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ESC GUIDELINES

2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death

The Task Force for the Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death of the European Society of Cardiology (ESC)

Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC)

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Abbreviations and acronyms

ACC	American College of Cardiology
ACE	angiotensin-converting enzyme
ACS	acute coronary syndrome
AF	atrial fibrillation
AGNES	Arrhythmia Genetics in the Netherlands
AHA	American Heart Association
AMIOVIRT	AMIOdarone Versus Implantable cardioverter-defibrillator: Randomized Trial in patients with non-ischaemic dilated cardiomyopathy and asymptomatic non-sustained ventricular tachycardia
ARB	angiotensin II receptor blocker
ARVC	arrhythmogenic right ventricular cardiomyopathy
AV	atrio-ventricular
AVID	Antiarrhythmic drugs Versus Implantable Defibrillator
BrS	Brugada Syndrome
CAD	coronary artery disease
CARE-HF	CArdiac REsynchronization − Heart Failure
CASH	Cardiac Arrest Study Hamburg
CAST	Cardiac Arrhythmia Suppression Trial
CAT	CArdiomyopathy Trial
CHD	congenital heart disease
CI	confidence interval
CIDS	Canadian Implantable Defibrillator Study
CMR	cardiac magnetic resonance
COMPANION	Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure
CPG	Committee for Practice Guidelines
CPVT	catecholaminergic polymorphic ventricular tachycardia
CRT	cardiac resynchronization therapy
CRT-D	cardiac resynchronization therapy defibrillator
CRT-P	cardiac resynchronization therapy pacemaker
CT	computed tomography
DCM	dilated cardiomyopathy
DEFINITE	DEFIbrillators in Non-Ischemic cardiomyopathy Treatment Evaluation
DFT	defibrillation threshold
DIAMOND	Danish Investigators of Arrhythmia and Mortality oN Dofetilide
ECG	electrocardiogram / electrocardiographic
EHRA	European Heart Rhythm Association
EPS	electrophysiological study
ESC	European Society of Cardiology
GWAS	genome-wide association study
HCM	hypertrophic cardiomyopathy
HF	heart failure
HFpEF	heart failure with preserved ejection fraction
HFrEF	heart failure with reduced ejection fraction
HR	hazard ratio
i.v.	intravenous

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ICD	implantable cardioverter defibrillator
ILCOR	International Liaison Committee On Resuscitation
IRIS	Immediate Risk stratification Improves Survival
LBBB	left bundle branch block
LMNA	lamin A/C
LQTS	long QT syndrome
LQTS1	long QT syndrome type 1
LQTS2	long QT syndrome type 2
LQTS3	long QT syndrome type 3
LV	left ventricle / left ventricular
LVEF	left ventricular ejection fraction
LVOT	left ventricular outflow tract
MADIT	Multicenter Automatic Defibrillator Implantation Trial
MIRACLE	Multicenter InSync Randomized Clinical Evaluation
MRA	mineralocorticoid receptor antagonist
ms	millisecond
MUSTT	Multicenter UnSustained Tachycardia Trial
NSTEMI	non–ST-segment elevation myocardial infarction
NSVT	non-sustained ventricular tachycardia
NYHA	New York Heart Association
OPTIC	Optimal Pharmacological Therapy In Cardioverter defibrillator patients
OR	odds ratio
OT	outflow tract
PRESERVE-EF	risk stratification in patients with preserved ejection fraction
PVC	premature ventricular complex
PVS	programmed ventricular stimulation
QTc	corrected QT
RAFT	Resynchronization–Defibrillation for Ambulatory Heart Failure Trial
RBBB	right bundle branch block
RCT	randomized controlled trial
REVERSE	REsynchronization reVErses Remodeling in Systolic left vEntricular dysfunction
REVERSE MIRACLE ICD	Multicenter InSync ICD Randomized Clinical Evaluation
RR	relative risk
RV	right ventricular
RVOT	right ventricular outflow tract
SA-ECG	signal-averaged ECG
SADS	sudden arrhythmic death syndrome
SCD	sudden cardiac death
SCD-HeFT	Sudden Cardiac Death in HEart Failure Trial
SCORE	Systematic Coronary Risk Evaluation
SIDS	sudden infant death syndrome
SMASH-VT	Substrate Mapping and Ablation in Sinus Rhythm to Halt Ventricular Tachycardia
SPECT	single-photon emission computed tomography
SQTS	short QT syndrome
STEMI	ST-segment elevation myocardial infarction
SUDEP	sudden unexpected death in epilepsy
SUDI	sudden unexplained death in infancy
SUDS	sudden unexplained death syndrome
TdP	torsade de pointes
US	United States
VA	ventricular arrhythmia
VF	ventricular fibrillation
VT	ventricular tachycardia
VTACH	Ventricular Tachycardia Ablation in Coronary Heart Disease
WCD	wearable cardioverter defibrillator
WPW	Wolff–Parkinson–White

1. Preamble

Guidelines summarize and evaluate all available evidence on a particular issue at the time of the writing process, with the aim of assisting health professionals 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 and recommendations should help health professionals to make decisions in their daily practice. However, the final decisions concerning an individual patient must be made by the responsible health professional(s) in consultation with the patient and caregiver as appropriate.

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-&-Education/Clinical-Practice-Guidelines/Guidelines-development/Writing-ESC-Guidelines). 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 management (including diagnosis, treatment, prevention and rehabilitation) of a given condition according to 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 the recommendation of particular management options were weighed and graded according to predefined scales, as outlined in *Tables 1* and *2*.

The experts of the writing and reviewing panels provided declarations of interest forms for all relationships that might be perceived as real or potential sources of conflicts of interest. 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 the healthcare industry.

The ESC CPG supervises and coordinates the preparation of new Guidelines produced by task forces, expert groups or consensus

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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

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 the Guidelines 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 Guidelines were developed after careful consideration of the scientific and medical knowledge and the evidence available at the time of their dating.

The task of developing ESC Guidelines covers not only 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 guidelines versions, summary slides, booklets with essential messages, summary cards for non-specialists, and an electronic version for digital applications (smartphones, etc.) are produced. These versions are abridged and thus, if needed, one should always refer to the full text version, which is freely available on the ESC website. The National Societies of the ESC are encouraged to endorse, translate and implement all 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, disseminating them and implementing them into clinical practice.

Health professionals are encouraged to take the ESC Guidelines fully into account when exercising their clinical judgment, as well as in the determination and the implementation of preventive, diagnostic or therapeutic medical strategies. However, the ESC Guidelines do not override in any way whatsoever the individual responsibility of health professionals to make appropriate and accurate decisions in consideration of each patient's health condition and in consultation with that patient and the patient's caregiver where appropriate and/or necessary. It is also the health professional's responsibility to verify the rules and regulations applicable to drugs and devices at the time of prescription.

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.

2. Introduction

The present document has been conceived as the European update to the American College of Cardiology (ACC)/American Heart Association (AHA)/ESC 2006 Guidelines for management of patients with ventricular arrhythmias (VA) and the prevention of sudden cardiac death (SCD).[1] In light of the very recent consensus documents for the management of patients with VA released by the major international heart rhythm societies,[2,3] the ESC Guidelines Committee decided to focus the content of this document on the prevention of SCD. The update is timely, considering the new insights into the natural history of diseases predisposing to SCD and the completion of major studies that will impact management strategies for heart failure (HF) involving both drug and device therapies.

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2.1 Structure of the guidelines

The document is divided in sections that cover specific topics. The risk evaluation scheme and treatment offered should be tailored in consideration of co-morbidities, limitation of life expectancy, impact on quality of life and other circumstances.

While preparing this update, the committee reviewed the most recent recommendations for each topic and modified the class and/or the strength of recommendations, considering whether new results from randomized trials, meta-analyses or clinical evidence would call for a change. Special care was taken to maintain consistency in the use of language with existing guidelines. Occasionally, however, wording changes were made to render some of the original recommendations more user friendly and precise.

The committee was composed of physicians and associated healthcare providers who are experts in the areas of SCD and prevention, complex VA, interventional electrophysiology, coronary artery disease (CAD), HF and cardiomyopathy, paediatric cardiology and arrhythmias, device therapy, cardiovascular care, cardiovascular genetics and nursing. Experts in different subspecialties in cardiology were identified with the help of the related working groups of the ESC.

All members of the writing committee approved the guideline recommendations. Seventy-four peer reviewers reviewed the document. An extensive literature survey was conducted that led to the incorporation of 810 references. The guidelines reviewed concerning prevention of SCD are listed in *Web Table 1*.[3–13]

3. Definitions, epidemiology and future perspectives for the prevention of sudden cardiac death

The definitions used for sudden death, aborted cardiac arrest, idiopathic ventricular fibrillation (VF) and for the prevention of sudden death are detailed in *Table 3*.

3.1 Epidemiology of sudden cardiac death

In the past 20 years, cardiovascular mortality has decreased in high-income countries[19] in response to the adoption of preventive measures to reduce the burden of CAD and HF. Despite these encouraging results, cardiovascular diseases are responsible for approximately 17 million deaths every year in the world, approximately 25% of which are SCD.[20] The risk of SCD is higher in men than in women, and it increases with age due to the higher prevalence of CAD in older age.[21] Accordingly, the SCD rate is estimated to range from 1.40 per 100 000 person-years [95% confidence interval (CI) 0.95, 1.98] in women to 6.68 per 100 000 person-years (95% CI 6.24, 7.14) in men.[21] SCD in younger individuals has an estimated incidence of 0.46–3.7 events per 100 000 person-years,[22,23] corresponding to a rough estimate of 1100–9000 deaths in Europe and 800–6200 deaths in the USA every year.[24]

Table 3 Definitions of commonly used terms

Term	Definition	Ref[a]
Sudden death	Non-traumatic, unexpected fatal event occurring within 1 hour of the onset of symptoms in an apparently healthy subject. If death is not witnessed, the definition applies when the victim was in good health 24 hours before the event.	1
SUDS and SUDI	Sudden death without an apparent cause and in which an autopsy has not been performed in an adult (SUDS) or in an infant <1 year of age (SUDI).	14
SCD	The term is used when: • A congenital, or acquired, potentially fatal cardiac condition was known to be present during life; OR • Autopsy has identified a cardiac or vascular anomaly as the probable cause of the event; OR • No obvious extra-cardiac causes have been identified by post-mortem examination and therefore an arrhythmic event is a likely cause of death.	1, 14, 15
SADS and SIDS	Both autopsy and toxicology investigations are inconclusive, the heart is structurally normal at gross and histological examination and non-cardiac aetiologies are excluded in adults (SADS) and in infants (SIDS).	16
Aborted cardiac arrest	Unexpected circulatory arrest, occurring within 1 hour of onset of acute symptoms, which is reversed by successful resuscitation manoeuvres (e.g. defibrillation).	-
Idiopathic ventricular fibrillation	Clinical investigations are negative in a patient surviving an episode of ventricular fibrillation.	17, 18
Primary prevention of SCD	Therapies to reduce the risk of SCD in individuals who are at risk of SCD but have not yet experienced an aborted cardiac arrest or life-threatening arrhythmias.	-
Secondary prevention of SCD	Therapies to reduce the risk of SCD in patients who have already experienced an aborted cardiac arrest or life-threatening arrhythmias.	1

SADS = sudden arrhythmic death syndrome; SCD = sudden cardiac death; SIDS = sudden infant death syndrome; SUDI = sudden unexplained death in infancy; SUDS = sudden unexplained death syndrome.
[a]References.

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3.1.1 Causes of sudden cardiac death in different age groups

Cardiac diseases associated with SCD differ in young vs. older individuals. In the young there is a predominance of channelopathies and cardiomyopathies (*Web Table 2*),[21,25–48] myocarditis and substance abuse,[49] while in older populations, chronic degenerative diseases predominate (CAD, valvular heart diseases and HF). Several challenges undermine identification of the cause of SCD in both age groups: older victims, for instance, may suffer from multiple chronic cardiovascular conditions so that it becomes difficult to determine which contributed most to SCD. In younger persons, the cause of SCD may be elusive even after autopsy, because conditions such as inherited channelopathies or drug-induced arrhythmias that are devoid of structural abnormalities are epidemiologically relevant in this age group.

