JM, Nixon J, Everett CC, Bijsterveld P, Ridgway JP, Radjenovic A, Dickinson CJ, Ball SG, Plein S. Cardiovascular magnetic resonance and single-photon emission computed tomography for diagnosis of coronary heart disease (CE-MARC): a prospective trial. *Lancet* 2012;**379**:453–460.
137. Heydari B, Jerosch-Herold M, Kwong RY. Assessment of myocardial ischemia with cardiovascular magnetic resonance. *Prog Cardiovasc Dis* 2011;**54**:191–203.
138. Lockie T, Ishida M, Perera D, Chiribiri A, De Silva K, Kozerke S, Marber M, Nagel E, Rezavi R, Redwood S, Plein S. High-resolution magnetic resonance myocardial perfusion imaging at 3.0-Tesla to detect hemodynamically significant coronary stenoses as determined by fractional flow reserve. *J Am Coll Cardiol* 2011;**57**:70–75.
139. Cheng AS, Pegg TJ, Karamitsos TD, Searle N, Jerosch-Herold M, Choudhury RP, Banning AP, Neubauer S, Robson MD, Selvanayagam JB. Cardiovascular magnetic resonance perfusion imaging at 3-tesla for the detection of coronary artery disease: a comparison with 1.5-tesla. *J Am Coll Cardiol* 2007;**49**:2440–2449.
140. Bernhardt P, Walcher T, Rottbauer W, Wohrle J. Quantification of myocardial perfusion reserve at 1.5 and 3.0 Tesla: a comparison to fractional flow reserve. *Int J Cardiovasc Imaging* 2012;**28**:2049–2056.
141. Gaemperli O, Bengel FM, Kaufmann PA. Cardiac hybrid imaging. *Eur Heart J* 2011;**32**:2100–2108.
142. Pazhenkottil AP, Nkoulou RN, Ghadri JR, Herzog BA, Buechel RR, Kuest SM, Wolfrum M, Fiechter M, Husmann L, Gaemperli O, Kaufmann PA. Prognostic value of cardiac hybrid imaging integrating single-photon emission computed tomography with coronary computed tomography angiography. *Eur Heart J* 2011;**32**:1465–1471.
143. Sabharwal NK, Stoykova B, Taneja AK, Lahiri A. A randomized trial of exercise treadmill ECG versus stress SPECT myocardial perfusion imaging as an initial diagnostic strategy in stable patients with chest pain and suspected CAD: cost analysis. *J Nucl Cardiol* 2007;**14**:174–186.

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144. Underwood SR, Anagnostopoulos C, Cerqueira M, Ell PJ, Flint EJ, Harbinson M, Kelion AD, Al-Mohammad A, Prvulovich EM, Shaw LJ, Tweddel AC. Myocardial perfusion scintigraphy: the evidence. *Eur J Nucl Med Mol Imaging* 2004;**31**:261–291.
145. Garber AM, Solomon NA. Cost-effectiveness of alternative test strategies for the diagnosis of coronary artery disease. *Ann Intern Med* 1999;**130**:719–728.
146. Yao SS, Qureshi E, Sherrid MV, Chaudhry FA. Practical applications in stress echocardiography: risk stratification and prognosis in patients with known or suspected ischemic heart disease. *J Am Coll Cardiol* 2003;**42**:1084–1090.
147. Berman DS, Hachamovitch R, Kiat H, Cohen I, Cabico JA, Wang FP, Friedman JD, Germano G, Van Train K, Diamond GA. Incremental value of prognostic testing in patients with known or suspected ischemic heart disease: a basis for optimal utilization of exercise technetium-99m sestamibi myocardial perfusion single-photon emission computed tomography. *J Am Coll Cardiol* 1995;**26**:639–647.
148. Doesch C, Seeger A, Doering J, Herdeg C, Burgstahler C, Claussen CD, Gawaz M, Miller S, May AE. Risk stratification by adenosine stress cardiac magnetic resonance in patients with coronary artery stenoses of intermediate angiographic severity. *JACC Cardiovasc Imaging* 2009;**2**:424–433.
149. Yao SS, Bangalore S, Chaudhry FA. Prognostic implications of stress echocardiography and impact on patient outcomes: an effective gatekeeper for coronary angiography and revascularization. *J Am Soc Echocardiogr* 2010;**23**:832–839.
150. Halliburton S, Arbab-Zadeh A, Dey D, Einstein AJ, Gentry R, George RT, Gerber T, Mahesh M, Weigold WG. State-of-the-art in CT hardware and scan modes for cardiovascular CT. *J Cardiovasc Comput Tomogr* 2012;**6**:154–163.
151. Hausleiter J, Martinoff S, Hadamitzky M, Martuscelli E, Pschierer I, Feuchtner GM, Catalan-Sanz P, Czermak B, Meyer TS, Hein F, Bischoff B, Kuse M, Schomig A, Achenbach S. Image quality and radiation exposure with a low tube voltage protocol for coronary CT angiography results of the PROTECTION II Trial. *JACC Cardiovasc Imaging* 2010;**3**:1113–1123.
152. Agatston AS, Janowitz WR, Hildner FJ, Zusmer NR, Viamonte M Jr., Detrano R. Quantification of coronary artery calcium using ultrafast computed tomography. *J Am Coll Cardiol* 1990;**15**:827–832.
153. O'Rourke RA, Brundage BH, Froelicher VF, Greenland P, Grundy SM, Hachamovitch R, Pohost GM, Shaw LJ, Weintraub WS, Winters WL Jr., Forrester JS, Douglas PS, Faxon DP, Fisher JD, Gregoratos G, Hochman JS, Hutter AM Jr., Kaul S, Wolk MJ. American College of Cardiology/American Heart Association Expert Consensus document on electron-beam computed tomography for the diagnosis and prognosis of coronary artery disease. *Circulation* 2000;**102**:126–140.
154. Marwan M, Ropers D, Pflederer T, Daniel WG, Achenbach S. Clinical characteristics of patients with obstructive coronary lesions in the absence of coronary calcification: an evaluation by coronary CT angiography. *Heart* 2009;**95**:1056–1060.
155. Brodoefel H, Burgstahler C, Tsiflikas I, Reimann A, Schroeder S, Claussen CD, Heuschmid M, Kopp AF. Dual-source CT: effect of heart rate, heart rate variability, and calcification on image quality and diagnostic accuracy. *Radiology* 2008;**247**:346–355.
156. Chen CC, Chen CC, Hsieh IC, Liu YC, Liu CY, Chan T, Wen MS, Wan YL. The effect of calcium score on the diagnostic accuracy of coronary computed tomography angiography. *Int J Cardiovasc Imaging* 2011;**27** Suppl 1:37–42.
157. van Werkhoven JM, de Boer SM, Schuijf JD, Cademartiri F, Maffei E, Jukema JW, Boogers MJ, Kroft LJ, de Roos A, Bax JJ. Impact of clinical presentation and pretest likelihood on the relation between calcium score and computed tomographic coronary angiography. *Am J Cardiol* 2010;**106**:1675–1679.
158. Meijs MF, Meijboom WB, Prokop M, Mollet NR, van Mieghem CA, Doevendans PA, de Feyter PJ, Cramer MJ. Is there a role for CT coronary angiography in patients with symptomatic angina? Effect of coronary calcium score on identification of stenosis. *Int J Cardiovasc Imaging* 2009;**25**:847–854.
159. Vavere AL, Arbab-Zadeh A, Rochitte CE, Dewey M, Niinuma H, Gottlieb I, Clouse ME, Bush DE, Hoe JW, de Roos A, Cox C, Lima JA, Miller JM. Coronary artery stenoses: accuracy of 64-detector row CT angiography in segments with mild, moderate, or severe calcification: a subanalysis of the CORE-64 trial. *Radiology* 2011;**261**:100–108.
160. Alkadhi H, Scheffel H, Desbiolles L, Gaemperli O, Stolzmann P, Plass A, Goerres GW, Luescher TF, Genoni M, Marincek B, Kaufmann PA, Leschka S. Dual-source computed tomography coronary angiography: influence of obesity, calcium load, and heart rate on diagnostic accuracy. *Eur Heart J* 2008;**29**:766–776.
161. Westwood ME, Raatz HD, Misso K, Burgers L, Redekop K, Lhachimi SK, Armstrong N, Kleijnen J. Systematic Review of the Accuracy of Dual-Source Cardiac CT for Detection of Arterial Stenosis in Difficult to Image Patient Groups. *Radiology* 2013; **267**(2):387–95.
162. Paech DC, Weston AR. A systematic review of the clinical effectiveness of 64-slice or higher computed tomography angiography as an alternative to invasive coronary angiography in the investigation of suspected coronary artery disease. *BMC Cardiovasc Disord* 2011;**11**:32.
163. Ropers D, Pohle FK, Kuettner A, Pflederer T, Anders K, Daniel WG, Bautz W, Baum U, Achenbach S. Diagnostic accuracy of noninvasive coronary angiography in patients after bypass surgery using 64-slice spiral computed tomography with 330-ms gantry rotation. *Circulation* 2006;**114**:2334–2341.
164. Weustink AC, Nieman K, Pugliese F, Mollet NR, Meijboom WB, van Mieghem C, ten Kate GJ, Cademartiri F, Krestin GP, de Feyter PJ. Diagnostic accuracy of computed tomography angiography in patients after bypass grafting: comparison with invasive coronary angiography. *JACC Cardiovasc Imaging* 2009;**2**:816–824.
165. Min JK, Dunning A, Lin FY, Achenbach S, Al-Mallah M, Budoff MJ, Cademartiri F, Callister TQ, Chang HJ, Cheng V, Chinnaiyan K, Chow BJ, Delago A, Hadamitzky M, Hausleiter J, Kaufmann P, Maffei E, Raff G, Shaw LJ, Villines T, Berman DS. Age- and sex-related differences in all-cause mortality risk based on coronary computed tomography angiography findings results from the International Multicenter CONFIRM (Coronary CT Angiography Evaluation for Clinical Outcomes: An International Multicenter Registry) of 23,854 patients without known coronary artery disease. *J Am Coll Cardiol* 2011;**58**:849–860.
166. Hadamitzky M, Freissmuth B, Meyer T, Hein F, Kastrati A, Martinoff S, Schomig A, Hausleiter J. Prognostic value of coronary computed tomographic angiography for prediction of cardiac events in patients with suspected coronary artery disease. *JACC Cardiovasc Imaging* 2009;**2**:404–411.
167. Chow BJ, Small G, Yam Y, Chen L, Achenbach S, Al-Mallah M, Berman DS, Budoff MJ, Cademartiri F, Callister TQ, Chang HJ, Cheng V, Chinnaiyan KM, Delago A, Dunning A, Hadamitzky M, Hausleiter J, Kaufmann P, Lin F, Maffei E, Raff GL, Shaw LJ, Villines TC, Min JK. Incremental prognostic value of cardiac computed tomography in coronary artery disease using CONFIRM: COroNary computed tomography angiography evaluation for clinical outcomes: an InteRnational Multicenter registry. *Circ Cardiovasc Imaging* 2011;**4**:463–472.
168. Meijboom WB, van Mieghem CA, Mollet NR, Pugliese F, Weustink AC, van Pelt N, Cademartiri F, Nieman K, Boersma E, de Jaegere P, Krestin GP, de Feyter PJ. 64-slice computed tomography coronary angiography in patients with high, intermediate, or low pretest probability of significant coronary artery disease. *J Am Coll Cardiol* 2007;**50**:1469–1475.
169. Min JK, Leipsic J, Pencina MJ, Berman DS, Koo BK, van Mieghem C, Erglis A, Lin FY, Dunning AM, Apruzzese P, Budoff MJ, Cole JH, Jaffer FA, Leon MB, Malpeso J, Mancini GB, Park SJ, Schwartz RS, Shaw LJ, Mauri L. Diagnostic accuracy of fractional flow reserve from anatomic CT angiography. *JAMA* 2012;**308**:1237–1245.
170. Kato S, Kitagawa K, Ishida N, Ishida M, Nagata M, Ichikawa Y, Katahira K, Matsumoto Y, Seo K, Ochiai R, Kobayashi Y, Sakuma H. Assessment of coronary artery disease using magnetic resonance coronary angiography: a national multicenter trial. *J Am Coll Cardiol* 2010;**56**:983–991.
171. Sakuma H. Coronary CT versus MR angiography: the role of MR angiography. *Radiology* 2011;**258**:340–349.
172. Wijns W, Kolh P, Danchin N, Di Mario C, Falk V, Folliguet T, Garg S, Huber K, James S, Knuuti J, Lopez-Sendon J, Marco J, Menicanti L, Ostojic M, Piepoli MF, Pirlet C, Pomar JL, Reifart N, Ribichini FL, Schalij MJ, Sergeant P, Serruys PW, Silber S, Sousa Uva M, Taggart D. Guidelines on myocardial revascularization. *Eur Heart J* 2010;**31**:2501–2555.
173. Jolly SS, Amlani S, Hamon M, Yusuf S, Mehta SR. Radial versus femoral access for coronary angiography or intervention and the impact on major bleeding and ischemic events: a systematic review and meta-analysis of randomized trials. *Am Heart J* 2009;**157**:132–140.
174. Arora N, Matheny ME, Sepke C, Resnic FS. A propensity analysis of the risk of vascular complications after cardiac catheterization procedures with the use of vascular closure devices. *Am Heart J* 2007;**153**:606–611.
175. Noto TJ Jr., Johnson LW, Krone R, Weaver WF, Clark DA, Kramer JR Jr., Vetrovec GW. Cardiac catheterization 1990: a report of the Registry of the Society for Cardiac Angiography and Interventions (SCA&I). *Cathet Cardiovasc Diagn* 1991;**24**:75–83.
176. Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE substudy. Heart Outcomes Prevention Evaluation Study Investigators. *Lancet* 2000;**355**:253–259.
177. Effect of nicorandil on coronary events in patients with stable angina: the Impact Of Nicorandil in Angina (IONA) randomised trial. *Lancet* 2002;**359**:1269–1275.
178. Hjemdahl P, Eriksson SV, Held C, Forslund L, Nasman P, Rehnqvist N. Favourable long term prognosis in stable angina pectoris: an extended follow up of the angina prognosis study in Stockholm (APSIS). *Heart* 2006;**92**:177–182.
179. Wilson PW, D'Agostino R Sr., Bhatt DL, Eagle K, Pencina MJ, Smith SC, Alberts MJ, Dallongeville J, Goto S, Hirsch AT, Liau CS, Ohman EM, Rother J, Reid C, Mas JL, Steg PG. An international model to predict recurrent cardiovascular disease. *Am J Med* 2012;**125**:695–703.
180. Weiner DA, Ryan TJ, McCabe CH, Chaitman BR, Sheffield LT, Ferguson JC, Fisher LD, Tristani F. Prognostic importance of a clinical profile and exercise test in medically treated patients with coronary artery disease. *J Am Coll Cardiol* 1984;**3**:772–779.
181. Hammermeister KE, DeRouen TA, Dodge HT. Variables predictive of survival in patients with coronary disease. Selection by univariate and multivariate analyses

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from the clinical, electrocardiographic, exercise, arteriographic, and quantitative angiographic evaluations. *Circulation* 1979;**59**:421–430.
182. Pryor DB, Shaw L, McCants CB, Lee KL, Mark DB, Harrell FE Jr., Muhlbaier LH, Califf RM. Value of the history and physical in identifying patients at increased risk for coronary artery disease. *Ann Intern Med* 1993;**118**:81–90.