3.2 Autopsy and molecular autopsy in sudden death victims

Indications for autopsy and molecular autopsy in sudden death victims

Recommendations	Class[a]	Level[b]	Ref.[c]
An autopsy is recommended to investigate the causes of sudden death and to define whether SCD is secondary to arrhythmic or non-arrhythmic mechanisms (e.g. rupture of an aortic aneurysm).	I	C	17
Whenever an autopsy is performed, a standard histological examination of the heart is recommended and it should include mapped labelled blocks of myocardium from representative transverse slices of both ventricles.	I	C	17
The analysis of blood and other adequately collected body fluids for toxicology and molecular pathology is recommended in all victims of unexplained sudden death.	I	C	17
Targeted post-mortem genetic analysis of potentially disease-causing genes should be considered in all sudden death victims in whom a specific inheritable channelopathy or cardiomyopathy is suspected.	IIa	C	17,50, 51

SCD = sudden cardiac death.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

Identification of the cause of an unexpected death provides the family with partial understanding and rationalization of the unexpected tragedy, which facilitates the coping process and allows an understanding of whether the risk of sudden death may extend to family members. Accordingly, it appears reasonable that all unexplained sudden death victims undergo post-mortem expert examination to investigate whether a cardiac origin should be suspected. Although CAD accounts for a large proportion of sudden deaths, especially for persons >40 years of age, other causes should be taken into account, including genetic disorders that affect either the integrity of the heart's muscle (see section 7) or its electrical function (see section 8). Every time a heritable disease is identified in a deceased individual, the relatives of the victim may be at risk of being affected and dying suddenly unless a timely diagnosis is made and preventive measures taken.

Unfortunately, even when an autopsy is performed, a proportion of sudden deaths, ranging from 2 to 54%,[48] remain unexplained (*Web Table 2*): this broad range of values is likely due to heterogeneity of the autopsy protocols. To promote a common standard for autopsy, targeted guidelines have been developed to define protocols for heart examination and histological sampling, as well as for toxicology and molecular investigation.[17,50] Overall, a properly conducted autopsy should provide answers to the following issues: (i) whether the death is attributable to a cardiac disease, (ii) the nature of the cardiac disease (if present), (iii) whether the mechanism of death was arrhythmic, (iv) whether there is evidence of a cardiac disease that may be inherited and thus requires screening and counselling of relatives and (v) the possibility of toxic or illicit drug use or other causes of unnatural deaths.

A standard histological examination of the heart should include mapped labelled blocks of myocardium from representative transverse slices of both ventricles. We encourage pathologists to contact specialized centres and send the heart to them for examination. The pathologist should perform a standard gross examination of the heart, including a transverse apical section, and take tissues, blood and other fluids for toxicology and molecular pathology before fixing the heart in formalin. Furthermore, the collection and storage of biological samples for DNA extraction to allow a 'molecular' autopsy is encouraged.[17] Molecular autopsy is an important addition to the standard autopsy, as it allows the diagnosis post-mortem of the presence of cardiac channelopathies that may explain 15–25% of sudden arrhythmic death syndrome (SADS) cases.[17] The value of the post-mortem diagnosis in a victim of SCD lies in extending genetic screening to the family members of SADS or SIDS victims. Recent expert consensus documents for the diagnosis and management of inheritable arrhythmias state that the use of a focused molecular autopsy/post-mortem genetic testing should be considered for SCD victims when the presence of channelopathies is suspected. We endorse this recommendation and refer interested readers to the most recent consensus documents on this topic.[14,52]

3.3 Risk prediction of sudden cardiac death

Prediction of SCD is the philosopher's stone of arrhythmology, and attempts to provide reliable indicators of SCD have fuelled one of the most active areas of investigation in arrhythmology during recent decades.[53] It is now clear that the propensity to die suddenly originates as a 'perfect storm'—interaction of a vulnerable substrate (genetic or acquired changes in the electrical or mechanical properties of the heart) with multiple transient factors that participate in triggering the fatal event. In the next section we provide a brief overview of the paucity of risk-stratification schemes for SCD in normal subjects, in patients with ischaemic heart disease and in patients with channelopathies and cardiomyopathies.

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3.3.1 Individuals without known heart disease

Approximately 50% of cardiac arrests occur in individuals without a known heart disease, but most suffer from concealed ischaemic heart disease.[54] As a consequence, the most effective approach to prevent SCD in the general population resides in quantification of the individual risk of developing ischaemic heart disease based on risk score charts, followed by the control of risk factors such as total serum cholesterol, glucose, blood pressure, smoking and body mass index.[55] Approximately 40% of the observed reduction in SCD is the direct consequence of a reduction of CAD and other cardiac conditions.[56]

Several studies[57–61] have provided evidence that there is a genetic predisposition to die suddenly. The research group led by X. Jouven was one of the first to investigate the predictive value of familial recurrence of sudden death. The authors demonstrated, in the Paris study published in 1999,[57] that one parental history of sudden death had a relative risk (RR) of sudden death of 1.89, which increased to 9.44 in those with two parental histories of sudden death ($P = 0.01$). At the same time, Friedlander *et al.*[58] confirmed, in a case-based cohort study from the Framingham study, an almost 50% increase [RR 1.46 (95% CI 1.23, 1.72)] in the likelihood of sudden death in the presence of a family history of SCD. In 2006, Dekker *et al.*[59] showed that familial sudden death occurs significantly more frequently in individuals resuscitated from primary VF than in controls [odds ratio (OR) 2.72 (95% CI 1.84, 4.03)]. The impressive consistency of these results suggests that the predisposition to die suddenly is written in the genes, even in the absence of a Mendelian disease, and encourages molecular investigations to identify DNA markers to predict SCD in the general population.

Among the studies that have searched for single nucleotide polymorphisms that predispose to SCD, the results of two genome-wide association studies (GWAS) are relevant: the Arrhythmia Genetics in the NEtherlandS (AGNES) study,[61] which involved patients with a first myocardial infarction and VF and compared them with a cohort of patients with a first myocardial infarction without VF. Only one single nucleotide polymorphism located in the 21q21 locus achieved genome-wide significance, with an OR of 1.78 (95% CI 1.47, 2.13; $P = 3.36 \times 10^{-10}$). This common single nucleotide polymorphism (47% frequency of the allele) is in an intergenic region and the closest gene, *CXADR* (~98 kb away), encodes a viral receptor implicated in viral myocarditis. The second GWAS study[62] was a very large study that identified a strong signal at the 2q24.2 locus, which contains three genes with unknown function that are all expressed in the heart. This locus increases the risk of SCD by 1.92 (95% CI 1.57, 2.34). The study did not, however, replicate the results of the AGNES study, raising concerns that either the size or the design of the AGNES study presented limitations. These genetic data are not yet being applied in clinics, but they show that genetics may evolve into a promising approach to quantify the risk of SCD early in life. The availability of novel technologies that allow faster and cheaper genotyping may soon provide data on very large populations and deliver the statistical power required for these investigations.

3.3.2 Patients with ischaemic heart disease

For more than two decades investigators throughout the world have envisioned a broad range of 'indicators' for SCD occurring in the setting of ischaemic heart disease. Several non-invasive markers of risk of SCD have been proposed for patients with myocardial ischaemia, including, among others, programmed ventricular stimulation (PVS), late potentials, heart rate variability, baroreflex sensitivity, QT interval dispersion, microvolt T-wave alternans and heart rate turbulence. However, despite the promising outcomes of the early studies, none of these 'predictors' has influenced clinical practice. As a consequence, the only indicator that has consistently shown an association with increased risk of sudden death in the setting of myocardial infarction and left ventricular (LV) dysfunction is LV ejection fraction (LVEF).[63,64] This variable has been used for more than a decade to target the use of an implantable cardioverter defibrillator (ICD) for primary prevention of SCD, often in combination with New York Heart Association (NYHA) class. Despite the fact that LVEF is not an accurate and highly reproducible clinical parameter, it is still used to select patients for ICD implantation in the primary prevention of SCD.

Among emerging variables that look promising for predicting SCD are biochemical indicators such as the B-type natriuretic peptide and N-terminal pro-B-type natriuretic peptide, which have shown encouraging results in preliminary investigations.[65,66]

3.3.3 Patients with inheritable arrhythmogenic diseases

The availability of risk stratification schemes is highly heterogeneous among the different channelopathies and cardiomyopathies: for example, while the duration of the corrected QT (QTc) interval is a reliable indicator of risk of cardiac events in long QT syndrome (LQTS),[67] and septal hypertrophy predicts outcome in hypertrophic cardiomyopathy (HCM),[68] in other diseases, such as Brugada syndrome or short QT syndrome (SQTS), risk stratification metrics are not robust, leaving uncertainties on how to target the prophylactic use of the ICD. So far, genetic information may be used to guide risk stratification only in a few diseases such as LQTS and lamin A/C dilated cardiomyopathy.[69–71]

3.4 Prevention of sudden cardiac death in special settings

3.4.1 Screening the general population for the risk of sudden cardiac death

Vigilance for electrocardiographic (ECG) and echocardiographic signs of inheritable arrhythmogenic diseases seems to be an important part of clinical practice and can contribute to the early identification of patients at risk of SCD. Whether such a careful approach should be extended to mass screening in populations at risk of sudden death is currently unclear. Italy and Japan have implemented ECG screening systems, which may identify asymptomatic patients with inheritable arrhythmogenic diseases.[72–74] While consensus exists among experts in Europe and the United States (US) that support preparticipation screening in athletes (an approach that has been endorsed by the International Olympic Committee),[75–77] a recent study reported no change in incidence rates of SCD in competitive athletes following implementation of screening programs in Israel.[78]

Similarly, there are no clear data supporting the benefit of broad screening programs in the general population. Narain *et al.*[79] screened 12 000 unselected healthy individuals 14–35 years of age. Screening was performed at a cost of GB£35 per individual and consisted of a health questionnaire, 12-lead ECG and consultation with a cardiologist. Individuals with abnormalities underwent a transthoracic echocardiogram on the same day or were referred for further evaluation.

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Although the screening identified only a few patients with inheritable channelopathies or cardiomyopathies (4/12 000), the authors concluded that the cost to identify individuals at increased risk of SCD might still support a mass-screening programme.

It is clear that the cost–benefit assessment of ECG population screening is influenced largely by the cost of identifying a single affected individual. Such a cost has not been determined by the Italian national healthcare system despite the fact that a universal screening programme has been in place for the past 35 years, and will vary depending on the regional organization of healthcare. The US cost estimate for screening athletes ranges from US$300 million–US$2 billion per year according to Kaltman *et al.*[80]

Overall, we cannot provide recommendations for population screening at this time because the consequences of screening strategies that detect a still-undefined number of 'false positives' and miss an unknown percentage of affected cases ('false negatives') have not been established. This inability to derive a recommendation from the evidence obtained from existing screening programmes illustrates the need for further work to collect quantitative data on the cost–benefit profile of performing ECG screening in different populations and in different healthcare systems and settings. Conversely, in consideration of the higher risk of arrhythmias and the worsening of structural or genetic diseases in individuals exposed to intense physical exercise,[81,82] we do support the existing recommendations for pre-participation screening in athletes. In Europe there is consensus that clinical evaluation, personal or family history taking and a baseline 12-lead ECG should be performed in this population (refer to section 12.7).

3.4.2 Screening family members of sudden death victims

The diagnosis of an inheritable arrhythmogenic disorder is established in up to 50%[83] of families with a SADS victim, especially channelopathies [e.g. LQTS, Brugada syndrome and catecholaminergic polymorphic ventricular tachycardia (CPVT)] and occasionally subtle forms of cardiomyopathy [HCM and arrhythmogenic right ventricular cardiomyopathy (ARVC) in particular] or familial hypercholesterolaemia. As a consequence of these findings, when an autopsy is either not available for the victim (i.e. SUDS or SUDI) and/or when the post-mortem examination fails to detect structural abnormalities and toxicology results are normal (i.e. SADS or SIDS), first-degree relatives of the victim should be informed of the potential risk of similar events to themselves and should undergo cardiac evaluation. A family history of recurrent premature SUDS or inheritable heart disease represents a 'red flag' that makes familial evaluation strongly recommended.

Family screening of first-degree relatives of victims of sudden death is an important intervention to identify individuals at risk, advise on available treatment and adequately prevent sudden death.[14,84] Currently only 40% of family members are screened,[85] partially due to a lack of adequate screening infrastructure, but also due to the anxiety and distress associated with the personal experience of a life-threatening arrhythmia or a recent family bereavement from an inheritable cardiac condition.[86,87] The psychosocial needs of these patients and their families should be evaluated and a multidisciplinary approach within specialized centres should be followed, as recently recommended.[14,84,88] The value of this approach has been demonstrated.[89,90]

Various protocols have been proposed for screening family members of sudden death victims.[14,91] These protocols usually follow a stepwise approach, starting with lower-cost and higher-yield investigations and moving on to further examinations based on both the initial findings and the family history.[91] Whenever a diagnosis is suspected, based on the presence of structural or electrical abnormalities, the standard procedure for the diagnosis of the suspected disease should be followed.

Accurate history taking is the first step to reach a post-mortem diagnosis, preliminary to active exploration of the family members. When the victim is young, the focus should be on cardiomyopathies and channelopathies. The evaluation of premonitory cardiac symptoms (including syncope or 'epilepsy'), together with an exhaustive exploration of the circumstances of death and the collection of ante-mortem clinical cardiac investigations, is recommended. When the victim is >40 years of age, the presence of risk factors for CAD should be assessed (e.g. active or passive smoking, dyslipoproteinaemia, hypertension or diabetes). In addition, a complete three-generation pedigree should be created, recording all sudden deaths and cardiac diseases.[14] Efforts to retrieve old medical records and/or post-mortem examinations should be made. Family members with symptoms suggestive of the presence of a cardiac condition, such as syncope, palpitations or chest pain, should be prioritized for evaluation.