183. Emond M, Mock MB, Davis KB, Fisher LD, Holmes DR Jr., Chaitman BR, Kaiser GC, Alderman E, Killip T 3rd. Long-term survival of medically treated patients in the Coronary Artery Surgery Study (CASS) Registry. *Circulation* 1994;**90**:2645–2657.
184. Mahmarian JJ, Dakik HA, Filipchuk NG, Shaw LJ, Iskander SS, Ruddy TD, Keng F, Henzlova MJ, Allam A, Moye LA, Pratt CM. An initial strategy of intensive medical therapy is comparable to that of coronary revascularization for suppression of scintigraphic ischemia in high-risk but stable survivors of acute myocardial infarction. *J Am Coll Cardiol* 2006;**48**:2458–2467.
185. Hachamovitch R, Rozanski A, Shaw LJ, Stone GW, Thomson LE, Friedman JD, Hayes SW, Cohen I, Germano G, Berman DS. Impact of ischaemia and scar on the therapeutic benefit derived from myocardial revascularization vs. medical therapy among patients undergoing stress-rest myocardial perfusion scintigraphy. *Eur Heart J* 2011;**32**:1012–1024.
186. Rihal CS, Davis KB, Kennedy JW, Gersh BJ. The utility of clinical, electrocardiographic, and roentgenographic variables in the prediction of left ventricular function. *Am J Cardiol* 1995;**75**:220–223.
187. Raymond I, Pedersen F, Steensgaard-Hansen F, Green A, Busch-Sorensen M, Tuxen C, Appel J, Jacobsen J, Atar D, Hildebrandt P. Prevalence of impaired left ventricular systolic function and heart failure in a middle aged and elderly urban population segment of Copenhagen. *Heart* 2003;**89**:1422–149.
188. Ashley EA, Myers J, Froelicher V. Exercise testing in clinical medicine. *Lancet* 2000; **356**:1592–1597.
189. Mark DB, Shaw L, Harrell FE Jr., Hlatky MA, Lee KL, Bengtson JR, McCants CB, Califf RM, Pryor DB. Prognostic value of a treadmill exercise score in outpatients with suspected coronary artery disease. *N Eng J Med* 1991;**325**:849–853.
190. Schinkel AF, Bax JJ, Geleijnse ML, Boersma E, Elhendy A, Roelandt JR, Poldermans D. Noninvasive evaluation of ischaemic heart disease: myocardial perfusion imaging or stress echocardiography? *Eur Heart J* 2003;**24**:789–800.
191. Marwick TH, Mehta R, Arheart K, Lauer MS. Use of exercise echocardiography for prognostic evaluation of patients with known or suspected coronary artery disease. *J Am Coll Cardiol* 1997;**30**:83–90.
192. Olmos LI, Dakik H, Gordon R, Dunn JK, Verani MS, Quinones MA, Zoghbi WA. Long-term prognostic value of exercise echocardiography compared with exercise 201Tl, ECG, and clinical variables in patients evaluated for coronary artery disease. *Circulation* 1998;**98**:2679–2686.
193. Marwick TH, Case C, Vasey C, Allen S, Short L, Thomas JD. Prediction of mortality by exercise echocardiography: a strategy for combination with the duke treadmill score. *Circulation* 2001;**103**:2566–2571.
194. Impact of an Automated Multimodality Point-of-Order Decision Support Tool on Rates of Appropriate Testing and Clinical Decision Making for Individuals With Suspected Coronary Artery Disease: A Prospective Multicenter Study.Lin FY, Dunning AM, Narula J, Shaw LJ, Gransar H, Berman DS, Min JK.*J Am Coll Cardiol*. 2013;**62**(4):308–16
195. Brown KA. Prognostic value of thallium-201 myocardial perfusion imaging. A diagnostic tool comes of age. *Circulation* 1991;**83**:363–381.
196. Hachamovitch R, Berman DS, Shaw LJ, Kiat H, Cohen I, Cabico JA, Friedman J, Diamond GA. Incremental prognostic value of myocardial perfusion single photon emission computed tomography for the prediction of cardiac death: differential stratification for risk of cardiac death and myocardial infarction. *Circulation* 1998;**97**:535–543.
197. Hachamovitch R, Hayes SW, Friedman JD, Cohen I, Berman DS. Comparison of the short-term survival benefit associated with revascularization compared with medical therapy in patients with no prior coronary artery disease undergoing stress myocardial perfusion single photon emission computed tomography. *Circulation* 2003;**107**:2900–2907.
198. Dorbala S, Di Carli MF, Beanlands RS, Merhige ME, Williams BA, Veledar E, Chow BJ, Min JK, Pencina MJ, Berman DS, Shaw LJ. Prognostic value of stress myocardial perfusion positron emission tomography: results from a multicenter observational registry. *J Am Coll Cardiol* 2013;**61**:176–184.
199. Murthy VL, Naya M, Foster CR, Gaber M, Hainer J, Klein J, Dorbala S, Blankstein R, Di Carli MF. Association between coronary vascular dysfunction and cardiac mortality in patients with and without diabetes mellitus. *Circulation* 2012;**126**: 1858–1868.
200. Korosoglou G, Elhmidi Y, Steen H, Schellberg D, Riedle N, Ahrens J, Lehrke S, Merten C, Lossnitzer D, Radeleff J, Zugck C, Giannitsis E, Katus HA. Prognostic value of high-dose dobutamine stress magnetic resonance imaging in 1,493 consecutive patients: assessment of myocardial wall motion and perfusion. *J Am Coll Cardiol* 2010;**56**:1225–1234.
201. Jahnke C, Nagel E, Gebker R, Kokocinski T, Kelle S, Manka R, Fleck E, Paetsch I. Prognostic value of cardiac magnetic resonance stress tests: adenosine stress perfusion and dobutamine stress wall motion imaging. *Circulation* 2007;**115**:1769–1776.
202. Motoyama S, Sarai M, Harigaya H, Anno H, Inoue K, Hara T, Naruse H, Ishii J, Hishida H, Wong ND, Virmani R, Kondo T, Ozaki Y, Narula J. Computed tomographic angiography characteristics of atherosclerotic plaques subsequently resulting in acute coronary syndrome. *J Am Coll Cardiol* 2009;**54**:49–57.
203. Ostrom MP, Gopal A, Ahmadi N, Nasir K, Yang E, Kakadiaris I, Flores F, Mao SS, Budoff MJ. Mortality incidence and the severity of coronary atherosclerosis assessed by computed tomography angiography. *J Am Coll Cardiol* 2008;**52**: 1335–1343.
204. Hulten EA, Carbonaro S, Petrillo SP, Mitchell JD, Villines TC. Prognostic value of cardiac computed tomography angiography: a systematic review and meta-analysis. *J Am Coll Cardiol* 2011;**57**:1237–1247.
205. Mark DB, Nelson CL, Califf RM, Harrell FE Jr., Lee KL, Jones RH, Fortin DF, Stack RS, Glower DD, Smith LR *et al.* Continuing evolution of therapy for coronary artery disease. Initial results from the era of coronary angioplasty. *Circulation* 1994;**89**: 2015–2025.
206. Christian TF, Miller TD, Bailey KR, Gibbons RJ. Exercise tomographic thallium-201 imaging in patients with severe coronary artery disease and normal electrocardiograms. *Ann Intern Med* 1994;**121**:825–832.
207. Hachamovitch R, Berman DS, Kiat H, Cohen I, Friedman JD, Shaw LJ. Value of stress myocardial perfusion single photon emission computed tomography in patients with normal resting electrocardiograms: an evaluation of incremental prognostic value and cost-effectiveness. *Circulation* 2002;**105**:823–829.
208. Daugherty SL, Magid DJ, Kikla JR, Hokanson JE, Baxter J, Ross CA, Masoudi FA. Gender differences in the prognostic value of exercise treadmill test characteristics. *Am Heart J* 2011;**161**:908–914.
209. Coelho-Filho OR, Seabra LF, Mongeon FP, Abdullah SM, Francis SA, Blankstein R, Di Carli MF, Jerosch-Herold M, Kwong RY. Stress myocardial perfusion imaging by CMR provides strong prognostic value to cardiac events regardless of patient's sex. *JACC Cardiovasc Imaging* 2011;**4**:850–861.
210. Metz LD, Beattie M, Hom R, Redberg RF, Grady D, Fleischmann KE. The prognostic value of normal exercise myocardial perfusion imaging and exercise echocardiography: a meta-analysis. *J Am Coll Cardiol* 2007;**49**:227–237.
211. Nallamothu N, Ghods M, Heo J, Iskandrian AS. Comparison of thallium-201 single-photon emission computed tomography and electrocardiographic response during exercise in patients with normal rest electrocardiographic results. *J Am Coll Cardiol* 1995;**25**:830–836.
212. Mahajan N, Polavaram L, Vankayala H, Ference B, Wang Y, Ager J, Kovach J, Afonso L. Diagnostic accuracy of myocardial perfusion imaging and stress echocardiography for the diagnosis of left main and triple vessel coronary artery disease: a comparative meta-analysis. *Heart* 2010;**96**:956–966.
213. Shaw LJ, Cerqueira MD, Brooks MM, Althouse AD, Sansing VV, Beller GA, Pop-Busui R, Taillefer R, Chaitman BR, Gibbons RJ, Heo J, Iskandrian AE. Impact of left ventricular function and the extent of ischemia and scar by stress myocardial perfusion imaging on prognosis and therapeutic risk reduction in diabetic patients with coronary artery disease: results from the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) trial. *J Nucl Cardiol* 2012;**19**:658–669.
214. Shaw LJ, Berman DS, Maron DJ, Mancini GB, Hayes SW, Hartigan PM, Weintraub WS, O'Rourke RA, Dada M, Spertus JA, Chaitman BR, Friedman J, Slomka P, Heller GV, Germano G, Gosselin G, Berger P, Kostuk WJ, Schwartz RG, Knudtson M, Veledar E, Bates ER, McCallister B, Teo KK, Boden WE. Optimal medical therapy with or without percutaneous coronary intervention to reduce ischemic burden: results from the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial nuclear substudy. *Circulation* 2008;**117**:1283–1291.
215. Shaw LJ, Hachamovitch R, Heller GV, Marwick TH, Travin MI, Iskandrian AE, Kesler K, Lauer MS, Hendel R, Borges-Neto S, Lewin HC, Berman DS, Miller D. Noninvasive strategies for the estimation of cardiac risk in stable chest pain patients. The Economics of Noninvasive Diagnosis (END) Study Group. *Am J Cardiol* 2000; **86**:1–7.
216. America YG, Bax JJ, Boersma E, Stokkel M, van der Wall EE. Prognostic value of gated SPECT in patients with left bundle branch block. *J Nucl Cardiol* 2007;**14**: 75–81.
217. Tandogan I, Yetkin E, Yanik A, Ulusoy FV, Temizhan A, Cehreli S, Sasmaz A. Comparison of thallium-201 exercise SPECT and dobutamine stress echocardiography for diagnosis of coronary artery disease in patients with left bundle branch block. *Int J Cardiovasc Imaging* 2001;**17**:339–345.
218. Biagini E, Shaw LJ, Poldermans D, Schinkel AF, Rizzello V, Elhendy A, Rapezzi C, Bax JJ. Accuracy of non-invasive techniques for diagnosis of coronary artery disease and prediction of cardiac events in patients with left bundle branch block: a meta-analysis. *Eur J Nucl Med Mol Imaging* 2006;**33**:1442–1451.
219. Biagini E, Schinkel AF, Elhendy A, Bax JJ, Rizzello V, van Domburg RT, Krenning BJ, Schouten O, Branzi A, Rocchi G, Simoons ML, Poldermans D. Pacemaker stress

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echocardiography predicts cardiac events in patients with permanent pacemaker. *Am J Med* 2005;**118**:1381–1386.

220. Picano E, Alaimo A, Chubuchny V, Plonska E, Baldo V, Baldini U, Pauletti M, Perticucci R, Fonseca L, Villarraga HR, Emanuelli C, Miracapillo G, Hoffmann E, De Nes M. Noninvasive pacemaker stress echocardiography for diagnosis of coronary artery disease: a multicenter study. *J Am Coll Cardiol* 2002;**40**:1305–1310.
221. Fowkes FG, Murray GD, Butcher I, Heald CL, Lee RJ, Chambless LE, Folsom AR, Hirsch AT, Dramaix M, deBacker G, Wautrecht JC, Kornitzer M, Newman AB, Cushman M, Sutton-Tyrrell K, Lee AJ, Price JF, d'Agostino RB, Murabito JM, Norman PE, Jamrozik K, Curb JD, Masaki KH, Rodriguez BL, Dekker JM, Bouter LM, Heine RJ, Nijpels G, Stehouwer CD, Ferrucci L, McDermott MM, Stoffers HE, Hooi JD, Knottnerus JA, Ogren M, Hedblad B, Witteman JC, Breteler MM, Hunink MG, Hofman A, Criqui MH, Langer RD, Fronek A, Hiatt WR, Hamman R, Resnick HE, Guralnik J. Ankle brachial index combined with Framingham Risk Score to predict cardiovascular events and mortality: a meta-analysis. *JAMA* 2008;**300**:197–208.
222. O'Leary DH, Polak JF, Kronmal RA, Manolio TA, Burke GL, Wolfson SK Jr. Carotid-artery intima and media thickness as a risk factor for myocardial infarction and stroke in older adults. Cardiovascular Health Study Collaborative Research Group. *N Eng J Med* 1999;**340**:14–22.
223. Greenland P, LaBree L, Azen SP, Doherty TM, Detrano RC. Coronary artery calcium score combined with Framingham score for risk prediction in asymptomatic individuals. *JAMA* 2004;**291**:210–215.
224. Detrano R, Guerci AD, Carr JJ, Bild DE, Burke G, Folsom AR, Liu K, Shea S, Szklo M, Bluemke DA, O'Leary DH, Tracy R, Watson K, Wong ND, Kronmal RA. Coronary calcium as a predictor of coronary events in four racial or ethnic groups. *N Eng J Med* 2008;**358**:1336–1345.
225. Belcaro G, Nicolaides AN, Ramaswami G, Cesarone MR, De Sanctis M, Incandela L, Ferrari P, Geroulakos G, Barsotti A, Griffin M, Dhanjil S, Sabetai M, Bucci M, Martines G. Carotid and femoral ultrasound morphology screening and cardiovascular events in low risk subjects: a 10-year follow-up study (the CAFES-CAVE study(1)). *Atherosclerosis* 2001;**156**:379–387.
226. Anand DV, Lim E, Hopkins D, Corder R, Shaw LJ, Sharp P, Lipkin D, Lahiri A. Risk stratification in uncomplicated type 2 diabetes: prospective evaluation of the combined use of coronary artery calcium imaging and selective myocardial perfusion scintigraphy. *Eur Heart J* 2006;**27**:713–721.
227. Elkeles RS, Godsland IF, Feher MD, Rubens MB, Roughton M, Nugara F, Humphries SE, Richmond W, Flather MD. Coronary calcium measurement improves prediction of cardiovascular events in asymptomatic patients with type 2 diabetes: the PREDICT study. *Eur Heart J* 2008;**29**:2244–2251.
228. Gulati M, Pandey DK, Arnsdorf MF, Lauderdale DS, Thisted RA, Wicklund RH, Al-Hani AJ, Black HR. Exercise capacity and the risk of death in women: the St James Women Take Heart Project. *Circulation* 2003;**108**:1554–1559.