The recommended core evaluation of a first-degree relative of a sudden death victim is illustrated in *Table 4*. In the absence of a diagnosis in the family, very young children should be screened at least with a baseline ECG and an echocardiogram.

As many inheritable arrhythmogenic diseases are characterized by age-related penetrance and incomplete expression, younger individuals should be followed-up at regular intervals. Asymptomatic and fully grown adults can be discharged from care unless symptoms appear or new information from the family becomes available.

When an inheritable arrhythmogenic disease is suspected, DNA samples from the victim are the best source of information when performing a molecular autopsy. If there is a positive result, family members should be offered the opportunity to undergo predictive genetic screening, in a cascade fashion. The 'right not to know' and the possibility to decline molecular screening should be included in any pre-informative communication with the relatives.

In the absence of biological samples from the deceased person, targeted molecular screening in first-degree relatives may be considered when there is the suspicion of the presence of an inheritable disease in family members. Conversely, genetic screening of a large panel of genes should not be performed in SUDS or SADS relatives without clinical clues for a specific disease after clinical evaluation. This is especially true in SIDS cases, where molecular autopsy identifies a lower burden of ion channel disease compared with SADS and sporadic genetic disease as a cause of sudden death may be more frequent.

3.4.3 Screening patients with documented or suspected ventricular arrhythmias

3.4.3.1 Clinical history

Palpitations (or sensation of sudden rapid heartbeats), presyncope and syncope are the three most important symptoms that

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Table 4 Diagnostic approach for family members of sudden unexplained death syndrome or sudden arrhythmic death syndrome victims

Approach	Action[a]
History taking and physical examination	• Personal clinical history • Family history focused on cardiac diseases or sudden deaths
ECG	• Baseline 12-lead ECG with standard and high precordial leads • 24-hour ambulatory ECG • Exercise stress test • Signal-averaged ECG • Provocative test with ajmaline/flecainide (when Brugada syndrome is suspected)
Cardiac imaging	• Two-dimensional echocardiography and/or CMR (with or without contrast)
Genetic testing	• Targeted molecular testing and genetic counselling if there is the clinical suspicion of a specific disease • Referral to a tertiary centre specialized in evaluation of the genetics of arrhythmias

CMR = cardiac magnetic resonance; ECG = electrocardiogram.
[a]The recommendations in this table are based on the consensus of this panel of experts and not on evidence-based data.

require a thorough clinical history taking and possibly further investigations to rule out a relation to VAs. Palpitations related to ventricular tachycardia (VT) are usually of a sudden onset/offset pattern and may be associated with presyncope and/or syncope. Episodes of sudden collapse with loss of consciousness without any premonition must raise the suspicion of bradyarrhythmias or VA. Syncope occurring during strenuous exercise, while sitting or in the supine position should always raise the suspicion of a cardiac cause, while other situational events may indicate vasovagal syncope or postural hypotension.[92] Symptoms related to underlying structural heart diseases, such as chest discomfort, dyspnoea and fatigue, may also be present and should be sought. Thorough inquiries about a family history of SCD and drugs, including dosages used, must be included in the evaluation of patients suspected of having a VA. A positive family history of SCD is a strong independent predictor of susceptibility to VA and SCD.[57,58] Although physical examination is seldom revealing, it may sometimes give valuable clues.

3.4.3.2 Non-invasive and invasive evaluation

Non-invasive evaluation of patients with suspected or known ventricular arrhythmias

Recommendations	Class[a]	Level[b]	Ref.[c]
Resting 12-lead ECG			
Resting 12-lead ECG is recommended in all patients who are evaluated for VA.	I	A	1
ECG monitoring			
Ambulatory ECG is recommended to detect and diagnose arrhythmias. Twelve-lead ambulatory ECG is recommended to evaluate QT-interval changes or ST changes.	I	A	93
Cardiac event recorders are recommended when symptoms are sporadic to establish whether they are caused by transient arrhythmias.	I	B	94
Implantable loop recorders are recommended when symptoms, e.g. syncope, are sporadic and suspected to be related to arrhythmias and when a symptom–rhythm correlation cannot be established by conventional diagnostic techniques.	I	B	95
SA-ECG is recommended to improve the diagnosis of ARVC in patients with VAs or in those who are at risk of developing life-threatening VAs.	I	B	96,97
Exercise stress testing			
Exercise stress testing is recommended in adult patients with VA who have an intermediate or greater probability of having CAD by age and symptoms to provoke ischaemic changes or VA.	I	B	98
Exercise stress testing is recommended in patients with known or suspected exercise-induced VA, including CPVT, to achieve a diagnosis and define prognosis.	I	B	99
Exercise stress testing should be considered in evaluating response to medical or ablation therapy in patients with known exercise-induced VA.	IIa	C	1
Imaging			
Echocardiography for assessment of LV function and detection of structural heart disease is recommended in all patients with suspected or known VA.	I	B	100, 101

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Echocardiography for assessment of LV and RV function and detection of structural heart disease is recommended for patients at high risk of developing serious VAs or SCD, such as those with dilated, hypertrophic or RV cardiomyopathies, survivors of acute myocardial infarction or relatives of patients with inherited disorders associated with SCD.	I	B	100
Exercise testing plus imaging (exercise stress echocardiography test or nuclear perfusion, SPECT) is recommended to detect silent ischaemia in patients with VAs who have an intermediate probability of having CAD by age or symptoms and in whom an ECG is less reliable (digoxin use, LV hypertrophy, >1-mm ST-segment depression at rest, WPW syndrome, or LBBB).	I	B	102
Pharmacological stress testing plus imaging modality is recommended to detect silent ischaemia in patients with VAs who have an intermediate probability of having CAD by age or symptoms and are physically unable to perform a symptom-limited exercise test.	I	B	103
CMR or CT should be considered in patients with VAs when echocardiography does not provide accurate assessment of LV and RV function and/or evaluation of structural changes.	IIa	B	1

ARVC = arrhythmogenic right ventricular cardiomyopathy; CAD = coronary artery disease; CMR = cardiac magnetic resonance; CPVT = catecholaminergic polymorphic ventricular tachycardia; CT = computed tomography; ECG = electrocardiogram; LBBB = left bundle branch block; LV = left ventricular; RV = right ventricular; SA-ECG = signal-averaged ECG; SCD = sudden cardiac death; SPECT = single-photon emission computed tomography; VA = ventricular arrhythmia; WPW = Wolff–Parkinson–White.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

Invasive evaluation of patients with suspected or known ventricular arrhythmias

Recommendations	Class[a]	Level[b]	Ref.[c]
Coronary angiography			
Coronary angiography should be considered to establish or exclude significant obstructive CAD in patients with life-threatening VAs or in survivors of SCD, who have an intermediate or greater probability of having CAD by age and symptoms.	IIa	C	104
Electrophysiological study			
Electrophysiological study in patients with CAD is recommended for diagnostic evaluation of patients with remote myocardial infarction with symptoms suggestive of ventricular tachyarrhythmias, including palpitations, presyncope and syncope.	I	B	105
Electrophysiological study in patients with syncope is recommended when bradyarrhythmias or tachyarrhythmias are suspected, based on symptoms (e.g. palpitations) or the results of non-invasive assessment, especially in patients with structural heart disease.	I	C	106
Electrophysiological study may be considered for the differential diagnosis of ARVC and benign RVOT tachycardia or sarcoidosis.	IIb	B	107

ARVC = arrhythmogenic right ventricular cardiomyopathy; CAD = coronary artery disease; RVOT = right ventricular outflow tract; SCD = sudden cardiac death; VA = ventricular arrhythmia.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

A standard resting 12-lead ECG may reveal signs of inherited disorders associated with VAs and SCD such as channelopathies (LQTS, SQTS, Brugada syndrome, CPVT) and cardiomyopathies (ARVC and HCM). Other ECG parameters suggesting underlying structural disease include bundle branch block, atrio-ventricular (AV) block, ventricular hypertrophy and Q waves consistent with ischaemic heart disease or infiltrative cardiomyopathy. Electrolyte disturbances and the effects of various drugs may result in repolarization abnormalities and/or prolongation of the QRS duration.

Exercise ECG is most commonly applied to detect silent ischaemia in adult patients with ventricular VAs. Exercise-induced non-sustained VT was reported in nearly 4% of asymptomatic middle-age adults and was not associated with an increased risk of total mortality.[108] Exercise testing in adrenergic-dependent rhythm disturbances, including monomorphic VT and polymorphic VT such as CPVT, is useful for diagnostic purposes and evaluating response to therapy. Exercise testing in patients with life-threatening VAs may be associated with arrhythmias requiring cardioversion, intravenous (i.v.) drugs or resuscitation, but may still be warranted because it is better to expose arrhythmias and evaluate risk under controlled circumstances. It should be performed where resuscitation equipment and trained personnel are immediately available.

Continuous or intermittent ambulatory recording techniques can aid in relating symptoms to the presence of the arrhythmia. Silent myocardial ischaemic episodes may also be detected. A 24- to 48-h continuous Holter recording is appropriate whenever the arrhythmia is known or suspected to occur at least once a day. For sporadic episodes, conventional event recorders are more useful because they can record over extended periods. Implantable subcutaneous devices that continuously monitor the heart rhythm

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and record events over a timeframe measured in years can record on patient activation or automatically for pre-specified criteria. They may be very useful in diagnosing serious tachyarrhythmias and bradyarrhythmias in patients with life-threatening symptoms such as syncope. The new 'injectable' loop recorders do not require conventional surgical preparations.

Signal-averaged ECG (SA-ECG) improves the signal:noise ratio of a surface ECG so that low-amplitude (microvolt level) signals, referred to as 'late potentials', can be identified at the end of the QRS complex. Late potentials indicate regions of abnormal myocardium with slow conduction, a substrate abnormality that may allow for re-entrant ventricular tachyarrhythmias. SA-ECG is recommended for differential diagnosis of structural heart disease, such as ARVC, in patients with VAs.

Echocardiography is the most commonly used imaging technique because, compared with cardiac magnetic resonance (CMR) and cardiac computed tomography (CT), it is inexpensive, readily available and provides accurate diagnosis of myocardial, valvular and congenital heart disorders associated with VA and SCD.[109] In addition, LV systolic function and regional wall motion can be evaluated in a majority of patients. Therefore echocardiography is indicated in patients with VA suspected of having structural heart disease and in the subset of patients at high risk for the development of serious VA or SCD, such as those with dilated, hypertrophic or right ventricular (RV) cardiomyopathies, survivors of acute myocardial infarction or relatives of patients with inherited disorders associated with SCD. The combination of echocardiography with exercise or pharmacological stress (commonly known as 'stress echo') is applicable to a selected group of patients who are suspected of having VA triggered by ischaemia and who are unable to exercise or have resting ECG abnormalities that limit the accuracy of the ECG for ischaemia detection.

Advances in CMR have made it possible to evaluate both the structure and function of the beating heart. The excellent image resolution obtained with current techniques allows for accurate quantification of chamber volumes, LV mass and ventricular function. This is of particular value to patients with suspected ARVC, in whom CMR provides excellent assessment of RV size, function and regional wall motion.

CT allows precise quantification of LV volumes, ejection fraction and mass, with results comparable with CMR, but in addition provides segmental images of the coronary arteries from which the extent of calcification can be quantified. Cardiac CT can be used in selected patients in whom evaluation of cardiac structures is not feasible with echocardiography and CMR is not available. An anomalous origin of coronary arteries can be detected by CT or other imaging techniques.

Myocardial perfusion single-photon emission CT (SPECT) using exercise or pharmacological agents is applicable for a selected group of patients who are suspected of having VA triggered by ischaemia and who are unable to exercise or have resting ECG abnormalities that limit the accuracy of the ECG for ischaemia detection. Accurate quantification of LVEF is possible with gated radionuclide angiography (multiple-gated acquisition scan) and may be helpful in patients for whom this measurement is not available with echocardiography.

Coronary angiography plays an important diagnostic role in establishing or excluding the presence of significant obstructive CAD in patients with life-threatening VA or in survivors of SCD.

An electrophysiological study (EPS) with PVS has been used to document the inducibility of VT, guide ablation, assess the risks of recurrent VT or SCD, evaluate loss of consciousness in selected patients with arrhythmias suspected as a cause and assess the indications for ICD therapy. The yield of EPS varies fundamentally with the kind and severity of the underlying heart disease, the presence or absence of spontaneous VT, concomitant drug therapy, the stimulation protocol and the site of stimulation. The highest induction rates and reproducibility are observed in patients after myocardial infarction, and recommendations for its use in selected cases are given in this document.

To evaluate patients with VAs, most centres use eight ventricular stimuli at drive cycle lengths between 600 ms and 400 ms at the RV apex, at twice-diastolic threshold and a pulse duration of 0.5–2 ms, delivering one to three ventricular extrastimuli at baseline. This test may be repeated during isoproterenol infusion.[110] The prematurity of extrastimuli is increased until refractoriness or induction of sustained ventricular tachyarrhythmia is achieved. Because premature ventricular stimulation with a very short coupling interval is more likely to induce VF as opposed to monomorphic VT, it may be reasonable to limit the prematurity of the extrastimuli to a minimum of 180 ms when studying patients for whom only inducible sustained monomorphic VT would be considered a positive endpoint. EPS may be repeated at the RV outflow tract (RVOT) or LV.

EPS may be used to document the arrhythmic cause of syncope and should be used to complement a full syncope workup. It is most useful in patients with CAD and LV dysfunction. EPS can be used to document or provoke bradyarrhythmias or AV block when other investigations have failed to provide conclusive information. The diagnostic yield varies greatly with the selected patient populations[111] and is low in the absence of structural heart disease or abnormal ECG. In patients with syncope, chronic bundle branch block and reduced ejection fraction ($< 45\%$), VT may be induced during EPS in up to 42% of cases. In patients with syncope and bundle branch block, false-negative EPS is common.[112] EPS can provoke non-specific tachyarrhythmic responses in patients with preserved LV function who do not have structural heart disease.

The utility of EPS to determine prognosis and to guide therapy in patients with cardiomyopathies and inherited primary arrhythmia syndromes is discussed in sections 7 and 8. Briefly, EPS might play a role in ARVC[113,114] or DCM patients,[115] while it does not contribute to identifying high-risk patients in HCM (class III).[116] Among the channelopathies, EPS is not indicated in LQTS,[117] CPVT[14] and SQTS,[118,119] while its utility is debated in Brugada syndrome.[120]

Syncope in patients with structural heart disease and, in particular, significant LV dysfunction is ominous. Non-sustained VT on Holter monitoring, syncope and structural heart disease are highly sensitive for predicting the presence of inducible VT. Syncope associated with heart disease and reduced ejection fraction has high recurrence and death rates,[121] even when EPS results are negative. EPS is useful in patients with LV dysfunction due to a previous myocardial infarction (ejection fraction $<40\%$) but is not sensitive in patients with non-ischaemic cardiomyopathy.

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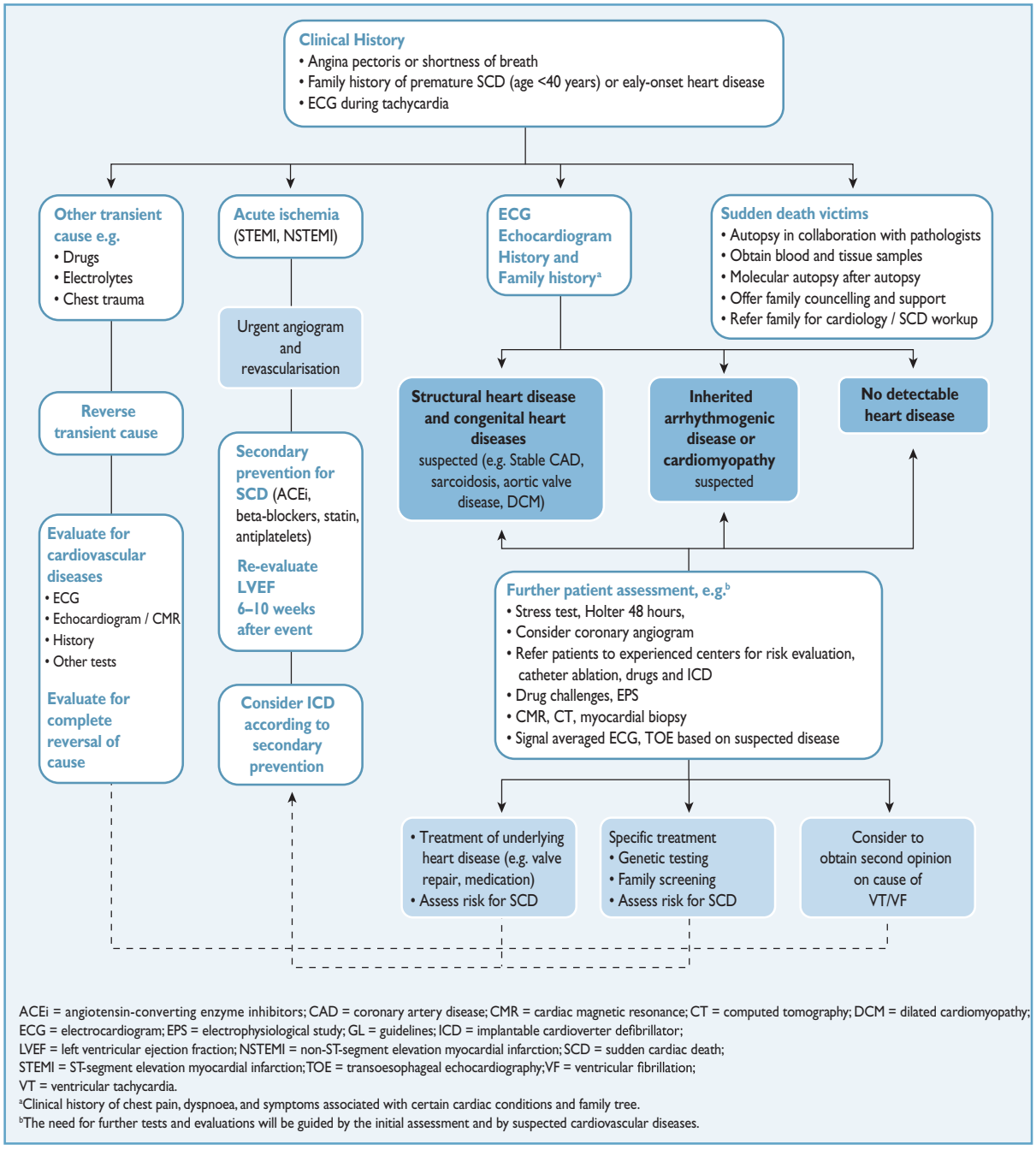
Induction of polymorphic VT or VF, especially with aggressive stimulation techniques, is not specific. In CAD, the diagnostic yield may reach 50%.

Figure 1 illustrates the proposed diagnostic workflow for patients who survived an aborted cardiac arrest, while the management of cardiac arrest in the setting of specific conditions is described in sections 5–12. *Web Table 3* presents the nomenclature adopted when referring to VAs across this document.[122] Investigations that may reveal disease-specific findings are detailed in *Web Table 4*.

4. Therapies for ventricular arrhythmias

4.1 Treatment of underlying heart disease

A fundamental aspect of the successful management of VA and the prevention of SCD is effective management of underlying diseases and co-morbidities. Acute worsening and progressive deterioration of these conditions must be avoided. Co-morbidities that may



ACEi = angiotensin-converting enzyme inhibitors; CAD = coronary artery disease; CMR = cardiac magnetic resonance; CT = computed tomography; DCM = dilated cardiomyopathy; ECG = electrocardiogram; EPS = electrophysiological study; GL = guidelines; ICD = implantable cardioverter defibrillator; LVEF = left ventricular ejection fraction; NSTEMI = non-ST-segment elevation myocardial infarction; SCD = sudden cardiac death; STEMI = ST-segment elevation myocardial infarction; TOE = transoesophageal echocardiography; VF = ventricular fibrillation; VT = ventricular tachycardia.

[a]Clinical history of chest pain, dyspnoea, and symptoms associated with certain cardiac conditions and family tree.

[b]The need for further tests and evaluations will be guided by the initial assessment and by suspected cardiovascular diseases.

Figure 1 Diagnostic workup in patients presenting with sustained ventricular tachycardia or ventricular fibrillation.

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encourage triggers for or contribute to the development of a substrate that will sustain a VA must also be controlled. The treatment of heart disease has changed considerably since the seminal trials of anti-arrhythmic drugs and the ICD were undertaken. As there is little prospect of repeating such trials, the therapeutic implications of the original trials must be extrapolated to the modern context. Nevertheless, up-to-date management of underlying cardiovascular disease must be optimized (relevant ESC Guidelines can be found at http://www.escardio.org/Guidelines-&-Education/Clinical-Practice-Guidelines/listing).

4.2 Pharmacotherapy for ventricular arrhythmia and prevention of sudden cardiac death

4.2.1 General management

The selection of appropriate therapy for the management of VA and for prevention of SCD is focused on arrhythmia, the associated medical conditions that may contribute to and/or exacerbate arrhythmia, the risk posed by arrhythmia and the risk–benefit aspects of potential therapy. Management of a manifest arrhythmia may involve discontinuation of offending pro-arrhythmic drugs (see section 12.5) and appropriate anti-arrhythmic therapy with drugs, implantable devices, ablation or surgery. For specific recommendations on pharmacotherapy, see the text and recommendation tables for the various indications detailed in later sections of this guideline.

4.2.2 Anti-arrhythmic drugs

With the exception of beta-blockers, currently available anti-arrhythmic drugs have not been shown in randomized clinical trials (RCTs) to be effective in the primary management of patients with life-threatening VAs or in the prevention of SCD. Occasional studies with amiodarone have shown positive results, but this is not a consistent finding.[123,124] As a general rule, anti-arrhythmic agents may be effective as adjunctive therapy in the management of arrhythmia-prone patients under specific circumstances. Because of potential adverse effects of anti-arrhythmic drugs, they must be used with caution. This section provides an overview of pharmacotherapy for VAs to prevent recurrent VT (*Table 5*).

Each drug has a significant potential for causing adverse events, including pro-arrhythmia. Many marketed cardiac and non-cardiac drugs induce sinus bradycardia and AV block, some impair His–Purkinje conduction and produce AV or bundle branch block, whereas others prolong ventricular repolarization and the QT interval. Thus anti-arrhythmic drugs may have the potential to precipitate life-threatening ventricular tachyarrhythmias, similar (but with a higher prevalence) to some non-cardiovascular drugs, which may also prolong the QT interval or slow intraventricular conduction.[125,126]

Of relevance to the cardiologist, class IA (e.g. quinidine, disopyramide) anti-arrhythmic drugs that block the sodium current also block the rapid component of the delayed rectifier potassium current and may therefore prolong the QT interval. For this reason a warning on the use of sodium channel blockers in patients on QT-prolonging medication or who are affected by the genetically transmitted LQTS has been issued. Recently, however, it has been demonstrated that some sodium current blockers (predominantly class IB like mexiletine and class IC like flecainide) actively inhibit both the peak sodium current and the late component of the sodium current. In doing so, these agents may induce an abbreviation of the QT interval in patients with LQTS type 3 because this form is caused by mutations that enhance the late sodium current.[127] For this reason, these drugs may be considered to abbreviate the QT interval in patients with type 3 LQTS (see section 8.1). Whether drug-induced QT prolongation and other genetic variants of LQTS also respond to late sodium current blockers with shortening of the QT interval is still unknown.

Recently a German study using an active surveillance approach reported a crude incidence of drug-induced LQTS leading to torsade de pointes (TdP) of 3.2 per million per year.[128] Once it is appreciated that a VA may be due to 'anti-arrhythmic' drug therapy, the possible offending therapies should be discontinued and appropriate follow-up ECG monitoring carried out.

In light of the results of the Cardiac Arrhythmia Suppression Trial (CAST),[129] showing an excessive mortality or non-fatal cardiac arrest rate (7.7%) among post–myocardial infarction patients treated with encainide or flecainide compared with that in placebo-treated patients (3.0%), a contraindication for the use of class IC sodium channel blockers after myocardial infarction has been issued. The contraindication has been extended to other class I anti-arrhythmic agents, because even if they do not increase mortality, when used to reduce the arrhythmic burden in post–myocardial infarction patients they fail to reduce mortality (for references and discussion of results see section 5).

The use of drugs for inherited primary arrhythmia syndromes (LQTS, SQTS, Brugada syndrome) and cardiomyopathies is an off-label indication.

4.2.2.1 Beta-blockers

The mechanism of anti-arrhythmic efficacy of beta-blockers includes competitive beta-adrenoreceptor blockade of sympathetically mediated triggering mechanisms, slowing of the sinus rate and possibly inhibition of excess calcium release by the ryanodine receptor channel.

Beta-blockers are effective in suppressing ventricular ectopic beats and arrhythmia as well as in reducing SCD in a spectrum of cardiac disorders in patients with and without HF. Beta-blockers are effective and generally safe anti-arrhythmic agents that can be considered the mainstay of anti-arrhythmic drug therapy. Recently, however, a registry study in 34 661 patients with ST-segment elevation myocardial infarction (STEMI) or non-STEMI (NSTEMI) found that in patients with two or more risk factors for shock (e.g. age >70 years, heart rate >110 bpm, systolic blood pressure <120 mmHg), the risk of shock or death was significantly increased in those treated with beta-blockers [NSTEMI: OR 1.23 (95% CI 1.08, 1.40), $P = 0.0016$; STEMI: OR 1.30 (95% CI 1.03, 1.63), $P = 0.025$].[130]

Overall, beta-blockers are first-line therapy in the management of VA and the prevention of SCD.