229. Wei M, Kampert JB, Barlow CE, Nichaman MZ, Gibbons LW, Paffenbarger RS Jr., Blair SN. Relationship between low cardiorespiratory fitness and mortality in normal-weight, overweight, and obese men. *JAMA* 1999;**282**:1547–1553.
230. Zellweger MJ, Hachamovitch R, Kang X, Hayes SW, Friedman JD, Germano G, Berman DS. Threshold, incidence, and predictors of prognostically high-risk silent ischemia in asymptomatic patients without prior diagnosis of coronary artery disease. *J Nucl Cardiol* 2009;**16**:193–200.
231. Steg G. ESC guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. *Eur Heart J* 2012.
232. Harb SC, Cook T, Jaber WA, Marwick TH. Exercise testing in asymptomatic patients after revascularization: are outcomes altered? *Arch Intern Med* 2012;**172**:854–861.
233. Hachamovitch R, Hayes S, Friedman JD, Cohen I, Shaw LJ, Germano G, Berman DS. Determinants of risk and its temporal variation in patients with normal stress myocardial perfusion scans: what is the warranty period of a normal scan? *J Am Coll Cardiol* 2003;**41**:1329–1340.
234. Carryer DJ, Askew JW, Hodge DO, Miller TD, Gibbons RJ. The timing and impact of follow-up studies after normal stress single-photon emission computed tomography sestamibi studies. *Circ Cardiovasc Imaging* 2010;**3**:520–526.
235. Proudfit WL, Shirey EK, Sones FM Jr. Selective cine coronary arteriography. Correlation with clinical findings in 1,000 patients. *Circulation* 1966;**33**:901–910.
236. Patel MR, Peterson ED, Dai D, Brennan JM, Redberg RF, Anderson HV, Brindis RG, Douglas PS. Low diagnostic yield of elective coronary angiography. *N Eng J Med* 2010;**362**:886–895.
237. Holubkov R, Laskey WK, Haviland A, Slater JC, Bourassa MG, Vlachos HA, Cohen HA, Williams DO, Kelsey SF, Detre KM. Angina 1 year after percutaneous coronary intervention: a report from the NHLBI Dynamic Registry. *Am Heart J* 2002;**144**:826–833.
238. Venkitachalam L, Kip KE, Mulukutla SR, Selzer F, Laskey W, Slater J, Cohen HA, Wilensky RL, Williams DO, Marroquin OC, Sutton-Tyrrell K, Bunker CH, Kelsey SF. Temporal trends in patient-reported angina at 1 year after percutaneous coronary revascularization in the stent era: a report from the National Heart, Lung, and Blood Institute-sponsored 1997–2006 dynamic registry. *Circ Cardiovasc Qual Outcomes* 2009;**2**:607–615.
239. Camici PG, Crea F. Coronary microvascular dysfunction. *N Eng J Med* 2007;**356**:830–840.
240. Panza JA, Laurienzo JM, Curiel RV, Unger EF, Quyyumi AA, Dilsizian V, Cannon RO 3rd. Investigation of the mechanism of chest pain in patients with angiographically normal coronary arteries using transesophageal dobutamine stress echocardiography. *J Am Coll Cardiol* 1997;**29**:293–301.
241. Ong P, Athanasiadis A, Mahrholdt H, Borgulya G, Sechtem U, Kaski JC. Increased coronary vasoconstrictor response to acetylcholine in women with chest pain and normal coronary arteriograms (cardiac syndrome X). *Clin Res Cardiol* 2012;**101**(8):673–81
242. Yilmaz A, Hill S, Schaufele T, Vohringer M, Geissler A, Sechtem U. Exercise-induced spastic coronary artery occlusion at the site of a moderate stenosis: neither Prinzmetal's angina nor cardiac syndrome X but "Prinzmetal X". *Circulation* 2010;**122**:e570–e574.
243. Prinzmetal M, Kennamer R, Merliss R, Wada T, Bor N. Angina pectoris. I. A variant form of angina pectoris; preliminary report. *Am J Med* 1959;**27**:375–388.
244. Sueda S, Kohno H, Fukuda H, Inoue K, Suzuki J, Watanabe K, Ochi T, Uraoka T. Clinical and angiographical characteristics of acetylcholine- induced spasm: relationship to dose of intracoronary injection of acetylcholine. *Coron Artery Dis* 2002;**13**:231–236.
245. Matsubara T, Tamura Y, Yamazoe M, Hori T, Konno T, Ida T, Higuchi K, Takemoto M, Imai S, Aizawa Y. Correlation between arteriographic and electrocardiographic features during spasm in the left anterior descending coronary artery. *Coron Artery Dis* 1997;**8**:525–535.
246. Guidelines for diagnosis and treatment of patients with vasospastic angina (coronary spastic angina) (JCS 2008): digest version. *Circ J* 2010;**74**:1745–1762.
247. Maseri A, Davies G, Hackett D, Kaski JC. Coronary artery spasm and vasoconstriction. The case for a distinction. *Circulation* 1990;**81**:1983–1991.
248. Mohri M, Koyanagi M, Egashira K, Tagawa H, Ichiki T, Shimokawa H, Takeshita A. Angina pectoris caused by coronary microvascular spasm. *Lancet* 1998;**351**:1165–1169.
249. Takagi Y, Yasuda S, Takahashi J, Tsunoda R, Ogata Y, Seki A, Sumiyoshi T, Matsui M, Goto T, Tanabe Y, Sueda S, Sato T, Ogawa S, Kubo N, Momomura S, Ogawa H, Shimokawa H, Japanese Coronary Spasm A. Clinical implications of provocation tests for coronary artery spasm: safety, arrhythmic complications, and prognostic impact: multicentre registry study of the Japanese Coronary Spasm Association. *Eur Heart J* 2013;**34**:258–267.
250. Sueda S, Saeki H, Otani T, Mineoi K, Kondou T, Yano K, Ochi T, Ochi N, Hayashi Y, Tsuruoka T, Kawada H, Matsuda S, Uraoka T. Major complications during spasm provocation tests with an intracoronary injection of acetylcholine. *Am J Cardiol* 2000;**85**:391–394, A10.
251. Morales MA, Lombardi M, Distante A, Carpeggiani C, Reisenhofer B, L'Abbate A. Ergonovine-echo test to assess the significance of chest pain at rest without ECG changes. *Eur Heart J* 1995;**16**:1361–1366.
252. Buxton A, Goldberg S, Hirshfeld JW, Wilson J, Mann T, Williams DO, Overlie P, Oliva P. Refractory ergonovine-induced coronary vasospasm: importance of intracoronary nitroglycerin. *Am J Cardiol* 1980;**46**:329–334.
253. Meyers DG, Neuberger JS, He J. Cardiovascular effect of bans on smoking in public places: a systematic review and meta-analysis. *J Am Coll Cardiol* 2009;**54**:1249–1255.
254. Lam Tea. *IARC Handbooks of Cancer Prevention, Tobacco Control, Vol. 11: Reversal of Risk After Quitting Smoking*. IARC, World Health Organization, 2007, 366.
255. Critchley J, Capewell S. Smoking cessation for the secondary prevention of coronary heart disease. *Cochrane Database Syst Rev* 2004(1):CD003041.
256. Hubbard R, Lewis S, Smith C, Godfrey C, Smeeth L, Farrington P, Britton J. Use of nicotine replacement therapy and the risk of acute myocardial infarction, stroke, and death. *Tob Control* 2005;**14**:416–421.
257. Ludvig J, Miner B, Eisenberg MJ. Smoking cessation in patients with coronary artery disease. *Am Heart J* 2005;**149**:565–572.
258. Rigotti NA, Thorndike AN, Regan S, McKool K, Pasternak RC, Chang Y, Swartz S, Torres-Finnerty N, Emmons KM, Singer DE. Bupropion for smokers hospitalized with acute cardiovascular disease. *Am J Med* 2006;**119**:1080–1087.
259. Tonstad S, Farsang C, Klaene G, Lewis K, Manolis A, Perruchoud AP, Silagy C, van Spiegel PI, Astbury C, Hider A, Sweet R. Bupropion SR for smoking cessation in smokers with cardiovascular disease: a multicentre, randomised study. *Eur Heart J* 2003;**24**:946–955.
260. Rigotti NA, Pipe AL, Benowitz NL, Arteaga C, Garza D, Tonstad S. Efficacy and safety of varenicline for smoking cessation in patients with cardiovascular disease: a randomized trial. *Circulation* 2010;**121**:221–229.
261. Singh S, Loke YK, Spangler JG, Furberg CD. Risk of serious adverse cardiovascular events associated with varenicline: a systematic review and meta-analysis. *CMAJ* 2011;**183**:1359–1366.

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262. Filion KB, El Khoury F, Bielinski M, Schiller I, Dendukuri N, Brophy JM. Omega-3 fatty acids in high-risk cardiovascular patients: a meta-analysis of randomized controlled trials. *BMC Cardiovasc Disord* 2010;**10**:24.
263. Mozaffarian D, Wu JH. Omega-3 fatty acids and cardiovascular disease: effects on risk factors, molecular pathways, and clinical events. *J Am Coll Cardiol* 2011;**58**: 2047–2067.
264. Kwak SM, Myung SK, Lee YJ, Seo HG. Efficacy of Omega-3 Fatty Acid Supplements (Eicosapentaenoic Acid and Docosahexaenoic Acid) in the Secondary Prevention of Cardiovascular Disease: A Meta-analysis of Randomized, Double-blind, Placebo-Controlled Trials. *Arch Intern Med* 2012;**172**(9):686–94..
265. Frishman WH. Carvedilol. *Indian Heart J* 1999;**51**:325–332.
266. Estruch R, Ros E, Salas-Salvado J, Covas MI, Pharm D, Corella D, Aros F, Gomez-Gracia E, Ruiz-Gutierrez V, Fiol M, Lapetra J, Lamuela-Raventos RM, Serra-Majem L, Pinto X, Basora J, Munoz MA, Sorli JV, Martinez JA, Martinez-Gonzalez MA, the PSI. Primary Prevention of Cardiovascular Disease with a Mediterranean Diet. *N Eng J Med* 2013;**368**(14):1279–90
267. Gupta BP, Murad MH, Clifton MM, Prokop L, Nehra A, Kopecky SL. The effect of lifestyle modification and cardiovascular risk factor reduction on erectile dysfunction: a systematic review and meta-analysis. *Arch Intern Med* 2011;**171**:1797–1803.
268. Kloner R, Padma-Nathan H. Erectile dysfunction in patients with coronary artery disease. *Int J Impot Res* 2005;**17**:209–215.
269. Russell ST, Khandheria BK, Nehra A. Erectile dysfunction and cardiovascular disease. *Mayo Clin Proc* 2004;**79**:782–794.
270. Kostis JB, Jackson G, Rosen R, Barrett-Connor E, Billups K, Burnett AL, Carson C 3rd, Cheitlin M, Debusk R, Fonseca V, Ganz P, Goldstein I, Guay A, Hatzichristou D, Hollander JE, Hutter A, Katz S, Kloner RA, Mittleman M, Montorsi F, Montorsi P, Nehra A, Sadovsky R, Shabsigh R. Sexual dysfunction and cardiac risk (the Second Princeton Consensus Conference). *Am J Cardiol* 2005;**96**:85M–93M.
271. Kohler M, Stradling JR. Mechanisms of vascular damage in obstructive sleep apnea. *Nat Rev Cardiol* 2010;**7**:677–685.
272. Pasceri V, Patti G, Nusca A, Pristipino C, Richichi G, Di Sciascio G. Randomized trial of atorvastatin for reduction of myocardial damage during coronary intervention: results from the ARMYDA (Atorvastatin for Reduction of MYocardial Damage during Angioplasty) study. *Circulation* 2004;**110**:674–678.
273. Umpierrez GE, Hellman R, Korytkowski MT, Kosiborod M, Maynard GA, Montori VM, Seley JJ, Van den Berghe G, Endocrine S. Management of hyperglycemia in hospitalized patients in non-critical care setting: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab* 2012;**97**:16–38.
274. Mancia G, Laurent S, Agabiti-Rosei E, Ambrosioni E, Burnier M, Caulfield MJ, Cifkova R, Clement D, Coca A, Dominiczak A, Erdine S, Fagard R, Farsang C, Grassi G, Haller H, Heagerty A, Kjeldsen SE, Kiowski W, Mallion JM, Manolis A, Narkiewicz K, Nilsson P, Olsen MH, Rahn KH, Redon J, Rodicio J, Ruilope L, Schmieder RE, Struijker-Boudier HA, van Zwieten PA, Viigimaa M, Zanchetti A. Reappraisal of European guidelines on hypertension management: a European Society of Hypertension Task Force document. *J Hypertens* 2009;**27**:2121–2158.
275. Mancia G FR, Narkiewicz K, Redon J, Zanchetti A, Böhm M, Christiaens T, Cifkova R, De Backer G, Dominiczak A, Galderisi M, Grobbee DE, Jaarsma T, Kirchhof P, Kjeldsen SE, Laurent S, Manolis AJ, Nilsson PM, Ruilope LM, Schmieder RE, Sirnes PA, Sleight P, Viigimaa M, Waeber B, Zannad F; ESH Scientific Council, Redon J, Dominiczak A, Narkiewicz K, Nilsson PM, Burnier M, Viigimaa M, Ambrosioni E, Caufield M, Coca A, Olsen MH, Schmieder RE, Tsioufis C, van de Borne P; ESC Committee for Practice Guidelines (CPG), Zamorano JL, Achenbach S, Baumgartner H, Bax JJ, Bueno H, Dean V, Deaton C, Erol C, Fagard R, Ferrari R, Hasdai D, Hoes AW, Kirchhof P, Knuuti J, Kolh P, Lancellotti P, Linhart A, Nihoyannopoulos P, Piepoli MF, Ponikowski P, Sirnes PA, Tamargo JL, Tendera M, Torbicki A, Wijns W, Windecker S; Document Reviewers, Clement DL, Coca A, Gillebert TC, Tendera M, Rosei EA, Ambrosioni E, Anker SD, Bauersachs J, Hitij JB, Caulfield M, De Buyzere M, De Geest S, Derumeaux GA, Erdine S, Farsang C, Funck-Brentano C, Gerc V, Germano G, Gielen S, Haller H, Hoes AW, Jordan J, Kahan T, Komajda M, Lovic D, Mahrholdt H, Olsen MH, Ostergren J, Parati G, Perk J, Polonia J, Popescu BA, Reiner Z, Rydén L, Sirenko Y, Stanton A, Struijker-Boudier H, Tsioufis C, van de Borne P, Vlachopoulos C, Volpe M, Wood DA. 2013 ESH/ESC Guidelines for the management of arterial hypertension: The Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *Eur Heart J* 2013 [Epub ahead of print] No abstract available.
276. Piepoli MF, Corra U, Benzer W, Bjarnason-Wehrens B, Dendale P, Gaita D, McGee H, Mendes M, Niebauer J, Zwisler AD, Schmid JP. Secondary prevention through cardiac rehabilitation: from knowledge to implementation. A position paper from the Cardiac Rehabilitation Section of the European Association of Cardiovascular Prevention and Rehabilitation. *Eur J Cardiovasc Prev Rehabil* 2010;**17**: 1–17.
277. Heran BS, Chen JM, Ebrahim S, Moxham T, Oldridge N, Rees K, Thompson DR, Taylor RS. Exercise-based cardiac rehabilitation for coronary heart disease. *Cochrane Database Syst Rev* 2011**7**:CD001800.