4.2.2.2 Amiodarone

Amiodarone has a broad spectrum of action that includes blockade of depolarizing sodium currents and potassium channels that conduct repolarizing currents; these actions may inhibit or terminate VAs by influencing automaticity and re-entry.

The Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) trial showed a lack of survival benefit for treatment with amiodarone vs. placebo in patients with LVEF $\leq$35%.[64] Unlike sodium channel blockers,[131] however, amiodarone can be used without increasing mortality in patients with HF.[132]

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Table 5 Anti-arrhythmic drugs available for the treatment of ventricular arrhythmias in most European countries

Anti-arrhythmic drugs (Vaughan Williams class)	Oral dose# (mg/day)[a]	Common or important adverse effects	Indications	Cardiac contra-indications and warnings
Amiodarone (III)	200–400	Pulmonary fibrosis, hypothyroidism and hyperthyroidism, neuropathies, corneal deposits, photosensitivity, skin discolouration, hepatotoxicity, sinus bradycardia, QT prolongation, and occasional TdP.	VT, VF	Conditions and concomitant treatments associated with QT interval prolongation; inherited LQTS; sinus bradycardia (except in cardiac arrest); sinus node disease (unless a pacemaker is present); severe AV conduction disturbances (unless a pacemaker is present); decompensated HF or cardiomyopathy.
Beta-blocker (II)	Various	Bronchospasm, hypotension, sinus bradycardia, AV block, fatigue, depression, sexual disturbances.	PVC, VT, LQTS	Severe sinus bradycardia and sinus node disease (unless a pacemaker is present); AV conduction disturbances (unless a pacemaker is present); acute phase of myocardial infarction (avoid if bradycardia, hypotension, LV failure); decompensated HF; Prinzmetal's angina.
Disopyramide (IA)	250–750	Negative inotrope, QRS prolongation, AV block, pro-arrhythmia (atrial flutter, monomorphic VT, occasional TdP), anticholinergic effects.	VT, PVC	Severe sinus node disease (unless a pacemaker is present); severe AV conduction disturbances (unless a pacemaker is present); severe intraventricular conduction disturbances; previous myocardial infarction; CAD; HF; reduced LVEF; hypotension.
Flecainide (IC)	200–400	Negative inotrope, QRS widening, AV block, sinus bradycardia, pro-arrhythmia (atrial flutter, monomorphic VT, occasional TdP), increased incidence of death after myocardial infarction.	PVC, VT	Sinus node dysfunction (unless a pacemaker is present); AF/flutter (without the concomitant use of AV-blocking agents); severe AV conduction disturbances (unless a pacemaker is present); severe intraventricular conduction disturbances; previous myocardial infarction; CAD; HF; reduced LVEF; haemodynamically significant valvular heart disease; Brugada syndrome; inherited LQTS (other than LQTS3); concomitant treatments associated with QT-interval prolongation.
Mexiletine (IB)	450–900	Tremor, dysarthria, dizziness, gastrointestinal disturbance, hypotension, sinus bradycardia.	VT, LQT3	Sinus node dysfunction (unless a pacemaker is present); severe AV conduction disturbances (unless a pacemaker is present); severe HF; reduced LVEF; inherited LQTS (other than LQTS3); concomitant treatments associated with QT-interval prolongation.
Procainamide (IA)	1000–4000	Rash, myalgia, vasculitis, hypotension, lupus, agranulocytosis, bradycardia, QT prolongation, TdP.	VT	Severe sinus node disease (unless a pacemaker is present); severe AV conduction disturbances (unless a pacemaker is present); severe intraventricular conduction disturbances; previous myocardial infarction; CAD; HF; reduced LVEF; hypotension; reduced LVEF, Brugada syndrome.
Propafenone (IC)	450–900	Negative inotrope, gastrointestinal disturbance, QRS prolongation, AV block, sinus bradycardia, pro-arrhythmia (atrial flutter, monomorphic VT, occasional TdP).	PVC, VT	Severe sinus bradycardia and sinus node dysfunction (unless a pacemaker is present); AF/flutter (without the concomitant use of AV-blocking agents); severe AV-conduction disturbances (unless a pacemaker is present); severe intraventricular conduction disturbances; previous myocardial infarction; CAD; HF; reduced LVEF; haemodynamically significant valvular heart disease; Brugada syndrome; inherited LQTS (other than LQTS3); concomitant treatments associated with QT interval prolongation.
Quinidine	600–1600	Nausea, diarrhoea, auditory and visual disturbance, confusion, hypotension, thrombocytopenia, haemolytic anaemia, anaphylaxis, QRS and QT prolongation, TdP.	VT, VF, SQTS, Brugada syndrome	Severe sinus node disease (unless a pacemaker is present); severe AV conduction disturbances (unless a pacemaker is present); severe intraventricular conduction disturbances; previous myocardial infarction; CAD; HF; reduced LVEF; hypotension; inherited Long QT Syndrome; concomitant treatments associated with QT interval prolongation.
Ranolazine (IB)	750 –2000	Dizziness, nausea, constipation, hypotension, gastrointestinal disturbance, headache, rash, sinus bradycardia, QT prolongation.	LQTS3[b]	Severe sinus bradycardia and sinus node disease; severe HF; inherited Long QT Syndrome (other than LQTS3); concomitant treatments associated with QT interval prolongation.
Sotalol (III)	160–320	As for other beta-blockers and TdP.	VT, (ARVC)[c]	Severe sinus bradycardia and sinus node disease (unless a pacemaker is present); AV conduction disturbances (unless a pacemaker is present); severe HF; Prinzmetal's angina; inherited LQTS; concomitant treatments associated with QT interval prolongation.
Verapamil (IV)	120–480	Negative inotrope (especially in patients with reduced LVEF), rash, gastrointestinal disturbance, hypotension, sinus bradycardia, AV block, VT.	LV fascicular tachycardia	Severe sinus bradycardia and sinus node disease (unless a pacemaker is present); severe AV conduction disturbances (unless a pacemaker is present); acute phase of myocardial infarction (avoid if bradycardia, hypotension, left ventricular failure); HF; significantly reduced LVEF; atrial flutter or fibrillation associated with accessory conducting pathways (e.g. WPW syndrome).

AF = atrial fibrillation; ARVC = arrhythmogenic right ventricular cardiomyopathy; AV = atrio-ventricular; CAD = coronary artery disease; HF = heart failure; LQTS3 = long QT syndrome type 3; LQTS = long QT syndrome; LV = left ventricle/ventricular; LVEF = left ventricular ejection fraction; PVC = premature ventricular complex; SQTS = short QT syndrome; TdP = Torsade de Pointes; VF = ventricular fibrillation; VT = ventricular tachycardia; WPW = Wolff–Parkinson–White.

[a]Adult drug doses are quoted in this table.

[b]Ranolazine is only approved for the treatment of chronic stable angina. Note that other doses may apply in special conditions.

[c]Sotalol has been indicated for ARVC but its use has been questioned.

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A meta-analysis including 8522 patients post–myocardial infarction or with systolic HF, randomized to amiodarone or placebo/control, showed that for every 1000 patients treated with amiodarone, 5 all-cause deaths, 24 cardiovascular deaths and 26 sudden deaths were averted.[133] The 1.5% absolute risk reduction of all-cause mortality did not reach statistical significance.

Chronic administration of amiodarone is associated with complex drug interactions and a host of extracardiac side effects involving the thyroid, skin and occasionally the lung and liver. Regular monitoring of lung, liver and thyroid function is needed. As a general rule, the longer the therapy and the higher the dose of amiodarone, the greater the likelihood that adverse side effects will require discontinuation of the drug. Compared with placebo, 10% of patients randomized to amiodarone discontinued therapy.[133]

4.2.2.3 Sotalol/d-sotalol

Racemic sotalol, a rapid delayed rectifier potassium current inhibitor with beta-blocker properties, is effective in suppressing VA. Sotalol can be used safely in patients with CAD[134,135] unless they have HF. For example, in a study in 146 patients with sustained VAs and ICD, sotalol significantly reduced the incidence of recurrences of sustained ventricular tachyarrhythmias in comparison with no anti-arrhythmic drug treatment, but it did not improve survival.[136]

Also, a study of d-sotalol, a pure rapid delayed rectifier potassium current inhibitor, in 3121 patients with LV dysfunction after myocardial infarction was stopped prematurely because of an increased mortality rate in the d-sotalol-treated group [RR 1.65 (95% CI 1.15, 2.36), $P = 0.006$], probably because of ventricular pro-arrhythmias, although very few cases of TdP were documented.[137] Thus sotalol should not be used in such patients unless an ICD has been implanted. The use of anti-arrhythmic doses of sotalol requires careful monitoring using ECG, especially in patients with a low body mass index or impaired renal function.

4.2.2.4 Combination therapy

There is a paucity of data to guide combination therapy with anti-arrhythmic drugs, and such combinations should be reserved for patients in whom other anti-arrhythmic treatments (including single-agent anti-arrhythmic drug therapy with different agents, amiodarone therapy and catheter ablation) have been tried without satisfactory suppression of arrhythmia episodes. In patients with frequent VT, combinations of sodium channel blockers and potassium channel blockers (e.g. mexiletine and sotalol, or amiodarone and flecainide/propafenone) have been used, usually in patients with frequent VT recurrences who have a defibrillator. Beta-blocker therapy in combination with amiodarone reduces the number of ICD shocks; however, side effects may result in drug discontinuation in a significant number of patients.[138] Ranolazine has been combined with other anti-arrhythmic agents to suppress VT in otherwise drug-refractory cases.[139] Careful monitoring of the ECG and cardiac function is needed to detect deterioration of LV function and/or signs of pro-arrhythmia in such patients.

4.2.3 Patients with a cardioverter defibrillator

Many patients fitted with a cardioverter defibrillator are treated with beta-blockers to minimize both appropriate and inappropriate ICD interventions. Patients with recurrent cardioverter defibrillator shocks may benefit by shifting to sotalol to suppress atrial arrhythmia as well as VA.[140] However, sotalol should be avoided in patients with severely depressed LV function. Because many such patients also have poor renal function, the more effective combination of amiodarone and beta-blockers may be preferred to sotalol.[138]

Anti-arrhythmic drug therapy has never been clearly shown to reduce sudden arrhythmic death in patients who have already suffered a life-threatening VA. However, in both post-myocardial infarction patients and in patients with HF, amiodarone reduces the occurrence of such arrhythmias,[123,124,133] and it has been assumed that the drug does offer some protection against serious VA in those that have already suffered such events. However, reduction of arrhythmic death does not seem to be associated with a reduction in total mortality, and adverse events associated with amiodarone further reduce treatment benefit. Nonetheless, in patients fitted with an ICD, amiodarone, especially in conjunction with beta-blockers, significantly reduces ICD interventions.[138]

In patients with an ICD who have paroxysmal or chronic atrial fibrillation (AF) with rapid rates and inappropriate cardioverter defibrillator shocks, control of the rapid ventricular response to atrial tachyarrhythmia is essential, and combination therapy with a beta-blocker and/or a non-dihydropyridine calcium channel blocker can be used with care. If ineffective, amiodarone may be helpful. Ablation of the AV node may be required if pharmacological therapy or AF ablation in selected cases is not effective.

4.2.4 Electrolytes

Administration of potassium to restore normal blood levels can favourably influence the substrate involved in VA. Magnesium administration can specifically help to suppress TdP arrhythmias.

Electrolyte disturbances are common in patients with HF, particularly those using high-doses of potassium-sparing diuretics. Recently a database study including 38 689 patients with acute myocardial infarction showed the lowest risk of VF, cardiac arrest or death with potassium concentrations of 3.5–4.5 mmol/L.[141]

4.2.5 Other drug therapy

Adverse remodelling occurs in the ventricle following myocardial infarction or in association with non-ischaemic cardiomyopathy. These structural changes as well as associated ion-channel alterations can exacerbate the potential for VA. Several drugs, such as angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs) and mineralocorticoid receptor antagonists (MRAs), improve reverse remodelling and reduce rates of SCD.[142,143] Also, anticoagulants and/or antiplatelets may be helpful for reducing the frequency of coronary thrombotic occlusions in high-risk patients.[144] Furthermore, findings indicate that statins may reduce the occurrence of life-threatening VAs in high-risk patients.[145]

4.3 Device therapy

4.3.1 Implantable cardioverter defibrillator

Implantable defibrillators have been used in patients for >30 years. The original ICD was implanted surgically and connected to leads fixed to the ventricles via a thoracotomy. This is still occasionally necessary, but the majority of devices use transvenous leads inserted predominantly into the right heart for both pacing (single or dual chamber and univentricular or biventricular) and for defibrillation via an intracavitary right heart coil(s) and/or the can of the implanted defibrillator. Most clinical trials supporting the use of ICD therapy

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have been conducted with transvenous ICD therapy. The first patients to receive defibrillators were survivors of VF or aborted cardiac arrest. Later trials demonstrated a benefit of defibrillator therapy in patients at risk of sudden death. ICD therapy prevents sudden death and prolongs life in patients at high risk of sudden arrhythmic death, provided that the patient does not suffer from other conditions that limit life expectancy to <1–2 years.[146] Long-term studies have demonstrated the efficacy of ICDs[147] and cardiac resynchronization therapy defibrillators (CRT-Ds)[148] over a mean follow-up of 8 and 7 years, respectively.