278. Lawler PR, Filion KB, Eisenberg MJ. Efficacy of exercise-based cardiac rehabilitation post-myocardial infarction: a systematic review and meta-analysis of randomized controlled trials. *Am Heart J* 2011;**162**:571–584 e2.
279. Nichol KL, Nordin J, Mullooly J, Lask R, Fillbrandt K, Iwane M. Influenza vaccination and reduction in hospitalizations for cardiac disease and stroke among the elderly. *N Eng J Med* 2003;**348**:1322–1332.
280. Ciszewski A, Bilinska ZT, Brydak LB, Kepka C, Kruk M, Romanowska M, Ksiezycka E, Przyluski J, Piotrowski W, Maczynska R, Ruzyllo W. Influenza vaccination in secondary prevention from coronary ischaemic events in coronary artery disease: FLUCAD study. *Eur Heart J* 2008;**29**:1350–1358.
281. Manson JE, Hsia J, Johnson KC, Rossouw JE, Assaf AR, Lasser NL, Trevisan M, Black HR, Heckbert SR, Detrano R, Strickland OL, Wong ND, Crouse JR, Stein E, Cushman M. Estrogen plus progestin and the risk of coronary heart disease. *N Eng J Med* 2003;**349**:523–534.
282. Rossouw JE, Prentice RL, Manson JE, Wu L, Barad D, Barnabei VM, Ko M, LaCroix AZ, Margolis KL, Stefanick ML. Postmenopausal hormone therapy and risk of cardiovascular disease by age and years since menopause. *JAMA* 2007;**297**: 1465–1477.
283. Henderson RA, O'Flynn N. Management of stable angina: summary of NICE guidance. *Heart* 2012;**98**:500–507.
284. Thadani U, Fung HL, Darke AC, Parker JO. Oral isosorbide dinitrate in angina pectoris: comparison of duration of action an dose-response relation during acute and sustained therapy. *Am J Cardiol* 1982;**49**:411–419.
285. Parker JO. Eccentric dosing with isosorbide-5-mononitrate in angina pectoris. *Am J Cardiol* 1993;**72**:871–876.
286. Chrysant SG, Glasser SP, Bittar N, Shahidi FE, Danisa K, Ibrahim R, Watts LE, Garutti RJ, Ferraresi R, Casareto R. Efficacy and safety of extended-release isosorbide mononitrate for stable effort angina pectoris. *Am J Cardiol* 1993;**72**: 1249–1256.
287. Yusuf S, Wittes J, Friedman L. Overview of results of randomized clinical trials in heart disease. I. Treatments following myocardial infarction. *JAMA* 1988;**260**: 2088–2093.
288. Bangalore S, Steg G, Deedwania P, Crowley K, Eagle KA, Goto S, Ohman EM, Cannon CP, Smith SC, Zeymer U, Hoffman EB, Messerli FH, Bhatt DL, Investigators RR. beta-Blocker use and clinical outcomes in stable outpatients with and without coronary artery disease. *JAMA* 2012;**308**:1340–1349.
289. Wallace WA, Wellington KL, Chess MA, Liang CS. Comparison of nifedipine gastrointestinal therapeutic system and atenolol on antianginal efficacies and exercise hemodynamic responses in stable angina pectoris. *Am J Cardiol* 1994;**73**:23–28.
290. de Vries RJ, van den Heuvel AF, Lok DJ, Claessens RJ, Bernink PJ, Pasteuning WH, Kingma JH, Dunselman PH. Nifedipine gastrointestinal therapeutic system versus atenolol in stable angina pectoris. The Netherlands Working Group on Cardiovascular Research (WCN). *Int J Cardiol* 1996;**57**:143–150.
291. Fox KM, Mulcahy D, Findlay I, Ford I, Dargie HJ. The Total Ischaemic Burden European Trial (TIBET). Effects of atenolol, nifedipine SR and their combination on the exercise test and the total ischaemic burden in 608 patients with stable angina. The TIBET Study Group. *Eur Heart J* 1996;**17**:96–103.
292. van de Ven LL, Vermeulen A, Tans JG, Tans AC, Liem KL, Lageweg NC, Lie KI. Which drug to choose for stable angina pectoris: a comparative study between bisoprolol and nitrates. *Int J Cardiol* 1995;**47**:217–223.
293. Kawanishi DT, Reid CL, Morrison EC, Rahimtoola SH. Response of angina and ischemia to long-term treatment in patients with chronic stable angina: a double-blind randomized individualized dosing trial of nifedipine, propranolol and their combination. *J Am Coll Cardiol* 1992;**19**:409–417.
294. Meyer TE, Adnams C, Commerford P. Comparison of the efficacy of atenolol and its combination with slow-release nifedipine in chronic stable angina. *Cardiovasc Drugs Ther* 1993;**7**:909–913.
295. Steffensen R, Grande P, Pedersen F, Haunso S. Effects of atenolol and diltiazem on exercise tolerance and ambulatory ischaemia. *Int J Cardiol* 1993;**40**:143–153.
296. Parameshwar J, Keegan J, Mulcahy D, Phadke K, Sparrow J, Sutton GC, Fox KM. Atenolol or nicardipine alone is as efficacious in stable angina as their combination: a double blind randomised trial. *Int J Cardiol* 1993;**40**:135–141.
297. Foale RA. Atenolol versus the fixed combination of atenolol and nifedipine in stable angina pectoris. *Eur Heart J* 1993;**14**:1369–1374.
298. Rehnqvist N, Hjemdahl P, Billing E, Bjorkander I, Eriksson SV, Forslund L, Held C, Nasman P, Wallen NH. Effects of metoprolol vs verapamil in patients with stable angina pectoris. The Angina Prognosis Study in Stockholm (APSIS). *Eur Heart J* 1996;**17**:76–81.
299. Hjalmarson A, Goldstein S, Fagerberg B, Wedel H, Waagstein F, Kjekshus J, Wikstrand J, El Allaf D, Vitovec J, Aldershvile J, Halinen M, Dietz R, Neuhaus KL, Janosi A, Thorgeirsson G, Dunselman PH, Gullestad L, Kuch J, Herlitz J, Rickenbacher P, Ball S, Gottlieb S, Deedwania P. Effects of controlled-release

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metoprolol on total mortality, hospitalizations, and well-being in patients with heart failure: the Metoprolol CR/XL Randomized Intervention Trial in congestive heart failure (MERIT-HF). MERIT-HF Study Group. *JAMA* 2000;**283**:1295–1302.

300. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial. *Lancet* 1999;**353**:9–13.
301. Packer M, Bristow MR, Cohn JN, Colucci WS, Fowler MB, Gilbert EM, Shusterman NH. The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. U.S. Carvedilol Heart Failure Study Group. *N Eng J Med* 1996;**334**:1349–1355.
302. Flather MD, Shibata MC, Coats AJ, Van Veldhuisen DJ, Parkhomenko A, Borbola J, Cohen-Solal A, Dumitrascu D, Ferrari R, Lechat P, Soler-Soler J, Tavazzi L, Spinarova L, Toman J, Bohm M, Anker SD, Thompson SG, Poole-Wilson PA. Randomized trial to determine the effect of nebivolol on mortality and cardiovascular hospital admission in elderly patients with heart failure (SENIORS). *Eur Heart J* 2005;**26**:215–225.
303. Pepine CJ, Handberg EM, Cooper-DeHoff RM, Marks RG, Kowey P, Messerli FH, Mancia G, Cangiano JL, Garcia-Barreto D, Keltai M, Erdine S, Bristol HA, Kolb HR, Bakris GL, Cohen JD, Parmley WW. A calcium antagonist vs a non-calcium antagonist hypertension treatment strategy for patients with coronary artery disease. The International Verapamil-Trandolapril Study (INVEST): a randomized controlled trial. *JAMA* 2003;**290**:2805–2816.
304. Ried LD, Tueth MJ, Handberg E, Kupfer S, Pepine CJ. A Study of Antihypertensive Drugs and Depressive Symptoms (SADD-Sx) in patients treated with a calcium antagonist versus an atenolol hypertension Treatment Strategy in the International Verapamil SR-Trandolapril Study (INVEST). *Psychosom Med* 2005;**67**:398–406.
305. Nissen SE, Tuzcu EM, Libby P, Thompson PD, Ghali M, Garza D, Berman L, Shi H, Buebendorf E, Topol EJ. Effect of antihypertensive agents on cardiovascular events in patients with coronary disease and normal blood pressure: the CAMELOT study: a randomized controlled trial. *JAMA* 2004;**292**:2217–2225.
306. Haasenritter J, Bosner S, Vaucher P, Herzig L, Heinzel-Gutenbrunner M, Baum E, Donner-Banzhoff N. Ruling out coronary heart disease in primary care: external validation of a clinical prediction rule. *Br J Gen Pract* 2012;**62**:e415–e421.
307. Tardif JC, Ford I, Tendera M, Bourassa MG, Fox K. Efficacy of ivabradine, a new selective I(f) inhibitor, compared with atenolol in patients with chronic stable angina. *Eur Heart J* 2005;**26**:2529–2536.
308. Tardif JC, Ponikowski P, Kahan T. Efficacy of the I(f) current inhibitor ivabradine in patients with chronic stable angina receiving beta-blocker therapy: a 4-month, randomized, placebo-controlled trial. *Eur Heart J* 2009;**30**:540–548.
309. Viswanathan S, Frishman LJ, Robson JG, Harwerth RS, Smith EL 3rd. The photopic negative response of the macaque electroretinogram: reduction by experimental glaucoma. *Invest Ophthalmol Vis Sci* 1999;**40**:1124–1136.
310. *Ranexa (Ranolazine)*. **http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Summary_for_the_public/human/000805/WC500045940.pdf (23 August 2013)**.
311. Izumiya Y, Kojima S, Kojima S, Araki S, Usuku H, Matsubara J, Sakamoto K, Tsujita K, Nagayoshi Y, Kaikita K, Sugiyama S, Ogawa H. Long-term use of oral nicorandil stabilizes coronary plaque in patients with stable angina pectoris. *Atherosclerosis* 2011;**214**:415–421.
312. Tuunanen H, Engblom E, Naum A, Nagren K, Scheinin M, Hesse B, Juhani Airaksinen KE, Nuutila P, Iozzo P, Ukkonen H, Opie LH, Knuuti J. Trimetazidine, a metabolic modulator, has cardiac and extracardiac benefits in idiopathic dilated cardiomyopathy. *Circulation* 2008;**118**:1250–1258.
313. Detry JM, Sellier P, Pennaforte S, Cokkinos D, Dargie H, Mathes P. Trimetazidine: a new concept in the treatment of angina. Comparison with propranolol in patients with stable angina. Trimetazidine European Multicenter Study Group. *Br J Clin Pharmacol* 1994;**37**:279–288.
314. El-Kady T, El-Sabban K, Gabaly M, Sabry A, Abdel-Hady S. Effects of trimetazidine on myocardial perfusion and the contractile response of chronically dysfunctional myocardium in ischemic cardiomyopathy: a 24-month study. *Am J Cardiovasc Drugs* 2005;**5**:271–278.
315. *Questions and answers on the review of medicines containing trimetazidine (20 mg tablets, 35 mg modified release tablet and 20 mg/ml oral solution)*. **http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/Trimetazidine_31/WC500129195.pdf (9 March 2012)**.
316. Fragasso G, Piatti Md PM, Monti L, Palloshi A, Setola E, Puccetti P, Calori G, Lopaschuk GD, Margonato A. Short- and long-term beneficial effects of trimetazidine in patients with diabetes and ischemic cardiomyopathy. *Am Heart J* 2003;**146**:e18.
317. Jerling M. Clinical pharmacokinetics of ranolazine. *Clin Pharmacokinet* 2006;**45**:469–491.
318. Timmis AD, Chaitman BR, Crager M. Effects of ranolazine on exercise tolerance and HbA1c in patients with chronic angina and diabetes. *Eur Heart J* 2006;**27**:42–48.
319. Morrow DA, Scirica BM, Karwatowska-Prokopczuk E, Murphy SA, Budaj A, Varshavsky S, Wolff AA, Skene A, McCabe CH, Braunwald E. Effects of ranolazine on recurrent cardiovascular events in patients with non-ST-elevation acute coronary syndromes: the MERLIN-TIMI 36 randomized trial. *JAMA* 2007;**297**:1775–1783.
320. Morrow DA, Scirica BM, Chaitman BR, McGuire DK, Murphy SA, Karwatowska-Prokopczuk E, McCabe CH, Braunwald E. Evaluation of the glycometabolic effects of ranolazine in patients with and without diabetes mellitus in the MERLIN-TIMI 36 randomized controlled trial. *Circulation* 2009;**119**:2032–2039.
321. Wilson SR, Scirica BM, Braunwald E, Murphy SA, Karwatowska-Prokopczuk E, Buros JL, Chaitman BR, Morrow DA. Efficacy of ranolazine in patients with chronic angina observations from the randomized, double-blind, placebo-controlled MERLIN-TIMI (Metabolic Efficiency With Ranolazine for Less Ischemia in Non-ST-Segment Elevation Acute Coronary Syndromes) 36 Trial. *J Am Coll Cardiol* 2009;**53**:1510–1516.
322. Kosiborod M, Arnold SV, Spertus JA, McGuire DK, Li Y, Yue P, Ben-Yehuda O, Katz A, Jones PG, Olmsted A, Belardinelli L, Chaitman BR. Evaluation of Ranolazine in Patients with Type 2 Diabetes Mellitus and Chronic Stable Angina. Results from the TERISA randomized clinical trial. *J Am Coll Cardiol* 2013; **61**(20):2038–45
323. Noman A, Ang DS, Ogston S, Lang CC, Struthers AD. Effect of high-dose allopurinol on exercise in patients with chronic stable angina: a randomised, placebo controlled crossover trial. *Lancet* 2010;**375**:2161–2167.
324. Opie LH. Allopurinol for heart failure: novel mechanisms. *J Am Coll Cardiol* 2012;**59**:809–812.
325. Wagner F, Gohlke-Barwolf C, Trenk D, Jahnchen E, Roskamm H. Differences in the antiischaemic effects of molsidomine and isosorbide dinitrate (ISDN) during acute and short-term administration in stable angina pectoris. *Eur Heart J* 1991;**12**:994–999.
326. Young LH, Wackers FJ, Chyun DA, Davey JA, Barrett EJ, Taillefer R, Heller GV, Iskandrian AE, Wittlin SD, Filipchuk N, Ratner RE, Inzucchi SE, Investigators D. Cardiac outcomes after screening for asymptomatic coronary artery disease in patients with type 2 diabetes: the DIAD study: a randomized controlled trial. *JAMA* 2009;**301**:1547–1555.
327. Kolloch R, Legler UF, Champion A, Cooper-Dehoff RM, Handberg E, Zhou Q, Pepine CJ. Impact of resting heart rate on outcomes in hypertensive patients with coronary artery disease: findings from the INternational VErapamil-SR/trandolapril STudy (INVEST). *Eur Heart J* 2008;**29**:1327–1334.
328. Fox K, Ford I, Steg PG, Tendera M, Robertson M, Ferrari R, investigators B. Heart rate as a prognostic risk factor in patients with coronary artery disease and left-ventricular systolic dysfunction (BEAUTIFUL): a subgroup analysis of a randomised controlled trial. *Lancet* 2008;**372**:817–821.