On the other hand, defibrillators may cause complications, including inappropriate shocks, which are especially frequent in children.[149] A recent study of >3000 patients with an ICD or CRT-D found a 12-year cumulative incidence of adverse events of 20% (95% CI 18, 22) for inappropriate shock, 6% (95% CI 5, 8) for device-related infection and 17% (95% CI 14, 21) for lead failure.[150]

Despite the indications for ICD therapy in post-myocardial infarction patients with reduced ejection fraction, which is strongly supported by evidence-based data, a clear gap exists between guidelines and clinical practices in several countries. A limiting factor in the use of an ICD is its high upfront costs.

4.3.1.1 Secondary prevention of sudden cardiac death an ventricular tachycardia

ICD for the secondary prevention of sudden cardiac death and ventricular tachycardia

Recommendations	Class[a]	Level[b]	Ref.[c]
ICD implantation is recommended in patients with documented VF or haemodynamically not tolerated VT in the absence of reversible causes or within 48 h after myocardial infarction who are receiving chronic optimal medical therapy and have a reasonable expectation of survival with a good functional status >1 year.	I	A	151–154
ICD implantation should be considered in patients with recurrent sustained VT (not within 48 h after myocardial infarction) who are receiving chronic optimal medical therapy, have a normal LVEF and have a reasonable expectation of survival with good functional status for >1 year.	IIa	C	This panel of experts
In patients with VF/VT and an indication for ICD, amiodarone may be considered when an ICD is not available, contraindicated for concurrent medical reasons or refused by the patient.	IIb	C	155, 156

ICD = implantable cardioverter defibrillator; LVEF = left ventricular ejection fraction; SCD = sudden cardiac death; VF = ventricular fibrillation; VT = ventricular tachycardia.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

Three trials [Antiarrhythmic drugs Versus Implantable Defibrillator (AVID),[153] Canadian Implantable Defibrillator Study (CIDS)[151] and Cardiac Arrest Study Hamburg (CASH)[152]] have been conducted in patients who had suffered a cardiac arrest or life-threatening VA (haemodynamically unstable VA or VT with syncope) in which treatment with an ICD was compared with anti-arrhythmic drug therapy, predominantly amiodarone. The results of all three trials were consistent, although only one showed a statistically significant reduction in the rate of total mortality; the ICD reduced rates of arrhythmic mortality in both the AVID and CASH trials. A meta-analysis of the three trials demonstrated that ICD therapy was associated with a 50% (95% CI 0.37, 0.67; $P = 0.0001$) reduction in arrhythmic mortality and a 28% (95% CI 0.60, 0.87; $P = 0.006$) reduction in total mortality (*Web Table 5*).[154] An analysis of the AVID trial results clearly demonstrated that the benefit was confined primarily to patients with an LVEF between 20 and 34%.[153] The therapy is moderately cost effective and guidelines for use of ICDs for secondary prevention have been generally accepted for some years. No recent trial evidence suggests that previous recommendations should be substantially changed.

4.3.2 Subcutaneous implantable cardioverter defibrillator

Subcutaneous implantable cardioverter defibrillator

Recommendations	Class[a]	Level[b]	Ref.[c]
Subcutaneous defibrillators should be considered as an alternative to transvenous defibrillators in patients with an indication for an ICD when pacing therapy for bradycardia support, cardiac resynchronization or antitachycardia pacing is not needed.	IIa	C	157, 158
The subcutaneous ICD may be considered as a useful alternative to the transvenous ICD system when venous access is difficult, after the removal of a transvenous ICD for infections or in young patients with a long-term need for ICD therapy.	IIb	C	This panel of experts

ICD = implantable cardioverter defibrillator.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

Problems with access to the heart via the vascular system and recurring problems with transvenous leads prompted the development of a subcutaneous defibrillator with an electrode system that is placed entirely subcutaneously, outside the thoracic cavity. The system consists of three electrodes: the ICD can, a distal electrode on the defibrillator lead and a proximal electrode

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located approximately 8 cm from the tip of the lead. Between the tip and proximal electrode is a coil for defibrillation against the defibrillator can. The electrode is positioned so that the distal part of the lead is placed at the left parasternal edge and the device is placed over the fifth intercostal space between the left anterior and mid-axillary line. The precise electrode configuration used for sensing can be configured by programming. The device is capable of defibrillating most patients with an output of 80 J.[159]

The available data suggest that subcutaneous defibrillators are effective in preventing sudden death. Data on the long-term tolerability and safety of the treatment are currently lacking but are being collected. In one of the largest trials, 330 patients, 304 of whom were successfully implanted, underwent appropriate defibrillation testing and were successfully followed for a mean of 11 months.[157] There were no lead failures or complications associated with lead placement. All induced episodes were successfully terminated and 118 of the 119 spontaneous ventricular tachyarrhythmias occurring in 21 subjects were terminated by the device and one episode subsided spontaneously during device charging. Thirteen per cent of patients received an inappropriate shock due largely to supraventricular tachycardia or to T-wave oversensing, which has also been described in younger patient groups.[160] A recently reported 'real-world' registry of 472 patients recorded 317 spontaneous episodes in 85 patients during a mean follow-up of 18 months. Of these, 169 (53%) received therapy for VT or VF and only one patient died of recurrent VF and severe bradycardia.[161] Trials of the subcutaneous ICD are summarized in *Web Table 6*.[157–165]

The subcutaneous device is not suitable for patients who require bradycardia pacing unless this need is confined to the period immediately following delivery of a shock (transcutaneous pacing can be delivered by the device for 30 seconds after the shock). Patients who need cardiac resynchronization therapy (CRT) are also unsuitable for treatment with the subcutaneous ICD. Similarly, the subcutaneous ICD is not appropriate for patients who suffer from tachyarrhythmia that can be easily terminated by antitachycardia pacing. The device may be useful when venous access is difficult, in young patients facing a lifetime of device therapy and in patients at particular risk of bacteraemia (e.g. with a current or recent transvenous ICD system). Although the general category of primary prevention of SCD should be suitable for subcutaneous ICD therapy, no long-term large-scale trials have been conducted in this population and the long-term performance of the device is not yet fully understood. For example, individual studies have presented a higher than average rate of inappropriate shocks and complications requiring reintervention:[160] whether these results belong to a learning curve or to a higher risk of inappropriate shocks in selected populations remains to be determined. A recent meta-analysis of 852 patients demonstrated that there were no electrode failures, devices were replaced because of a need for RV pacing in only 3 patients and inappropriate pacing was <5% in the latest quartile of enrolment.[166] Prospective randomized trials comparing the efficacy and complications of subcutaneous ICD with conventional ICD are currently ongoing.[158]

4.3.3 Wearable cardioverter defibrillator

Wearable cardioverter defibrillator

Recommendation	Class[a]	Level[b]	Ref.[c]
The WCD may be considered for adult patients with poor LV systolic function who are at risk of sudden arrhythmic death for a limited period, but are not candidates for an implantable defibrillator (e.g. bridge to transplant, bridge to transvenous implant, peripartum cardiomyopathy, active myocarditis and arrhythmias in the early post-myocardial infarction phase).	IIb	C	167, 168

LV = left ventricular; WCD = wearable cardioverter defibrillator.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

An external defibrillator (plus leads and electrode pads) attached to a wearable vest has been shown to successfully identify and interrupt VT and VF.[168] No prospective RCTs evaluating this device have been reported, but there are many case reports, case series and registries (held by the manufacturer or independently) that have reported the successful use of the wearable cardioverter defibrillator (WCD) in a relatively small proportion of patients at risk of potentially fatal VAs. For example, Chung *et al.*[169] found that 80 sustained VT or VF events occurred in 59 of 3569 (1.7%) patients wearing the WCD. The first shock was successful in 76 of 76 (100%) patients with unconscious VT or VF and 79 of 80 (99%) with any VT or VF. More recently, Epstein *et al.*[170] reported that 133 of 8453 (1.6%) patients received 309 appropriate shocks and 91% were resuscitated from a VA. Thus this device can save lives in vulnerable patients, but its efficacy has not been validated. In patients with transient impaired LVEF, the WCD may be used until LV function has recovered sufficiently, following insults such as myocardial infarction, post-partum cardiomyopathy, myocarditis or interventions such as revascularization associated with transient LV dysfunction.[171] Similarly, patients with a history or at risk of life-threatening VAs or who are scheduled for cardiac transplantation may be temporarily protected with the WCD.[172]

4.3.4 Public access defibrillation

Public access defibrillation

Recommendations	Class[a]	Level[b]	Ref.[c]
It is recommended that public access defibrillation be established at sites where cardiac arrest is relatively common and suitable storage is available (e.g. schools, sports stadiums, large stations, casinos, etc.) or at sites where no other access to defibrillation is available (e.g. trains, cruise ships, airplanes, etc.).	I	B	173, 174

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It may be considered to teach basic life support to the families of patients at high risk of SCD	IIb	C	This panel of experts

SCD = sudden cardiac death.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

In patients presenting with sustained haemodynamically tolerated VT in the absence of structural heart disease (e.g. idiopathic RVOT), i.v. flecainide or a conventional beta-blocker, verapamil or amiodarone may be considered.	IIb	C	

i.v. = intravenous; RVOT = right ventricular outflow tract; VT = ventricular tachycardia.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

Most cardiac arrests occur out of hospital.[175] Prompt defibrillation is much more likely than deferred defibrillation to restore an organized rhythm and stable cardiac output. Public access defibrillation linked with cardiopulmonary resuscitation has been shown to be more effective than cardiopulmonary resuscitation alone,[173] and public access defibrillation is now well established, especially in locations where crowds and stress are common, and particularly where trained volunteers can be readily available (e.g. casinos, airports, sports stadiums), even when training does not extend to cardiopulmonary resuscitation.[174] Out-of-hospital cardiac arrests occur most commonly (~70%) in the home, even in younger patients,[176] but these are infrequently witnessed and therefore cannot be prevented by home-based defibrillators.[177]

Implementation of automatic external defibrillator programmes reduces mortality in public places where cardiac arrests are usually witnessed.[178] Basic and advanced life support activities have led to the generation of protocols to guide responders. These documents, published by the European Resuscitation Council and the International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care,[179] cover the broad expanse of clinical circumstances and considerations of mechanisms. They provide clear management information, and the reader is referred to the source documents for details. As management guidelines, these documents are classified as level of evidence C, but they are derived from a combination of varied studies and opinions that range from level of evidence A to B or C.

4.4 Acute treatment of sustained ventricular arrhythmias

Cardioversion or defibrillation and acute treatment of sustained ventricular arrhythmias

Recommendations	Class[a]	Level[b]	Ref.[c]
Direct current cardioversion is recommended for patients presenting with sustained VT and haemodynamic instability.	I	C	180

The most common electrical mechanisms for cardiac arrest are VF or VT, bradyarrhythmias, asystole and electromechanical dissociation (pulseless electrical activity). Overall, survival is better for patients presenting with ventricular tachyarrhythmias compared with asystole. In 2010, International Liaison Committee on Resuscitation (ILCOR) member councils updated the conclusions and recommendations derived from an international consensus conference held in Dallas, Texas, in 2010. In the case of cardiac arrest, the universal algorithm should be applied (*Figure 2*).