329. Opie LH, Horowitz JD. Nitrates and newer anti-anginals. In. *Drugs for the Heart*. 8th ed: Elsevier, 2012.
330. Short PM, Lipworth SI, Elder DH, Schembri S, Lipworth BJ. Effect of beta blockers in treatment of chronic obstructive pulmonary disease: a retrospective cohort study. *BMJ* 2011;**342**:d2549.
331. Lievre MM, Moulin P, Thivolet C, Rodier M, Rigalleau V, Penfornis A, Pradignac A, Ovize M, investigators D. Detection of silent myocardial ischemia in asymptomatic patients with diabetes: results of a randomized trial and meta-analysis assessing the effectiveness of systematic screening. *Trials* 2011;**12**:23.
332. Collaborative overview of randomised trials of antiplatelet therapy: I: Prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. Antiplatelet Trialists' Collaboration. *BMJ* 1994;**308**:81–106.
333. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ* 2002;**324**:71–86.
334. Juul-Moller S, Edvardsson N, Jahnmatz B, Rosen A, Sorensen S, Omblus R. Double-blind trial of aspirin in primary prevention of myocardial infarction in patients with stable chronic angina pectoris. The Swedish Angina Pectoris Aspirin Trial (SAPAT) Group. *Lancet* 1992;**340**:1421–1425.
335. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). CAPRIE Steering Committee. *Lancet* 1996;**348**:1329–1339.
336. Gurbel PA, Bliden KP, Butler K, Tantry US, Gesheff T, Wei C, Teng R, Antonino MJ, Patil SB, Karunakaran A, Kereiakes DJ, Parris C, Purdy D, Wilson V, Ledley GS, Storey RF. Randomized double-blind assessment of the ONSET and OFFSET of the antiplatelet effects of ticagrelor versus clopidogrel in patients with stable coronary artery disease: the ONSET/OFFSET study. *Circulation* 2009;**120**:2577–2585.
337. Jernberg T, Payne CD, Winters KJ, Darstein C, Brandt JT, Jakubowski JA, Naganuma H, Siegbahn A, Wallentin L. Prasugrel achieves greater inhibition of platelet aggregation and a lower rate of non-responders compared with clopidogrel in aspirin-treated patients with stable coronary artery disease. *Eur Heart J* 2006;**27**:1166–1173.
338. Wiviott SD, Braunwald E, McCabe CH, Montalescot G, Ruzyllo W, Gottlieb S, Neumann FJ, Ardissino D, De Servi S, Murphy SA, Riesmeyer J, Weerakkody G, Gibson CM, Antman EM. Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Eng J Med* 2007;**357**:2001–2015.

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339. Cannon CP, Harrington RA, James S, Ardissino D, Becker RC, Emanuelsson H, Husted S, Katus H, Keltai M, Khurmi NS, Kontny F, Lewis BS, Steg PG, Storey RF, Wojdyla D, Wallentin L. Comparison of ticagrelor with clopidogrel in patients with a planned invasive strategy for acute coronary syndromes (PLATO): a randomised double-blind study. *Lancet* 2010;**375**:283–293.
340. Roe MT, Armstrong PW, Fox KA, White HD, Prabhakaran D, Goodman SG, Cornel JH, Bhatt DL, Clemmensen P, Martinez F, Ardissino D, Nicolau JC, Boden WE, Gurbel PA, Ruzyllo W, Dalby AJ, McGuire DK, Leiva-Pons JL, Parkhomenko A, Gottlieb S, Topacio GO, Hamm C, Pavlides G, Goudev AR, Oto A, Tseng CD, Merkely B, Gasparovic V, Corbalan R, Cinteza M, McLendon RC, Winters KJ, Brown EB, Lokhnygina Y, Aylward PE, Huber K, Hochman JS, Ohman EM. Prasugrel versus Clopidogrel for Acute Coronary Syndromes without Revascularization. *N Eng J Med* 2012; **367**(14):1297–309
341. Morrow DA, Braunwald E, Bonaca MP, Ameriso SF, Dalby AJ, Fish MP, Fox KA, Lipka LJ, Liu X, Nicolau JC, Ophuis AJ, Paolasso E, Scirica BM, Spinar J, Theroux P, Wiviott SD, Strony J, Murphy SA. Vorapaxar in the secondary prevention of atherothrombotic events. *N Eng J Med* 2012;**366**:1404–1413.
342. Yusuf S, Zhao F, Mehta SR, Chrolavicius S, Tognoni G, Fox KK. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *N Eng J Med* 2001;**345**:494–502.
343. Bhatt DL, Fox KA, Hacke W, Berger PB, Black HR, Boden WE, Cacoub P, Cohen EA, Creager MA, Easton JD, Flather MD, Haffner SM, Hamm CW, Hankey GJ, Johnston SC, Mak KH, Mas JL, Montalescot G, Pearson TA, Steg PG, Steinhubl SR, Weber MA, Brennan DM, Fabry-Ribaudo L, Booth J, Topol EJ. Clopidogrel and aspirin versus aspirin alone for the prevention of atherothrombotic events. *N Eng J Med* 2006;**354**:1706–1717.
344. Bhatt DL, Flather MD, Hacke W, Berger PB, Black HR, Boden WE, Cacoub P, Cohen EA, Creager MA, Easton JD, Hamm CW, Hankey GJ, Johnston SC, Mak KH, Mas JL, Montalescot G, Pearson TA, Steg PG, Steinhubl SR, Weber MA, Fabry-Ribaudo L, Hu T, Topol EJ, Fox KA. Patients with prior myocardial infarction, stroke, or symptomatic peripheral arterial disease in the CHARISMA trial. *J Am Coll Cardiol* 2007;**49**:1982–1988.
345. Larson DM, Menssen KM, Sharkey SW, Duval S, Schwartz RS, Harris J, Meland JT, Unger BT, Henry TD. "False-positive" cardiac catheterization laboratory activation among patients with suspected ST-segment elevation myocardial infarction. *JAMA* 2007;**298**:2754–2760.
346. Mega JL, Simon T, Collet JP, Anderson JL, Antman EM, Bliden K, Cannon CP, Danchin N, Giusti B, Gurbel P, Horne BD, Hulot JS, Kastrati A, Montalescot G, Neumann FJ, Shen L, Sibbing D, Steg PG, Trenk D, Wiviott SD, Sabatine MS. Reduced-function CYP2C19 genotype and risk of adverse clinical outcomes among patients treated with clopidogrel predominantly for PCI: a meta-analysis. *JAMA* 2010;**304**:1821–1830.
347. Collet JP, Cuisset T, Range G, Cayla G, Elhadad S, Pouillot C, Henry P, Motreff P, Carrie D, Boueri Z, Belle L, Van Belle E, Rousseau H, Aubry P, Monsegu J, Sabouret P, O'Connor SA, Abtan J, Kerneis M, Saint-Etienne C, Barthelemy O, Beygui F, Silvain J, Vicaut E, Montalescot G, Investigators A. Bedside monitoring to adjust antiplatelet therapy for coronary stenting. *N Eng J Med* 2012;**367**:2100–2109.
348. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. The SOLVD Investigators. *N Eng J Med* 1991;**325**:293–302.
349. Pfeffer MA, Braunwald E, Moye LA, Basta L, Brown EJ Jr., Cuddy TE, Davis BR, Geltman EM, Goldman S, Flaker GC *et al.* Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. Results of the survival and ventricular enlargement trial. The SAVE Investigators. *N Eng J Med* 1992;**327**:669–677.
350. Flather MD, Yusuf S, Kober L, Pfeffer M, Hall A, Murray G, Torp-Pedersen C, Ball S, Pogue J, Moye L, Braunwald E. Long-term ACE-inhibitor therapy in patients with heart failure or left-ventricular dysfunction: a systematic overview of data from individual patients. ACE-Inhibitor Myocardial Infarction Collaborative Group. *Lancet* 2000;**355**:1575–1581.
351. Yusuf S, Sleight P, Pogue J, Bosch J, Davies R, Dagenais G. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study Investigators. *N Eng J Med* 2000;**342**:145–153.
352. Fox KM. Efficacy of perindopril in reduction of cardiovascular events among patients with stable coronary artery disease: randomised, double-blind, placebo-controlled, multicentre trial (the EUROPA study). *Lancet* 2003;**362**:782–788.
353. Dagenais GR, Pogue J, Fox K, Simoons ML, Yusuf S. Angiotensin-converting-enzyme inhibitors in stable vascular disease without left ventricular systolic dysfunction or heart failure: a combined analysis of three trials. *Lancet* 2006;**368**:581–588.
354. Patel A, MacMahon S, Chalmers J, Neal B, Woodward M, Billot L, Harrap S, Poulter N, Marre M, Cooper M, Glasziou P, Grobbee DE, Hamet P, Heller S, Liu LS, Mancia G, Mogensen CE, Pan CY, Rodgers A, Williams B. Effects of a fixed combination of perindopril and indapamide on macrovascular and microvascular outcomes in patients with type 2 diabetes mellitus (the ADVANCE trial): a randomised controlled trial. *Lancet* 2007;**370**:829–840.
355. Braunwald E, Domanski MJ, Fowler SE, Geller NL, Gersh BJ, Hsia J, Pfeffer MA, Rice MM, Rosenberg YD, Rouleau JL, Investigators PT. Angiotensin-converting-enzyme inhibition in stable coronary artery disease. *N Eng J Med* 2004;**351**:2058–2068.
356. Dahlof B, Sever PS, Poulter NR, Wedel H, Beevers DG, Caulfield M, Collins R, Kjeldsen SE, Kristinsson A, McInnes GT, Mehlsen J, Nieminen M, O'Brien E, Ostergren J. Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required versus atenolol adding bendroflumethiazide as required, in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA): a multicentre randomised controlled trial. *Lancet* 2005;**366**:895–906.
357. Jamerson K, Weber MA, Bakris GL, Dahlof B, Pitt B, Shi V, Hester A, Gupte J, Gatlin M, Velazquez EJ. Benazepril plus amlodipine or hydrochlorothiazide for hypertension in high-risk patients. *N Eng J Med* 2008;**359**:2417–2428.
358. Yusuf S, Teo KK, Pogue J, Dyal L, Copland I, Schumacher H, Dagenais G, Sleight P, Anderson C. Telmisartan, ramipril, or both in patients at high risk for vascular events. *N Eng J Med* 2008;**358**:1547–1559.
359. Mann JF, Schmieder RE, McQueen M, Dyal L, Schumacher H, Pogue J, Wang X, Maggioni A, Budaj A, Chaithiraphan S, Dickstein K, Keltai M, Metsarinne K, Oto A, Parkhomenko A, Piegas LS, Svendsen TL, Teo KK, Yusuf S. Renal outcomes with telmisartan, ramipril, or both, in people at high vascular risk (the ONTARGET study): a multicentre, randomised, double-blind, controlled trial. *Lancet* 2008;**372**:547–553.
360. Pitt B, Remme W, Zannad F, Neaton J, Martinez F, Roniker B, Bittman R, Hurley S, Kleiman J, Gatlin M. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. *N Eng J Med* 2003;**348**:1309–1321.
361. Mukherjee D, Nissen SE, Topol EJ. Risk of cardiovascular events associated with selective COX-2 inhibitors. *JAMA* 2001;**286**:954–959.
362. Bresalier RS, Sandler RS, Quan H, Bolognese JA, Oxenius B, Horgan K, Lines C, Riddell R, Morton D, Lanas A, Konstam MA, Baron JA. Cardiovascular events associated with rofecoxib in a colorectal adenoma chemoprevention trial. *N Eng J Med* 2005;**352**:1092–1102.
363. Solomon SD, McMurray JJ, Pfeffer MA, Wittes J, Fowler R, Finn P, Anderson WF, Zauber A, Hawk E, Bertagnolli M. Cardiovascular risk associated with celecoxib in a clinical trial for colorectal adenoma prevention. *N Eng J Med* 2005;**352**:1071–1080.
364. Salisbury AC, Kosiborod M. Hospital-acquired anemia in patients with cardiovascular disease: incidence, outcomes, and opportunities for prevention. *Rev Cardiovasc Med* 2012;**13**:e150–e160.
365. Goyal A, Spertus JA, Gosch K, Venkitachalam L, Jones PG, Van den Berghe G, Kosiborod M. Serum potassium levels and mortality in acute myocardial infarction. *JAMA* 2012;**307**:157–164.
366. Collaborative overview of randomised trials of antiplatelet therapy: III: Reduction in venous thrombosis and pulmonary embolism by antiplatelet prophylaxis among surgical and medical patients. Antiplatelet Trialists' Collaboration. *BMJ* 1994;**308**:235–246.
367. Cannon RO 3rd, Watson RM, Rosing DR, Epstein SE. Efficacy of calcium channel blocker therapy for angina pectoris resulting from small-vessel coronary artery disease and abnormal vasodilator reserve. *Am J Cardiol* 1985;**56**:242–246.
368. Chen JW, Lee WL, Hsu NW, Lin SJ, Ting CT, Wang SP, Chang MS. Effects of short-term treatment of nicorandil on exercise-induced myocardial ischemia and abnormal cardiac autonomic activity in microvascular angina. *Am J Cardiol* 1997;**80**:32–38.
369. Albertsson PA, Emanuelsson H, Milsom I. Beneficial effect of treatment with transdermal estradiol-17-beta on exercise-induced angina and ST segment depression in syndrome X. *Int J Cardiol* 1996;**54**:13–20.
370. Amin AP, Salisbury AC, McCullough PA, Gosch K, Spertus JA, Venkitachalam L, Stolker JM, Parikh CR, Masoudi FA, Jones PG, Kosiborod M. Trends in the incidence of acute kidney injury in patients hospitalized with acute myocardial infarction. *Arch Intern Med* 2012;**172**:246–253.
371. Fabian E, Varga A, Picano E, Vajo Z, Ronaszeki A, Csanady M. Effect of simvastatin on endothelial function in cardiac syndrome X patients. *Am J Cardiol* 2004;**94**:652–655.
372. Lanza GA, Colonna G, Pasceri V, Maseri A. Atenolol versus amlodipine versus isosorbide-5-mononitrate on anginal symptoms in syndrome X. *Am J Cardiol* 1999;**84**:854–856, A8.
373. Emdin M, Picano E, Lattanzi F, L'Abbate A. Improved exercise capacity with acute aminophylline administration in patients with syndrome X. *J Am Coll Cardiol* 1989;**14**:1450–1453.
374. Cannon RO 3rd, Quyyumi AA, Mincemoyer R, Stine AM, Gracely RH, Smith WB, Geraci MF, Black BC, Uhde TW, Waclawiw MA *et al.* Imipramine in patients with chest pain despite normal coronary angiograms. *N Eng J Med* 1994;**330**:1411–1417.

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375. Sgueglia GA, Sestito A, Spinelli A, Cioni B, Infusino F, Papacci F, Bellocci F, Meglio M, Crea F, Lanza GA. Long-term follow-up of patients with cardiac syndrome X treated by spinal cord stimulation. *Heart* 2007;**93**:591–597.
376. Yasue H, Takizawa A, Nagao M, Nishida S, Horie M, Kubota J, Omote S, Takaoka K, Okumura K. Long-term prognosis for patients with variant angina and influential factors. *Circulation* 1988;**78**:1–9.
377. Frenneaux M, Kaski JC, Brown M, Maseri A. Refractory variant angina relieved by guanethidine and clonidine. *Am J Cardiol* 1988;**62**:832–833.
378. Gaspardone A, Tomai F, Versaci F, Ghini AS, Polisca P, Crea F, Chiariello L, Gioffre PA. Coronary artery stent placement in patients with variant angina refractory to medical treatment. *Am J Cardiol* 1999;**84**:96–98, A8.
379. Abbate A, Hamza M, Cassano AD, Melchior R, Roberts C, Grizzard J, Shah K, Hastillo A, Kasirajan V, Crea F, Lanza GA, Vetrovec GW. Sympathectomy as a treatment for refractory coronary artery spasm. *Int J Cardiol* 2012;**161**(1):e7–9.
380. Montalescot G, White HD, Gallo R, Cohen M, Steg PG, Aylward PE, Bode C, Chiariello M, King SB 3rd, Harrington RA, Desmet WJ, Macaya C, Steinhubl SR. Enoxaparin versus unfractionated heparin in elective percutaneous coronary intervention. *N Eng J Med* 2006;**355**:1006–1017.
381. Lincoff AM, Bittl JA, Harrington RA, Feit F, Kleiman NS, Jackman JD, Sarembock IJ, Cohen DJ, Spriggs D, Ebrahimi R, Keren G, Carr J, Cohen EA, Betriu A, Desmet W, Kereiakes DJ, Rutsch W, Wilcox RG, de Feyter PJ, Vahanian A, Topol EJ. Bivalirudin and provisional glycoprotein IIb/IIIa blockade compared with heparin and planned glycoprotein IIb/IIIa blockade during percutaneous coronary intervention: REPLACE-2 randomized trial. *JAMA* 2003;**289**:853–863.
382. Singh M, Gersh BJ, Lennon RJ, Ting HH, Holmes DR Jr., Doyle BJ, Rihal CS. Outcomes of a system-wide protocol for elective and nonelective coronary angioplasty at sites without on-site surgery: the Mayo Clinic experience. *Mayo Clin Proc* 2009;**84**:501–508.
383. Stettler C, Wandel S, Allemann S, Kastrati A, Morice MC, Schomig A, Pfisterer ME, Stone GW, Leon MB, de Lezo JS, Goy JJ, Park SJ, Sabate M, Suttorp MJ, Kelbaek H, Spaulding C, Menichelli M, Vermeersch P, Dirksen MT, Cervinka P, Petronio AS, Nordmann AJ, Diem P, Meier B, Zwahlen M, Reichenbach S, Trelle S, Windecker S, Juni P. Outcomes associated with drug-eluting and bare-metal stents: a collaborative network meta-analysis. *Lancet* 2007;**370**:937–948.
384. Schomig A, Dibra A, Windecker S, Mehilli J, Suarez de Lezo J, Kaiser C, Park SJ, Goy JJ, Lee JH, Di Lorenzo E, Wu J, Juni P, Pfisterer ME, Meier B, Kastrati A. A meta-analysis of 16 randomized trials of sirolimus-eluting stents versus paclitaxel-eluting stents in patients with coronary artery disease. *J Am Coll Cardiol* 2007;**50**:1373–1380.
385. Sarno G, Lagerqvist B, Frobert O, Nilsson J, Olivecrona G, Omerovic E, Saleh N, Venetzanos D, James S. Lower risk of stent thrombosis and restenosis with unrestricted use of 'new-generation' drug-eluting stents: a report from the nationwide Swedish Coronary Angiography and Angioplasty Registry (SCAAR). *Eur Heart J* 2012;**33**:606–613.
386. Bellemain-Appaix A, O'Connor SA, Silvain J, Cucherat M, Beygui F, Barthelemy O, Collet JP, Jacq L, Bernasconi F, Montalescot G, Group A. Association of clopidogrel pretreatment with mortality, cardiovascular events, and major bleeding among patients undergoing percutaneous coronary intervention: a systematic review and meta-analysis. *JAMA* 2012;**308**:2507–2516.
387. Hung MJ, Cherng WJ, Yang NI, Cheng CW, Li LF. Relation of high-sensitivity C-reactive protein level with coronary vasospastic angina pectoris in patients without hemodynamically significant coronary artery disease. *Am J Cardiol* 2005;**96**:1484–1490.
388. Mori F, Uchida T, Byun T, Tanino S, Imamura K, Oomori H, Nagashima M, Enta K, Tanaka M, Kasahara S, Hirosawa K. [Cardiac events in vasospastic angina: site and morphology of coronary artery spasm is related to the long-term prognosis of vasospastic angina]. *J Cardiol* 1999;**33**:191–199.
389. Iakovou I, Schmidt T, Bonizzoni E, Ge L, Sangiorgi GM, Stankovic G, Airoldi F, Chieffo A, Montorfano M, Carlino M, Michev I, Corvaja N, Briguori C, Gerckens U, Grube E, Colombo A. Incidence, predictors, and outcome of thrombosis after successful implantation of drug-eluting stents. *JAMA* 2005;**293**:2126–2130.
390. Eisenberg MJ, Richard PR, Libersan D, Filion KB. Safety of short-term discontinuation of antiplatelet therapy in patients with drug-eluting stents. *Circulation* 2009;**119**:1634–1642.
391. Stefanini GG, Kalesan B, Serruys PW, Heg D, Buszman P, Linke A, Ischinger T, Klauss V, Eberli F, Wijns W, Morice MC, Di Mario C, Corti R, Antoni D, Sohn HY, Eerdmans P, van Es GA, Meier B, Windecker S, Juni P. Long-term clinical outcomes of biodegradable polymer biolimus-eluting stents versus durable polymer sirolimus-eluting stents in patients with coronary artery disease (LEADERS): 4 year follow-up of a randomised non-inferiority trial. *Lancet* 2011;**378**:1940–1948.
392. Baber U, Mehran R, Sharma SK, Brar S, Yu J, Suh JW, Kim HS, Park SJ, Kastrati A, de Waha A, Krishnan P, Moreno P, Sweeny J, Kim MC, Suleman J, Pyo R, Wiley J, Kovacic J, Kini AS, Dangas GD. Impact of the everolimus-eluting stent on stent thrombosis: a meta-analysis of 13 randomized trials. *J Am Coll Cardiol* 2011;**58**:1569–1577.
393. Airoldi F, Colombo A, Morici N, Latib A, Cosgrave J, Buellesfeld L, Bonizzoni E, Carlino M, Gerckens U, Godino C, Melzi G, Michev I, Montorfano M, Sangiorgi GM, Qasim A, Chieffo A, Briguori C, Grube E. Incidence and predictors of drug-eluting stent thrombosis during and after discontinuation of thienopyridine treatment. *Circulation* 2007;**116**:745–754.
394. Schulz S, Schuster T, Mehilli J, Byrne RA, Ellert J, Massberg S, Goedel J, Bruskina O, Ulm K, Schomig A, Kastrati A. Stent thrombosis after drug-eluting stent implantation: incidence, timing, and relation to discontinuation of clopidogrel therapy over a 4-year period. *Eur Heart J* 2009;**30**:2714–2721.
395. Valgimigli M, Campo G, Monti M, Vranckx P, Percoco G, Tumscitz C, Castriota F, Colombo F, Tebaldi M, Fuca G, Kubbajeh M, Cangiano E, Minarelli M, Scalone A, Cavazza C, Frangione A, Borghesi M, Marchesini J, Parrinello G, Ferrari R. Short- versus long-term duration of dual-antiplatelet therapy after coronary stenting: a randomized multicenter trial. *Circulation* 2012;**125**:2015–2026.
396. Gwon HC, Hahn JY, Park KW, Song YB, Chae IH, Lim DS, Han KR, Choi JH, Choi SH, Kang HJ, Koo BK, Ahn T, Yoon JH, Jeong MH, Hong TJ, Chung WY, Choi YJ, Hur SH, Kwon HM, Jeon DW, Kim BO, Park SH, Lee NH, Jeon HK, Jang Y, Kim HS. Six-month versus 12-month dual antiplatelet therapy after implantation of drug-eluting stents: the Efficacy of Xience/Promus Versus Cypher to Reduce Late Loss After Stenting (EXCELLENT) randomized, multicenter study. *Circulation* 2012;**125**:505–513.
397. Dewilde WJ, Oirbans T, Verheugt FW, Kelder JC, De Smet BJ, Herrman JP, Adriaenssens T, Vrolix M, Heestermans AA, Vis MM, Tijsen JG, van 't Hof AW, ten Berg JM, investigators Ws. Use of clopidogrel with or without aspirin in patients taking oral anticoagulant therapy and undergoing percutaneous coronary intervention: an open-label, randomised, controlled trial. *Lancet* 2013;**381**:1107–1115.
398. Lindstrom J, Tuomilehto J. The diabetes risk score: a practical tool to predict type 2 diabetes risk. *Diabetes Care* 2003;**26**:725–731.
399. Pijls NH, Fearon WF, Tonino PA, Siebert U, Ikeno F, Bornschein B, van't Veer M, Klauss V, Manoharan G, Engstrom T, Oldroyd KG, Ver Lee PN, MacCarthy PA, De Bruyne B. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention in patients with multivessel coronary artery disease: 2-year follow-up of the FAME (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation) study. *J Am Coll Cardiol* 2010;**56**:177–184.
400. de Bruyne B, Pijls NH, Kalesan B, Barbato E, Tonino PA, Piroth Z, Jagic N, Mobius-Winckler S, Rioufol G, Witt N, Kala P, MacCarthy P, Engstrom T, Oldroyd KG, Mavromatis K, Manoharan G, Verlee P, Frobert O, Curzen N, Johnson JB, Juni P, Fearon WF. Fractional flow reserve-guided PCI versus medical therapy in stable coronary disease. *N Eng J Med* 2012;**367**:991–1001.
401. Hamilos M, Muller O, Cuisset T, Ntalianis A, Chlouverakis G, Sarno G, Nelis O, Bartunek J, Vanderheyden M, Wyffels E, Barbato E, Heyndrickx GR, Wijns W, De Bruyne B. Long-term clinical outcome after fractional flow reserve-guided treatment in patients with angiographically equivocal left main coronary artery stenosis. *Circulation* 2009;**120**:1505–1512.
402. Ntalianis A, Sels JW, Davidavicius G, Tanaka N, Muller O, Trana C, Barbato E, Hamilos M, Mangiacapra F, Heyndrickx GR, Wijns W, Pijls NH, De Bruyne B. Fractional flow reserve for the assessment of nonculprit coronary artery stenoses in patients with acute myocardial infarction. *JACC Cardiovasc Interv* 2010;**3**:1274–1281.
403. Jasti V, Ivan E, Yalamanchili V, Wongpraparut N, Leesar MA. Correlations between fractional flow reserve and intravascular ultrasound in patients with an ambiguous left main coronary artery stenosis. *Circulation* 2004;**110**:2831–2836.
404. Barlis P, Schmitt JM. Current and future developments in intracoronary optical coherence tomography imaging. *EuroIntervention* 2009;**4**:529–533.
405. Pijls NH, van Schaardenburgh P, Manoharan G, Boersma E, Bech JW, van't Veer M, Bar F, Hoorntje J, Koolen J, Wijns W, de Bruyne B. Percutaneous coronary intervention of functionally nonsignificant stenosis: 5-year follow-up of the DEFER Study. *J Am Coll Cardiol* 2007;**49**:2105–2111.
406. Prati F, Regar E, Mintz GS, Arbustini E, Di Mario C, Jang IK, Akasaka T, Costa M, Guagliumi G, Grube E, Ozaki Y, Pinto F, Serruys PW. Expert review document on methodology, terminology, and clinical applications of optical coherence tomography: physical principles, methodology of image acquisition, and clinical application for assessment of coronary arteries and atherosclerosis. *Eur Heart J* 2010;**31**:401–415.
407. Loop FD, Lytle BW, Cosgrove DM, Stewart RW, Goormastic M, Williams GW, Golding LA, Gill CC, Taylor PC, Sheldon WC *et al.* Influence of the internal-mammary-artery graft on 10-year survival and other cardiac events. *N Eng J Med* 1986;**314**:1–6.
408. Endo M, Nishida H, Tomizawa Y, Kasanuki H. Benefit of bilateral over single internal mammary artery grafts for multiple coronary artery bypass grafting. *Circulation* 2001;**104**:2164–2170.

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409. Dion R, Glineur D, Derouck D, Verhelst R, Noirhomme P, El Khoury G, Degrave E, Hanet C. Long-term clinical and angiographic follow-up of sequential internal thoracic artery grafting. *Eur J Cardiothorac Surg* 2000;**17**:407–414.
410. Taggart DP, D'Amico R, Altman DG. Effect of arterial revascularisation on survival: a systematic review of studies comparing bilateral and single internal mammary arteries. *Lancet* 2001;**358**:870–875.
411. Grau JB, Ferrari G, Mak AW, Shaw RE, Brizzio ME, Mindich BP, Strobeck J, Zapolanski A. Propensity matched analysis of bilateral internal mammary artery versus single left internal mammary artery grafting at 17-year follow-up: validation of a contemporary surgical experience. *Eur J Cardiothorac Surg* 2012;**41**:770–775; discussion 776.
412. Kurlansky PA, Traad EA, Dorman MJ, Galbut DL, Zucker M, Ebra G. Thirty-year follow-up defines survival benefit for second internal mammary artery in propensity-matched groups. *Ann Thorac Surg* 2010;**90**:101–108.
413. Taggart DP, Altman DG, Gray AM, Lees B, Nugara F, Yu LM, Campbell H, Flather M. Randomized trial to compare bilateral vs. single internal mammary coronary artery bypass grafting: 1-year results of the Arterial Revascularisation Trial (ART). *Eur Heart J* 2010;**31**:2470–2481.
414. Athanasiou T, Saso S, Rao C, Vecht J, Grapsa J, Dunning J, Lemma M, Casula R. Radial artery versus saphenous vein conduits for coronary artery bypass surgery: forty years of competition: which conduit offers better patency? A systematic review and meta-analysis. *Eur J Cardiothorac Surg* 2011;**40**:208–220.
415. Benedetto U, Angeloni E, Refice S, Sinatra R. Radial artery versus saphenous vein graft patency: meta-analysis of randomized controlled trials. *J Thorac Cardiovasc Surg* 2010;**139**:229–231.
416. Collins P, Webb CM, Chong CF, Moat NE. Radial artery versus saphenous vein patency randomized trial: five-year angiographic follow-up. *Circulation* 2008;**117**:2859–2864.
417. Deb S, Cohen EA, Singh SK, Une D, Laupacis A, Fremes SE. Radial artery and saphenous vein patency more than 5 years after coronary artery bypass surgery: results from RAPS (Radial Artery Patency Study). *J Am Coll Cardiol* 2012;**60**:28–35.
418. Takagi H, Tanabashi T, Kawai N, Kato T, Umemoto T. Off-pump coronary artery bypass sacrifices graft patency: meta-analysis of randomized trials. *J Thorac Cardiovasc Surg* 2007;**133**:e2–e3.
419. Shroyer AL, Grover FL, Hattler B, Collins JF, McDonald GO, Kozora E, Lucke JC, Baltz JH, Novitzky D. On-pump versus off-pump coronary-artery bypass surgery. *N Eng J Med* 2009;**361**:1827–1837.
420. Buffolo E, Andrade JC, Succi JE, Leao LE, Cueva C, Branco JN, Gallucci C. [Direct revascularization of the myocardium without extracorporeal circulation. Description of the technic and preliminary results]. *Arq Bras Cardiol* 1982;**38**:365–373.