Whether cardiopulmonary resuscitation before defibrillation should be performed is still debatable. In cases of out-of-hospital cardiac arrest, cardiopulmonary resuscitation with chest compression should be performed immediately until defibrillation is possible. In cases of in-hospital cardiac arrest, immediate defibrillation should be attempted because, in this case, the likelihood that cardiac arrest is due to sustained ventricular tachyarrhythmia is greater. It is advised to start defibrillation at the maximum output. Semi-automated defibrillators provide an excellent technology to spread defibrillation capability within hospitals. In patients with an ICD, the defibrillator patches should be placed on the chest wall ideally at least 8 cm from the generator position. Intravenous amiodarone may facilitate defibrillation and/or prevent VT or VF recurrences in an acute situation. Advanced life-support activities other than those related to electrical measures for termination of ventricular tachyarrhythmias are summarized in the 2010 ILCOR document.[181]

Patients presenting with sustained VT should be treated according to symptoms and tolerance of the arrhythmia. Patients presenting with monomorphic VT and haemodynamic instability (syncopal VT) should undergo direct cardioversion. In patients who are hypotensive and yet conscious, immediate sedation should be given before undergoing cardioversion. In patients with wide complex tachycardia who are haemodynamically stable, electrical cardioversion should be the first-line approach. Intravenous procainamide or flecainide may be considered for those who do not present with severe HF or acute myocardial infarction. Intravenous amiodarone may be considered in patients with HF or suspected ischaemia. Intravenous lidocaine is only moderately effective in

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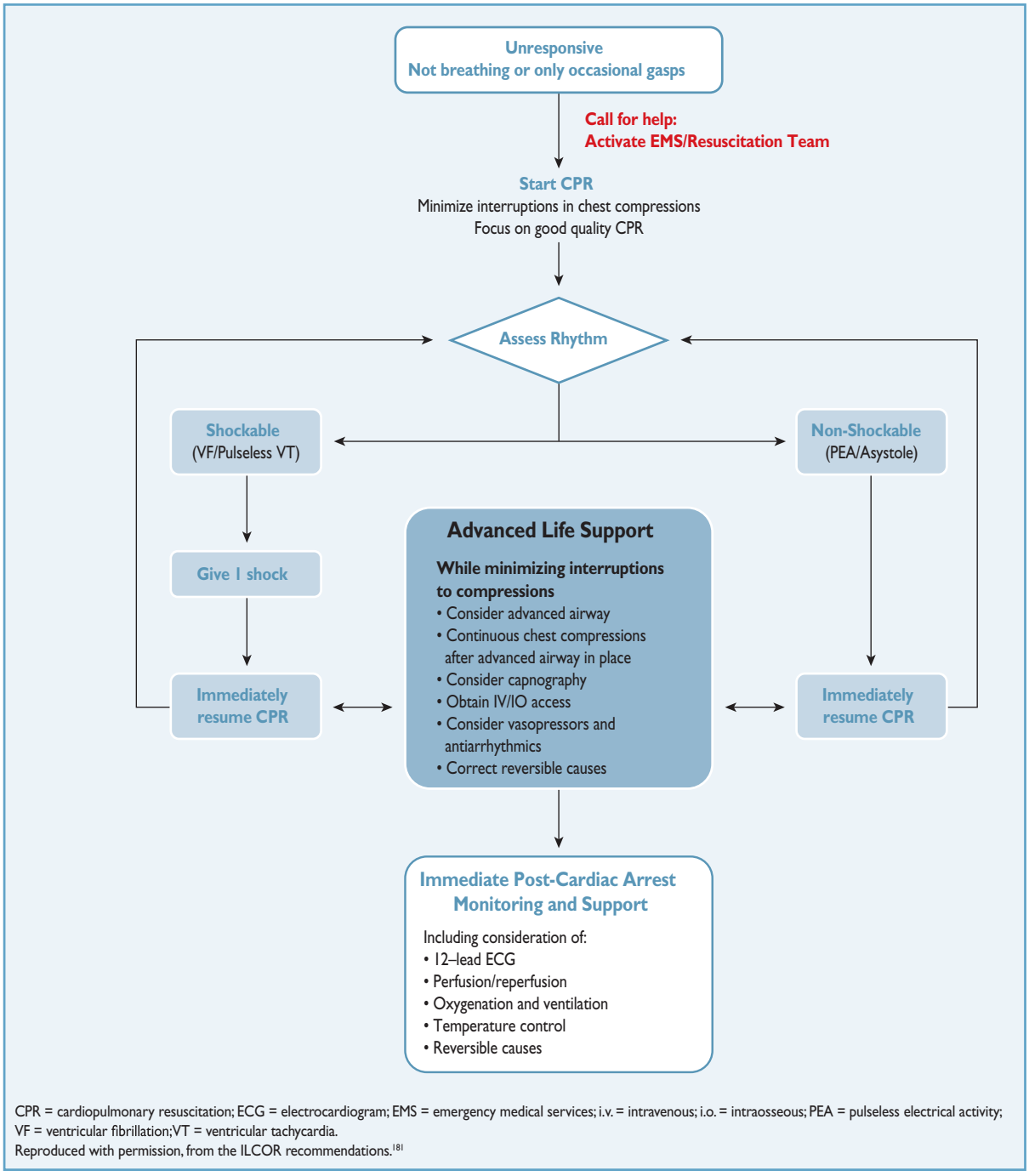

CPR = cardiopulmonary resuscitation; ECG = electrocardiogram; EMS = emergency medical services; i.v. = intravenous; i.o. = intraosseous; PEA = pulseless electrical activity; VF = ventricular fibrillation; VT = ventricular tachycardia.
Reproduced with permission, from the ILCOR recommendations.[181]

Figure 2 Universal cardiac arrest algorithm

patients presenting with monomorphic VT. As a general rule, a 12-lead ECG should be recorded for all patients with sustained VT who present in a haemodynamically stable condition.

Intravenous verapamil or beta-blockers should be given in patients presenting with LV fascicular VT [right bundle branch block (RBBB) morphology and left axis deviation].[182]

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4.5 Interventional therapy

4.5.1 Catheter ablation

Catheter ablation for the treatment of sustained monomorphic ventricular tachycardia

Recommendations	Class[a]	Level[b]	Ref.[c]
Urgent catheter ablation is recommended in patients with scar-related heart disease presenting with incessant VT or electrical storm.	I	B	183
Catheter ablation is recommended in patients with ischaemic heart disease and recurrent ICD shocks due to sustained VT.	I	B	184–186
Catheter ablation should be considered after a first episode of sustained VT in patients with ischaemic heart disease and an ICD.	IIa	B	184–186

ICD = implantable cardioverter defibrillator; VT = ventricular tachycardia.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

4.5.1.1 Patients with scar-related heart disease

Catheter ablation has evolved into an important treatment option for patients with scar-related heart disease presenting with VT or VF. Data from two prospective randomized multicentre trials on outcome in patients with ischaemic heart disease demonstrated that catheter ablation for VT decreases the likelihood of subsequent ICD shocks and prevents recurrent episodes of VT.[187,188] Moreover, catheter ablation is often used to control incessant VT or electrical storms (i.e. recurrent VT/VF with frequent appropriate ICD firing) and to reduce or prevent recurrent episodes of sustained VT.[183,184,187,188]

While ICDs can effectively terminate VT in patients with ischaemic or non-ischaemic cardiomyopathy, they may not prevent arrhythmia recurrence. Several studies have shown that ICD shocks are associated with higher mortality and impaired quality of life.[189,190] Beta-blocker therapy in combination with amiodarone reduces the number of ICD shocks; however, side effects may result in drug discontinuation.[156] Generally, scar tissue is the underlying substrate in patients presenting with VT.[191] Catheter ablation targets the isthmus of slow conduction (critical isthmus) within the VT re-entry circuit. The re-entry circuit may span several centimetres and involve the endo-, mid-, or epicardium within a complex three-dimensional structure.[192,193] Scar-related VT is typically monomorphic and multiple VT morphologies may be induced in the same patient. The QRS morphology is determined by the exit site where the re-entry wavefronts propagate away from the scar to depolarize the ventricular myocardium. Hence, a 12-lead surface ECG recording of the clinical VT can aid in the mapping and ablation procedure. In patients with non-ischaemic cardiomyopathy, the QRS morphology can identify those patients in whom an epicardial ablation is likely to be required.[194–197] Furthermore, pre-procedural CMR imaging may facilitate non-invasive identification of the arrhythmic substrate in patients with a history of myocardial infarction[198] or in patients presenting with epicardial VT.[199]

Polymorphic VT is defined as a continually changing QRS morphology often associated with acute myocardial ischaemia, acquired or inheritable channelopathies or ventricular hypertrophy. In some of these patients who are refractory to drug treatment, Purkinje-fibre triggered polymorphic VT may be amenable to catheter ablation.[200,201]

Non-invasive imaging of cardiac structure, best done by magnetic resonance imaging, can be used to plan and guide ablation procedures for VT.[198] Mapping and ablation may be performed during ongoing VT (activation mapping). A three-dimensional electro-anatomical mapping system may aid in localization of abnormal ventricular tissue and permits catheter ablation in sinus rhythm (substrate ablation) without induction of VT that may prove haemodynamically unstable. A non-contact mapping system may be utilized in patients with haemodynamically unstable VT. Several techniques, including point-by-point ablation at the exit site of the re-entry circuit (scar dechanneling), deployment of linear lesion sets or ablation of local abnormal ventricular activity to scar homogenization, can be used.[202–205] Epicardial mapping and ablation are more often required in patients with dilated cardiomyopathy (DCM)[206] or ARVC[207] undergoing VT ablation. Potential complications of epicardial puncture and ablation are damage to the coronary vasculature or inadvertent puncture of surrounding organs, left phrenic nerve palsy or significant bleeding resulting in pericardial tamponade.

Patients with VT related to post-myocardial scar tend to have a better outcome following catheter ablation than patients with VT due to non-ischaemic cardiomyopathy.[208] Five prospective multicentre studies have evaluated the role of catheter ablation in the treatment of sustained VT.[184–188] Approximately 50% of patients enrolled in these studies had favourable outcomes (i.e. no further clinical VT recurrences during the trial follow-up period), with catheter ablation being more effective than anti-arrhythmic drug therapy.

In an individual, the success rate of catheter ablation for VT is determined by the amount of infarct-related scar burden, represented as low-voltage areas on electro-anatomic mapping systems,[209] while dedicated units for the treatment of patients undergoing catheter ablation of VT may positively affect outcome.[210] Furthermore, the experience of the team and centre will influence outcomes, and all published data stem from experienced centres.

Possible complications related to catheter ablation of VT in patients with heart disease include stroke, valve damage, cardiac tamponade or AV block. Procedure-related mortality ranges from 0 to 3% and most commonly is due to uncontrollable VT when the procedure fails.[183–185,187,211] While catheter ablation is an accepted treatment option for a wide range of VT substrates, there is a lack of evidence from prospective, randomized trials that catheter ablation reduces mortality.

4.5.1.2 Patients without overt structural heart disease

VT in patients without overt structural heart disease most commonly emanates from the RV or LV outflow tracts (OTs). The 12-lead surface ECG demonstrates a left bundle branch block (LBBB) inferior axis morphology if VT arises from the RV OT or a

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left or RBBB inferior axis morphology if arising from the LVOT. Triggered activity is the most common underlying pathophysiological mechanism and targeting the earliest site of activation during catheter ablation results in a high rate of procedural success, while the rate of SCD in this patient population is generally low. Infrequently patients may present with idiopathic left VT involving the distal Purkinje network. Catheter ablation is curative in most affected patients and procedural complications are rare.

4.5.2 Anti-arrhythmic surgery

Surgical ablation of ventricular tachycardia

Recommendations	Class[a]	Level[b]	Ref.[c]
Surgical ablation guided by preoperative and intraoperative electrophysiological mapping performed at an experienced centre is recommended in patients with VT refractory to anti-arrhythmic drug therapy after failure of catheter ablation by experienced electrophysiologists.	I	B	212–215
Surgical ablation at the time of cardiac surgery (bypass or valve surgery) may be considered in patients with clinically documented VT or VF after failure of catheter ablation.	IIb	C	216, 217

VF = ventricular fibrillation; VT = ventricular tachycardia.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

In the era of transvascular catheter ablation for the treatment of VA, the requirement for surgical ablation has become a rarity. Anatomically guided LV aneurysmectomy was first described >50 years ago. Large aneurysms may be accompanied by VAs, and map-guided resection of the aneurysm not only improves LV function, but also eliminates VAs. Sub-endocardial resection for the management of VAs was first described by Josephson *et al.*[218] This technique was associated with significant periprocedural morbidity and mortality (10%) and was therefore performed only in very specialized surgical centres.[212–214,216–219] If patients survived the initial postoperative phase, their long-term outcome was excellent. More recent studies have demonstrated that perisurgical EPS after subtotal endocardiectomy and cryoablation has a VT recurrence rate of approximately 10–20%, predominantly within the first 90 days.[213] Therefore early ICD implantation is recommended in patients with VT inducibility post-surgery.[213,215,220,221] Most of the surgical techniques have become the basis for catheter ablation techniques, including a recent technique of substrate encircling.[222]

In summary, surgical ablation should be performed in experienced centres with preoperative and intraoperative electrophysiological mapping. Patients with VT refractory to anti-arrhythmic drug therapy and/or after failed catheter ablation in a highly experienced ablation centre may be considered for arrhythmia surgery, particularly if an LV aneurysm secondary to myocardial infarction is present and revascularization is required.[216–219]

4.6 Psychosocial impact of implantable cardioverter defibrillator treatment

Psychosocial management after cardioverter defibrillator implantation

Recommendations	Class[a]	Level[b]	Ref.[c]
Assessment of psychological status and treatment of distress are recommended in patients with recurrent inappropriate shocks.	I	C	223–225
Discussion of quality-of-life issues is recommended before ICD implantation and during disease progression in all patients.	I	C	226, 227