421. Lamy A, Devereaux PJ, Prabhakaran D, Taggart DP, Hu S, Paolasso E, Straka Z, Piegas LS, Akar AR, Jain AR, Noiseux N, Padmanabhan C, Bahamondes JC, Novick RJ, Vaijyanath P, Reddy S, Tao L, Olavegogeascoechea PA, Airan B, Sulling TA, Whitlock RP, Ou Y, Ng J, Chrolavicius S, Yusuf S. Off-pump or on-pump coronary-artery bypass grafting at 30 days. *N Eng J Med* 2012;**366**:1489–1497.
422. Afilalo J, Rasti M, Ohayon SM, Shimony A, Eisenberg MJ. Off-pump vs. on-pump coronary artery bypass surgery: an updated meta-analysis and meta-regression of randomized trials. *Eur Heart J* 2012;**33**:1257–1267.
423. Hannan EL, Wu C, Smith CR, Higgins RS, Carlson RE, Culliford AT, Gold JP, Jones RH. Off-pump versus on-pump coronary artery bypass graft surgery: differences in short-term outcomes and in long-term mortality and need for subsequent revascularization. *Circulation* 2007;**116**:1145–1152.
424. Puskas JD, Thourani VH, Kilgo P, Cooper W, Vassiliades T, Vega JD, Morris C, Chen E, Schmotzer BJ, Guyton RA, Lattouf OM. Off-pump coronary artery bypass disproportionately benefits high-risk patients. *Ann Thorac Surg* 2009;**88**:1142–1147.
425. Kuss O, von Salviati B, Borgermann J. Off-pump versus on-pump coronary artery bypass grafting: a systematic review and meta-analysis of propensity score analyses. *J Thorac Cardiovasc Surg* 2010;**140**:829–835; 835 e1–e13.
426. Chatterjee S, Chaudhuri D, Vedanthan R, Fuster V, Ibanez B, Bangalore S, Mukherjee D. Early intravenous beta-blockers in patients with acute coronary syndrome-A meta-analysis of randomized trials. *Int J Cardiol* 2012.
427. Serruys PW, Morice MC, Kappetein AP, Colombo A, Holmes DR, Mack MJ, Stahle E, Feldman TE, van den Brand M, Bass EJ, Van Dyck N, Leadley K, Dawkins KD, Mohr FW. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. *N Eng J Med* 2009;**360**:961–972.
428. Serruys PW, Onuma Y, Garg S, Sarno G, van den Brand M, Kappetein AP, Van Dyck N, Mack M, Holmes D, Feldman T, Morice MC, Colombo A, Bass E, Leadley K, Dawkins KD, van Es GA, Morel MA, Mohr FW. Assessment of the SYNTAX score in the Syntax study. *EuroIntervention* 2009;**5**:50–56.
429. Bonow RO, Maurer G, Lee KL, Holly TA, Binkley PF, Desvigne-Nickens P, Drozdz J, Farsky PS, Feldman AM, Doenst T, Michler RE, Berman DS, Nicolau JC, Pellikka PA, Wrobel K, Alotti N, Asch FM, Favaloro LE, She L, Velazquez EJ, Jones RH, Panza JA. Myocardial viability and survival in ischemic left ventricular dysfunction. *N Eng J Med* 2011;**364**:1617–1625.
430. Velazquez EJ, Lee KL, Deja MA, Jain A, Sopko G, Marchenko A, Ali IS, Pohost G, Gradinac S, Abraham WT, Yii M, Prabhakaran D, Szwed H, Ferrazzi P, Petrie MC, O'Connor CM, Panchavinnin P, She L, Bonow RO, Rankin GR, Jones RH, Rouleau JL. Coronary artery bypass surgery in patients with left ventricular dysfunction. *N Eng J Med* 2011;**364**:1607–1616.
431. Erne P, Schoenenberger AW, Burckhardt D, Zuber M, Kiowski W, Buser PT, Dubach P, Resink TJ, Pfisterer M. Effects of percutaneous coronary interventions in silent ischemia after myocardial infarction: the SWISSI II randomized controlled trial. *JAMA* 2007;**297**:1985–1991.
432. Madsen JK, Grande P, Saunamaki K, Thayssen P, Kassis E, Eriksen U, Rasmussen K, Haunso S, Nielsen TT, Haghfelt T, Fritz-Hansen P, Hjelms E, Paulsen PK, Alstrup P, Arendrup H, Niebuhr-Jorgensen U, Andersen LI. Danish multicenter randomized study of invasive versus conservative treatment in patients with inducible ischemia after thrombolysis in acute myocardial infarction (DANAMI). DANish trial in Acute Myocardial Infarction. *Circulation* 1997;**96**:748–755.
433. Madsen JK, Nielsen TT, Grande P, Eriksen UH, Saunamaki K, Thayssen P, Kassis E, Rasmussen K, Haunso S, Haghfelt T, Fritz-Hansen P, Hjelms E, Paulsen PK, Alstrup P, Arendrup H, Niebuhr-Jorgensen U, Andersen LI. Revascularization compared to medical treatment in patients with silent vs. symptomatic residual ischemia after thrombolyzed myocardial infarction: the DANAMI study. *Cardiology* 2007;**108**:243–251.
434. Hochman JS, Lamas GA, Buller CE, Dzavik V, Reynolds HR, Abramsky SJ, Forman S, Ruzyllo W, Maggioni AP, White H, Sadowski Z, Carvalho AC, Rankin JM, Renkin JP, Steg PG, Mascette AM, Sopko G, Pfisterer ME, Leor J, Fridrich V, Mark DB, Knatterud GL. Coronary intervention for persistent occlusion after myocardial infarction. *N Eng J Med* 2006;**355**:2395–2407.
435. Yousef ZR, Redwood SR, Bucknall CA, Sulke AN, Marber MS. Late intervention after anterior myocardial infarction: effects on left ventricular size, function, quality of life, and exercise tolerance: results of the Open Artery Trial (TOAT Study). *J Am Coll Cardiol* 2002;**40**:869–876.
436. Steg PG, Thuaire C, Himbert D, Carrie D, Champagne S, Coisne D, Khalife K, Cazaux P, Logeart D, Slama M, Spaulding C, Cohen A, Tirouvanziam A, Montely JM, Rodriguez RM, Garbarz E, Wijns W, Durand-Zaleski I, Porcher R, Brucker L, Chevret S, Chastang C. DECOPI (DEsobstruction COronaire en Post-Infarctus): a randomized multi-centre trial of occluded artery angioplasty after acute myocardial infarction. *Eur Heart J* 2004;**25**:2187–2194.
437. Thrombolysis in myocardial infarction (TIMI) phase II trial. *N Eng J Med* 1989;**321**:612.
438. SWIFT trial of delayed elective intervention v conservative treatment after thrombolysis with anistreplase in acute myocardial infarction. SWIFT (Should We Intervene Following Thrombolysis?) Trial Study Group. *BMJ* 1991;**302**:555–560.
439. Barbash GI, Roth A, Hod H, Modan M, Miller HI, Rath S, Zahav YH, Keren G, Motro M, Shachar A *et al.* Randomized controlled trial of late in-hospital angiography and angioplasty versus conservative management after treatment with recombinant tissue-type plasminogen activator in acute myocardial infarction. *Am J Cardiol* 1990;**66**:538–545.
440. Verheugt FW. Lyse now, stent later: the grace of GRACIA. *Lancet* 2004;**364**:1014–1015.
441. Collet JP, Montalescot G, Le May M, Borentain M, Gershlick A. Percutaneous coronary intervention after fibrinolysis: a multiple meta-analyses approach according to the type of strategy. *J Am Coll Cardiol* 2006;**48**:1326–1335.
442. Pfisterer ME, Zellweger MJ, Gersh BJ. Management of stable coronary artery disease. *Lancet* 2010;**375**:763–772.
443. Cassar A, Holmes DR Jr., Rihal CS, Gersh BJ. Chronic coronary artery disease: diagnosis and management. *Mayo Clin Proc* 2009;**84**:1130–1146.
444. Kaiser GC, Davis KB, Fisher LD, Myers WO, Foster ED, Passamani ER, Gillespie MJ. Survival following coronary artery bypass grafting in patients with severe angina pectoris (CASS). An observational study. *J Thorac Cardiovasc Surg* 1985;**89**:513–524.
445. Yusuf S, Zucker D, Chalmers TC. Ten-year results of the randomized control trials of coronary artery bypass graft surgery: tabular data compiled by the collaborative effort of the original trial investigators. Part 1 of 2. *Online J Curr Clin Trials* 1994;**Doc No 145**.
446. Jones RH, Kesler K, Phillips HR 3rd, Mark DB, Smith PK, Nelson CL, Newman MF, Reves JG, Anderson RW, Califf RM. Long-term survival benefits of coronary artery bypass grafting and percutaneous transluminal angioplasty in patients with coronary artery disease. *J Thorac Cardiovasc Surg* 1996;**111**:1013–1125.
447. Rihal CS, Raco DL, Gersh BJ, Yusuf S. Indications for coronary artery bypass surgery and percutaneous coronary intervention in chronic stable angina: review of the evidence and methodological considerations. *Circulation* 2003;**108**:2439–2445.
448. Vlietstra RE, Assad-Morell JL, Frye RL, Elveback LR, Connolly DC, Ritman EL, Pluth JR, Barnhorst DA, Danielson GK, Wallace RB. Survival predictors in coronary artery disease. Medical and surgical comparisons. *Mayo Clin Proc* 1977;**52**:85–90.

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449. Alderman EL, Fisher LD, Litwin P, Kaiser GC, Myers WO, Maynard C, Levine F, Schloss M. Results of coronary artery surgery in patients with poor left ventricular function (CASS). *Circulation* 1983;**68**:785–795.
450. O'Connor CM, Velazquez EJ, Gardner LH, Smith PK, Newman MF, Landolfo KP, Lee KL, Califf RM, Jones RH. Comparison of coronary artery bypass grafting versus medical therapy on long-term outcome in patients with ischemic cardiomyopathy (a 25-year experience from the Duke Cardiovascular Disease Databank). *Am J Cardiol* 2002;**90**:101–107.
451. Tarakji KG, Brunken R, McCarthy PM, Al-Chekakie MO, Abdel-Latif A, Pothier CE, Blackstone EH, Lauer MS. Myocardial viability testing and the effect of early intervention in patients with advanced left ventricular systolic dysfunction. *Circulation* 2006;**113**:230–237.
452. Tsuyuki RT, Shrive FM, Galbraith PD, Knudtson ML, Graham MM. Revascularization in patients with heart failure. *CMAJ* 2006;**175**:361–365.
453. Passamani E, Davis KB, Gillespie MJ, Killip T. A randomized trial of coronary artery bypass surgery. Survival of patients with a low ejection fraction. *N Eng J Med* 1985; **312**:1665–1671.
454. Dzavik V, Ghali WA, Norris C, Mitchell LB, Koshal A, Saunders LD, Galbraith PD, Hui W, Faris P, Knudtson ML. Long-term survival in 11,661 patients with multivessel coronary artery disease in the era of stenting: a report from the Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease (APPROACH) Investigators. *Am Heart J* 2001;**142**:119–126.
455. Jones EL, Weintraub WS. The importance of completeness of revascularization during long-term follow-up after coronary artery operations. *J Thorac Cardiovasc Surg* 1996;**112**:227–237.
456. Myers WO, Schaff HV, Gersh BJ, Fisher LD, Kosinski AS, Mock MB, Holmes DR, Ryan TJ, Kaiser GC. Improved survival of surgically treated patients with triple vessel coronary artery disease and severe angina pectoris. A report from the Coronary Artery Surgery Study (CASS) registry. *J Thorac Cardiovasc Surg* 1989;**97**: 487–495.
457. Smith PK, Califf RM, Tuttle RH, Shaw LK, Lee KL, Delong ER, Lilly RE, Sketch MH Jr., Peterson ED, Jones RH. Selection of surgical or percutaneous coronary intervention provides differential longevity benefit. *Ann Thorac Surg* 2006;**82**:1420–1428; discussion 1428–1429.
458. Varnauskas E. Twelve-year follow-up of survival in the randomized European Coronary Surgery Study. *N Eng J Med* 1988;**319**:332–337.
459. Hueb W, Lopes N, Gersh BJ, Soares PR, Ribeiro EE, Pereira AC, Favarato D, Rocha AS, Hueb AC, Ramires JA. Ten-year follow-up survival of the Medicine, Angioplasty, or Surgery Study (MASS II): a randomized controlled clinical trial of 3 therapeutic strategies for multivessel coronary artery disease. *Circulation* 2010; **122**:949–957.
460. Myers WO, Gersh BJ, Fisher LD, Mock MB, Holmes DR, Schaff HV, Gillispie S, Ryan TJ, Kaiser GC. Medical versus early surgical therapy in patients with triple-vessel disease and mild angina pectoris: a CASS registry study of survival. *Ann Thorac Surg* 1987;**44**:471–486.
461. Davies RF, Goldberg AD, Forman S, Pepine CJ, Knatterud GL, Geller N, Sopko G, Pratt C, Deanfield J, Conti CR. Asymptomatic Cardiac Ischemia Pilot (ACIP) study two-year follow-up: outcomes of patients randomized to initial strategies of medical therapy versus revascularization. *Circulation* 1997;**95**:2037–2043.
462. Di Carli MF, Maddahi J, Rokhsar S, Schelbert HR, Bianco-Batlles D, Brunken RC, Fromm B. Long-term survival of patients with coronary artery disease and left ventricular dysfunction: implications for the role of myocardial viability assessment in management decisions. *J Thorac Cardiovasc Surg* 1998;**116**:997–1004.
463. Sorajja P, Chareonthaitawee P, Rajagopalan N, Miller TD, Frye RL, Hodge DO, Gibbons RJ. Improved survival in asymptomatic diabetic patients with high-risk SPECT imaging treated with coronary artery bypass grafting. *Circulation* 2005; **112**:I311–316.
464. Hlatky MA, Cotugno HE, Mark DB, O'Connor C, Califf RM, Pryor DB. Trends in physician management of uncomplicated acute myocardial infarction, 1970 to 1987. *Am J Cardiol* 1988;**61**:515–518.
465. Shaw LJ, Weintraub WS, Maron DJ, Hartigan PM, Hachamovitch R, Min JK, Dada M, Mancini GB, Hayes SW, O'Rourke RA, Spertus JA, Kostuk W, Gosselin G, Chaitman BR, Knudtson M, Friedman J, Slomka P, Germano G, Bates ER, Teo KK, Boden WE, Berman DS. Baseline stress myocardial perfusion imaging results and outcomes in patients with stable ischemic heart disease randomized to optimal medical therapy with or without percutaneous coronary intervention. *Am Heart J* 2012;**164**:243–250.
466. Takaro T, Hultgren HN, Lipton MJ, Detre KM. The VA cooperative randomized study of surgery for coronary arterial occlusive disease II. Subgroup with significant left main lesions. *Circulation* 1976;**54**:III107–117.
467. Takaro T, Hultgren HN, Detre KM, Peduzzi P. The Veterans Administration Cooperative Study of stable angina: current status. *Circulation* 1982;**65**:60–67.
468. Yusuf S, Zucker D, Peduzzi P, Fisher LD, Takaro T, Kennedy JW, Davis K, Killip T, Passamani E, Norris R *et al.* Effect of coronary artery bypass graft surgery on survival: overview of 10-year results from randomised trials by the Coronary Artery Bypass Graft Surgery Trialists Collaboration. *Lancet* 1994;**344**:563–570.
469. Taylor HA, Deumite NJ, Chaitman BR, Davis KB, Killip T, Rogers WJ. Asymptomatic left main coronary artery disease in the Coronary Artery Surgery Study (CASS) registry. *Circulation* 1989;**79**:1171–1179.
470. Caracciolo EA, Davis KB, Sopko G, Kaiser GC, Corley SD, Schaff H, Taylor HA, Chaitman BR. Comparison of surgical and medical group survival in patients with left main equivalent coronary artery disease. Long-term CASS experience. *Circulation* 1995;**91**:2335–2344.
471. Patel MR, Dehmer GJ, Hirshfeld JW, Smith PK, Spertus JA. ACCF/SCAI/STS/AATS/AHA/ASNC/HFSA/SCCT 2012 Appropriate use criteria for coronary revascularization focused update: a report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, Society for Cardiovascular Angiography and Interventions, Society of Thoracic Surgeons, American Association for Thoracic Surgery, American Heart Association, American Society of Nuclear Cardiology, and the Society of Cardiovascular Computed Tomography. *J Am Coll Cardiol* 2012;**59**:857–881.
472. Parisi AF, Folland ED, Hartigan P. A comparison of angioplasty with medical therapy in the treatment of single-vessel coronary artery disease. Veterans Affairs ACME Investigators. *N Eng J Med* 1992;**326**:10–16.
473. Pitt B, Waters D, Brown WV, van Boven AJ, Schwartz L, Title LM, Eisenberg D, Shurzinske L, McCormick LS. Aggressive lipid-lowering therapy compared with angioplasty in stable coronary artery disease. Atorvastatin versus Revascularization Treatment Investigators. *N Eng J Med* 1999;**341**:70–76.
474. Coronary angioplasty versus medical therapy for angina: the second Randomised Intervention Treatment of Angina (RITA-2) trial. RITA-2 trial participants. *Lancet* 1997;**350**:461–468.
475. Trial of invasive versus medical therapy in elderly patients with chronic symptomatic coronary-artery disease (TIME): a randomised trial. *Lancet* 2001;**358**:951–957.
476. Pfisterer M. Long-term outcome in elderly patients with chronic angina managed invasively versus by optimized medical therapy: four-year follow-up of the randomized Trial of Invasive versus Medical therapy in Elderly patients (TIME). *Circulation* 2004;**110**:1213–1218.
477. Nishigaki K, Yamazaki T, Kitabatake A, Yamaguchi T, Kanmatsuse K, Kodama I, Takekoshi N, Tomoike H, Hori M, Matsuzaki M, Takeshita A, Shimbo T, Fujiwara H. Percutaneous coronary intervention plus medical therapy reduces the incidence of acute coronary syndrome more effectively than initial medical therapy only among patients with low-risk coronary artery disease a randomized, comparative, multicenter study. *JACC Cardiovasc Interv* 2008;**1**:469–479.
478. Dagenais GR, Lu J, Faxon DP, Kent K, Lago RM, Lezama C, Hueb W, Weiss M, Slater J, Frye RL. Effects of optimal medical treatment with or without coronary revascularization on angina and subsequent revascularizations in patients with type 2 diabetes mellitus and stable ischemic heart disease. *Circulation* 2011;**123**: 1492–1500.
479. Hueb W, Lopes NH, Gersh BJ, Soares P, Machado LA, Jatene FB, Oliveira SA, Ramires JA. Five-year follow-up of the Medicine, Angioplasty, or Surgery Study (MASS II): a randomized controlled clinical trial of 3 therapeutic strategies for multivessel coronary artery disease. *Circulation* 2007;**115**:1082–1089.
480. Bugiardini R, Bairey Merz CN. Angina with "normal" coronary arteries: a changing philosophy. *JAMA* 2005;**293**:477–484.
481. Taggart DP, Boyle R, de Belder MA, Fox KA. The 2010 ESC/EACTS guidelines on myocardial revascularisation. *Heart* 2011;**97**:445–446.
482. Kolh P, Wijns W, Danchin N, Di Mario C, Falk V, Folliguet T, Garg S, Huber K, James S, Knuuti J, Lopez-Sendon J, Marco J, Menicanti L, Ostojic M, Piepoli MF, Pirlet C, Pomar JL, Reifart N, Ribichini FL, Schalij MJ, Sergeant P, Serruys PW, Silber S, Sousa Uva M, Taggart D. Guidelines on myocardial revascularization. *Eur J Cardiothorac Surg* 2010;38 Suppl:S1–S52.
483. Kappetein AP, Feldman TE, Mack MJ, Morice MC, Holmes DR, Stahle E, Dawkins KD, Mohr FW, Serruys PW, Colombo A. Comparison of coronary bypass surgery with drug-eluting stenting for the treatment of left main and/or three-vessel disease: 3-year follow-up of the SYNTAX trial. *Eur Heart J* 2011;**32**: 2125–2134.
484. Mohr FW, Morice MC, Kappetein AP, Feldman TE, Stahle E, Colombo A, Mack MJ, Holmes DR Jr., Morel MA, Van Dyck N, Houle VM, Dawkins KD, Serruys PW. Coronary artery bypass graft surgery versus percutaneous coronary intervention in patients with three-vessel disease and left main coronary disease: 5-year follow-up of the randomised, clinical SYNTAX trial. *Lancet* 2013;**381**:629–638.
485. Hannan EL, Racz MJ, Walford G, Jones RH, Ryan TJ, Bennett E, Culliford AT, Isom OW, Gold JP, Rose EA. Long-term outcomes of coronary-artery bypass grafting versus stent implantation. *N Eng J Med* 2005;**352**:2174–2183.
486. Malenka DJ, Leavitt BJ, Hearne MJ, Robb JF, Baribeau YR, Ryan TJ, Helm RE, Kellett MA, Dauerman HL, Dacey LJ, Silver MT, VerLee PN, Weldner PW, Hettleman BD, Olmstead EM, Piper WD, O'Connor GT. Comparing long-term survival of patients with multivessel coronary disease after CABG or PCI: analysis of BARI-like patients in northern New England. *Circulation* 2005;**112**:I371–376.

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487. Wu C, Zhao S, Wechsler AS, Lahey S, Walford G, Culliford AT, Gold JP, Smith CR, Holmes DR Jr., King SB 3rd, Higgins RS, Jordan D, Hannan EL. Long-term mortality of coronary artery bypass grafting and bare-metal stenting. *Ann Thorac Surg* 2011;**92**: 2132–2138.
488. Weintraub WS, Grau-Sepulveda MV, Weiss JM, O'Brien SM, Peterson ED, Kolm P, Zhang Z, Klein LW, Shaw RE, McKay C, Ritzenthaler LL, Popma JJ, Messenger JC, Shahian DM, Grover FL, Mayer JE, Shewan CM, Garratt KN, Moussa ID, Dangas GD, Edwards FH. Comparative effectiveness of revascularization strategies. *N Eng J Med* 2012;**366**:1467–1476.
489. Park SJ, Kim YH, Park DW, Yun SC, Ahn JM, Song HG, Lee JY, Kim WJ, Kang SJ, Lee SW, Lee CW, Park SW, Chung CH, Lee JW, Lim DS, Rha SW, Lee SG, Gwon HC, Kim HS, Chae IH, Jang Y, Jeong MH, Tahk SJ, Seung KB. Randomized trial of stents versus bypass surgery for left main coronary artery disease. *N Eng J Med* 2011;**364**:1718–1727.
490. Taggart DP. ThomasB. Ferguson Lecture. Coronary artery bypass grafting is still the best treatment for multivessel and left main disease, but patients need to know. *Ann Thorac Surg* 2006;**82**:1966–1975.
491. Frishman WH. Silent myocardial ischemia: is it a clinical entity that requires therapy? *Heart Dis* 1999;**1**:263.
492. Chan PS, Patel MR, Klein LW, Krone RJ, Dehmer GJ, Kennedy K, Nallamothu BK, Weaver WD, Masoudi FA, Rumsfeld JS, Brindis RG, Spertus JA. Appropriateness of percutaneous coronary intervention. *JAMA* 2011;**306**:53–61.
493. Allender S, Scarborough P, O'Flaherty M, Capewell S. Patterns of coronary heart disease mortality over the 20th century in England and Wales: Possible plateaus in the rate of decline. *BMC Public Health* 2008;**8**:148.
494. Maas AH, van der Schouw YT, Regitz-Zagrosek V, Swahn E, Appelman YE, Pasterkamp G, Ten Cate H, Nilsson PM, Huisman MV, Stam HC, Eizema K, Stramba-Badiale M. Red alert for women's heart: the urgent need for more research and knowledge on cardiovascular disease in women: proceedings of the workshop held in Brussels on gender differences in cardiovascular disease, 29 September 2010. *Eur Heart J* 2011;**32**:1362–1368.
495. Hemingway H, Langenberg C, Damant J, Frost C, Pyorala K, Barrett-Connor E. Prevalence of angina in women versus men: a systematic review and meta-analysis of international variations across 31 countries. *Circulation* 2008;**117**:1526–1536.
496. Jacobs AK, Kelsey SF, Brooks MM, Faxon DP, Chaitman BR, Bittner V, Mock MB, Weiner BH, Dean L, Winston C, Drew L, Sopko G. Better outcome for women compared with men undergoing coronary revascularization: a report from the bypass angioplasty revascularization investigation (BARI). *Circulation* 1998;**98**: 1279–1285.
497. Boden WE, O'Rourke RA, Teo KK, Maron DJ, Hartigan PM, Sedlis SP, Dada M, Labedi M, Spertus JA, Kostuk WJ, Berman DS, Shaw LJ, Chaitman BR, Mancini GB, Weintraub WS. Impact of optimal medical therapy with or without percutaneous coronary intervention on long-term cardiovascular end points in patients with stable coronary artery disease (from the COURAGE Trial). *Am J Cardiol* 2009;**104**:1–4.
498. Bugiardini R, Pozzati A, Ottani F, Morgagni GL, Puddu P. Vasotonic angina: a spectrum of ischemic syndromes involving functional abnormalities of the epicardial and microvascular coronary circulation. *J Am Coll Cardiol* 1993;**22**:417–425.
499. Khuddus MA, Pepine CJ, Handberg EM, Bairey Merz CN, Sopko G, Bavry AA, Denardo SJ, McGorray SP, Smith KM, Sharaf BL, Nicholls SJ, Nissen SE, Anderson RD. An intravascular ultrasound analysis in women experiencing chest pain in the absence of obstructive coronary artery disease: a substudy from the National Heart, Lung and Blood Institute-Sponsored Women's Ischemia Syndrome Evaluation (WISE). *J Interv Cardiol* 2010;**23**:511–519.
500. Piepoli MF, Corra U, Benzer W, Bjarnason-Wehrens B, Dendale P, Gaita D, McGee H, Mendes M, Niebauer J, Zwisler AD, Schmid JP. Secondary prevention through cardiac rehabilitation: from knowledge to implementation. A position paper from the Cardiac Rehabilitation Section of the European Association of Cardiovascular Prevention and Rehabilitation. *Eur J Cardiovasc Prev Rehabil* 2010;**17**: 1–17.
501. Hillis LD, Smith PK, Anderson JL, Bittl JA, Bridges CR, Byrne JG, Cigarroa JE, Disesa VJ, Hiratzka LF, Hutter AM Jr., Jessen ME, Keeley EC, Lahey SJ, Lange RA, London MJ, Mack MJ, Patel MR, Puskas JD, Sabik JF, Selnes O, Shahian DM, Trost JC, Winniford MD. 2011 ACCF/AHA Guideline for Coronary Artery Bypass Graft Surgery. A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Developed in collaboration with the American Association for Thoracic Surgery, Society of Cardiovascular Anesthesiologists, and Society of Thoracic Surgeons. *J Am Coll Cardiol* 2011;**58**:e123–e210.
502. Levine GN, Bates ER, Blankenship JC, Bailey SR, Bittl JA, Cercek B, Chambers CE, Ellis SG, Guyton RA, Hollenberg SM, Khot UN, Lange RA, Mauri L, Mehran R, Moussa ID, Mukherjee D, Nallamothu BK, Ting HH, Jacobs AK, Anderson JL, Albert N, Creager MA, Ettinger SM, Halperin JL, Hochman JS, Kushner FG, Ohman EM, Stevenson W, Yancy CW. 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention: A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. *Catheter Cardiovasc Interv* 2011.
503. Baigent C, Blackwell L, Collins R, Emberson J, Godwin J, Peto R, Buring J, Hennekens C, Kearney P, Meade T, Patrono C, Roncaglioni MC, Zanchetti A. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. *Lancet* 2009; **373**:1849–1860.
504. Schomig A, Neumann FJ, Kastrati A, Schuhlen H, Blasini R, Hadamitzky M, Walter H, Zitzmann-Roth EM, Richardt G, Alt E, Schmitt C, Ulm K. A randomized comparison of antiplatelet and anticoagulant therapy after the placement of coronary-artery stents. *N Eng J Med* 1996;**334**:1084–1089.
505. Pfisterer M, Kaiser C, Jeger R. No one-size-fits-all: A tailored approach to antithrombotic therapy after stent implantation. *Circulation* 2012;**125**:471–473.
506. Goldman S, Zadina K, Moritz T, Ovitt T, Sethi G, Copeland JG, Thottapurathu L, Krasnicka B, Ellis N, Anderson RJ, Henderson W. Long-term patency of saphenous vein and left internal mammary artery grafts after coronary artery bypass surgery: results from a Department of Veterans Affairs Cooperative Study. *J Am Coll Cardiol* 2004;**44**:2149–2156.
507. Fitzgibbon GM, Kafka HP, Leach AJ, Keon WJ, Hooper GD, Burton JR. Coronary bypass graft fate and patient outcome: angiographic follow-up of 5,065 grafts related to survival and reoperation in 1,388 patients during 25 years. *J Am Coll Cardiol* 1996;**28**:616–626.
508. Riley RF, Don CW, Powell W, Maynard C, Dean LS. Trends in coronary revascularization in the United States from 2001 to 2009: recent declines in percutaneous coronary intervention volumes. *Circ Cardiovasc Qual Outcomes* 2011;**4**:193–197.
509. Arora RR, Chou TM, Jain D, Fleishman B, Crawford L, McKiernan T, Nesto RW. The multicenter study of enhanced external counterpulsation (MUST-EECP): effect of EECP on exercise-induced myocardial ischemia and anginal episodes. *J Am Coll Cardiol* 1999;**33**:1833–1840.
510. Warshafsky S, Packard D, Marks SJ, Sachdeva N, Terashita DM, Kaufman G, Sang K, Deluca AJ, Peterson SJ, Frishman WH. Efficacy of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors for prevention of stroke. *J Gen Intern Med* 1999;**14**: 763–774.
511. Andrell P, Yu W, Gersbach P, Gillberg L, Pehrsson K, Hardy I, Stahle A, Andersen C, Mannheimer C. Long-term effects of spinal cord stimulation on angina symptoms and quality of life in patients with refractory angina pectoris: results from the European Angina Registry Link Study (EARL). *Heart* 2010;**96**:1132–1136.
512. Taylor RS, De Vries J, Buchser E, Dejongste MJ. Spinal cord stimulation in the treatment of refractory angina: systematic review and meta-analysis of randomised controlled trials. *BMC Cardiovasc Disord* 2009;**9**:13.
513. Fox K, Ford I, Steg PG, Tendera M, Ferrari R. Ivabradine for patients with stable coronary artery disease and left-ventricular systolic dysfunction (BEAUTIFUL): a randomised, double-blind, placebo-controlled trial. *Lancet* 2008;**372**:807–816.
514. Frishman WH. Recent advances in cardiovascular pharmacology. *Heart Dis* 1999;**1**: 68–90.

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