ICD = implantable cardioverter defibrillator.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

Controlled defibrillator trials demonstrated preserved or improved quality of life in recipients of a defibrillator compared with that in controls.[223,224] Nonetheless, anxiety (8–63%) and depression (5–41%) are common in defibrillator patients[228] and are most pronounced in patients experiencing inappropriate and/or frequent shocks (e.g. more than five shocks).[223–225,229] These problems frequently go unrecognized and untreated in clinical practice.[230,231] While immediate management should isolate the cause of the device firing, treating psychological distress is an important adjunct.[229] The levels of distress vary, but patients can present with more severe forms, such as post-traumatic stress disorder,[232,233] which is associated with prior shock therapy and pre-implantation distress.[234] ICD patients with recent tachyarrhythmia can also display anticipatory shock anxiety.[235] Patients with high levels of pre-implantation ICD-related concerns are more prone to develop post-implant problems, and depression may be particularly malignant in this population.[236,237] Thus, adequate assessment and treatment of psychological distress should be integral to clinical management. All ICD patients, in particular those exhibiting distress, require support on how to live with their device in order to improve outcomes.[238]

ICD implantation can affect many areas of life, including the ability to drive,[239,240] intimate relations,[241,242] sleep quality,[226] body image concerns (particularly in younger women)[227] and participation in organized sports (particularly in children and adolescents).[243] Support from healthcare professionals mitigates these concerns, but further research is required to optimize the progression of care and develop evidence-based interventions.[233]

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5. Management of ventricular arrhythmias and prevention of sudden cardiac death in coronary artery disease

5.1 Acute coronary syndromes

5.1.1 Ventricular arrhythmias associated with acute coronary syndromes

Despite the clear reduction in rates of SCD through better revascularization and prevention of CAD through smoking cessation and statin treatment, acute coronary syndrome (ACS) and late arrhythmias after acute myocardial infarction remain a common cause of SCD (see section 3.1). A significant number of SCD events occur in the pre-hospital phase of ACS, underlining the critical role of screening programmes to identify patients at risk. The incidence of VA in the hospital phase of ACS has declined in recent decades, mainly due to early and intense revascularization strategies and the early introduction of adequate pharmacological treatment. However, up to 6% of patients with ACS develop VT or VF within the first 48 hours after the onset of symptoms, most often before or during reperfusion. In addition to quick and complete coronary revascularization, non-pharmacological interventions (cardioversion, defibrillation, pacing and catheter ablation) as well as pharmacological treatment (non–anti-arrhythmic and anti-arrhythmic drugs) may be necessary to control VAs in this situation.

Diagnostic workup in patients with sustained VAs in the context of an ACS is represented in *Figure 3*.

5.1.2 Prevention and management of sudden cardiac death associated with acute coronary syndromes: pre-hospital phase

Prevention of sudden cardiac death associated with acute coronary syndromes: pre-hospital phase

Recommendations	Class[a]	Level[b]	Ref.[c]
In patients with chest pain, it is recommended to reduce delays both from symptom onset to first medical contact and from first medical contact to reperfusion.	I	A	244
It is recommended that ambulance teams are trained and equipped to identify ACS (with the use of ECG recorders and telemetry as necessary) and treat cardiac arrest by performing basic life support and defibrillation.	I	B	178
It is recommended that basic and advanced life support are performed following the algorithm protocols defined by the European Resuscitation Council or by national or international resuscitation expert groups.	I	C	179
It is recommended that post-resuscitation care is performed in high-volume expert centres capable of offering multidisciplinary intensive care treatment, including primary coronary interventions, electrophysiology, cardiac assist devices, cardiac and vascular surgery and therapeutic hypothermia.	I	B	245, 246
The creation of regional networks for the treatment of cardiac arrest should be considered to improve outcomes.	IIa	B	245

ACS = acute coronary syndrome; ECG = electrocardiogram.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

Although in-hospital mortality from ST-segment elevation myocardial infarction (STEMI) has been reduced substantially through the use of modern reperfusion therapy, the overall short-term mortality is still of concern. Infarction presenting as sudden death during the first few hours after the onset of symptoms is currently a major cause of mortality in acute myocardial infarction.

5.1.3 Prevention of sudden cardiac death associated with acute coronary syndromes: in-hospital phase

Prevention and management of sudden cardiac death associated with acute coronary syndromes: in hospital phase. Indications for revascularization

Recommendations	Class[a]	Level[b]	Ref.[c]
Urgent reperfusion is recommended in patients with STEMI.	I	A	247–249
Coronary revascularization is recommended in patients with NSTEMI or unstable angina according to the ESC NSTEMI guidelines.	I	C	13,250
A coronary angiogram followed, if necessary, by coronary angioplasty within 2 h of hospital admission is recommended in patients with high-risk NSTEMI, which also includes life-threatening VA.	I	C	13,250
Prompt and complete coronary revascularization is recommended to treat myocardial ischaemia that may be present in patients with recurrent VT or VF.	I	C	251, 252
Prompt opening of the infarct vessels is recommended to reverse new-onset ischaemic AV conduction disturbances. This is especially true for AV block due to inferior infarction, even in the case of late (>12 h) presentation.	I	C	253

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Direct admission to the catheterization laboratory is recommended in comatose survivors of out-of-hospital cardiac arrest with electrocardiographic criteria for STEMI on the post-resuscitation ECG.	I	B	251, 252
An intensive care unit stop should be considered in comatose survivors of out-of-hospital cardiac arrest without electrocardiographic criteria for ST-segment elevation on the post-resuscitation ECG to exclude non-coronary causes and, in the absence of an obvious non-coronary cause, a coronary angiogram should be considered as soon as possible (<2 h), particularly in haemodynamically unstable patients.	IIa (for both recommendations)	B	251, 252
Implantation of an LV assist device or extracorporeal life support should be considered in haemodynamically unstable patients with recurrent VT or VF despite optimal therapy.	IIa	B	254
Cardiac assist support and revascularization in specialized centres may be considered in patients with refractory cardiac arrest.	IIb	C	255, 256

ACS = acute coronary syndromes; AV = atrio-ventricular; ECG = electrocardiogram; ESC = European Society of Cardiology; LV = left ventricular; NSTEMI = non–ST-segment elevation myocardial infarction; SCD = sudden cardiac death; STEMI = ST-segment elevation myocardial infarction; VA = ventricular arrhythmia; VF = ventricular fibrillation; VT = ventricular tachycardia.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

Prevention and management of sudden cardiac death associated with acute coronary syndromes: in-hospital phase. Defibrillation/cardioversion/drugs/catheter ablation

Recommendations	Class[a]	Level[b]	Ref.[c]
Beta-blocker treatment is recommended for recurrent polymorphic VT.	I	B	257
Intravenous amiodarone is recommended for the treatment of polymorphic VT.	I	C	258
Immediate electrical cardioversion or defibrillation is recommended in patients with sustained VT or VF.	I	C	180
Urgent coronary angiography followed, when indicated, by revascularization is recommended in patients with recurrent VT or VF when myocardial ischaemia cannot be excluded.	I	C	251, 252
Correction of electrolyte imbalances is recommended in patients with recurrent VT or VF.	I	C	179
Oral treatment with beta-blockers should be considered during the hospital stay and continued thereafter in all ACS patients without contraindications.	IIa	B	130, 257, 259, 260
Radiofrequency catheter ablation at a specialized ablation centre followed by the implantation of an ICD should be considered in patients with recurrent VT, VF or electrical storms despite complete revascularization and optimal medical treatment.	IIa	C	261–267
Transvenous catheter overdrive stimulation should be considered if VT is frequently recurrent despite use of anti-arrhythmic drugs and catheter ablation is not possible.	IIa	C	
Intravenous lidocaine may be considered for the treatment of recurrent sustained VT or VF not responding to beta-blockers or amiodarone or in the presence of contraindications to amiodarone.	IIb	C	268
Prophylactic treatment with anti-arrhythmic drugs (other than beta-blockers) is not recommended.	III	B	269, 270

ACS = acute coronary syndromes; ICD = implantable cardioverter defibrillator; SCD = sudden cardiac death; VF = ventricular fibrillation; VT = ventricular tachycardia.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

Prevention and management of sudden cardiac death associated with acute coronary syndromes: in-hospital phase. Pacing/implantable cardioverter defibrillator

Recommendations	Class[a]	Level[b]	Ref.[c]
Temporary transvenous pacing is recommended in patients symptomatic for sinus bradycardia despite treatment with positive chronotropic medication.	I	C	271
Temporary transvenous pacing is recommended in patients with symptomatic high-degree AV block without stable escape rhythm.	I	C	271
Urgent angiography is recommended in patients symptomatic for high-degree AV block who have not received reperfusion.	I	C	271
Reprogramming a previously implanted ICD is recommended for patients with recurrent inappropriate ICD therapies.	I	C	272

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Reprogramming a previously implanted ICD should be considered to avoid unnecessary ICD shocks.	IIa	C	272
ICD implantation or temporary use of a WCD may be considered <40 days after myocardial infarction in selected patients (incomplete revascularization,[d] pre-existing LVEF dysfunction, occurrence of arrhythmias >48 h after the onset of ACS, polymorphic VT or VF).	IIb	C	170, 273
ICD implantation for the primary prevention of SCD is generally not indicated <40 days after myocardial infarction.	III	A	274, 275

ACS = acute coronary syndrome; AV = atrio-ventricular; ICD = implantable cardioverter defibrillator; LVEF = left ventricular ejection fraction; SCD = sudden cardiac death; VF = ventricular fibrillation; VT = ventricular tachycardia; WCD = wearable cardioverter defibrillator.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.
[d]Incomplete revascularization refers to a failure to treat the culprit lesion or the presence of non-culprit lesions, which cannot be treated.

ESC Guidelines for the treatment of ACS with or without ST-segment elevation and coronary revascularization have been published and all information relevant to the diagnosis of ACS, NSTEMI or STEMI and treatment recommendations are provided in detail.[13,250,271] This section focuses on the specific role of reperfusion and/or revascularization for the prevention and treatment of VT or VF in patients with ACS.

Owing to the implementation of public awareness programmes on SCD, an increasing number of survivors of out-of-hospital cardiac arrest are being admitted to hospital. If ST-segment elevation on pre-resuscitation or early post-resuscitation ECG is present, urgent angiography and revascularization is recommended as in all patients with STEMI.[251] However, the absence of ST-segment elevation does not exclude obstructive or even thrombotic coronary 'culprit' lesions, which may be present in 25–58% of cases.[251,252] Given the high prevalence of coronary occlusions and potential difficulties in interpreting the ECG in patients after cardiac arrest, a coronary angiogram should be considered in survivors of out-of-hospital cardiac arrest after an emergency department or intensive care unit stop to exclude the presence of non-cardiac causes of arrest.[276]

In the setting of ACS and recurrent sustained and/or haemodynamically relevant VT or VF, successful prompt revascularization is key to further arrhythmia prevention and should be attempted immediately.[13,250,271]

5.1.3.1 *Ventricular arrhythmias in acute coronary syndromes*

Acute ischaemia causes electrical instability, provoking VA in ACS patients.[266] Early use of beta-blockers in the setting of ACS reduces VT/VF and is therefore recommended.[257,269] Correction of hypomagnesaemia and hypokalaemia may help in selected patients. Statin therapy reduces mortality in patients with CAD, mostly through prevention of recurrent coronary events, and is therefore part of the recommended routine medication.[250,271]

5.1.3.2 *Use of anti-arrhythmic drugs in acute coronary syndromes—general considerations*

Electrical cardioversion or defibrillation is the intervention of choice to acutely terminate VAs in ACS patients.[1,271] Early (possibly i.v.) administration of beta-blockers can help prevent recurrent arrhythmias.[257,269,271] Anti-arrhythmic drug treatment with amiodarone should be considered only if episodes of VT or VF are frequent and can no longer be controlled by successive electrical cardioversion or defibrillation.[1,271] Intravenous lidocaine may be considered for recurrent sustained VT or VF not responding to beta-blockers or amiodarone or in the case of contraindications to amiodarone. In patients with recurrent VT or VF triggered by premature ventricular complex (PVC) arising from partially injured Purkinje fibres, catheter ablation is very effective and should be considered[261–265] (see section 6.3.2).

5.1.3.3 *Patients with acute coronary syndromes and no ventricular arrhythmias*

Beta-blocker treatment is recommended to prevent VA.[257,271] Prophylactic treatment with anti-arrhythmic drugs has not proven beneficial and may even be harmful and is not therefore indicated.[257,269]

5.1.3.4 *Premature ventricular complexes*

PVCs and non-sustained ventricular tachycardia (NSVT) occur frequently in patients with ACS, especially during primary percutaneous coronary intervention for STEMI (known as reperfusion arrhythmias). They are very rarely of haemodynamic relevance and do not require specific treatment. Prolonged and frequent ventricular ectopy can be a sign that further revascularization (e.g. a repeat angiogram/percutaneous coronary intervention) is needed.[250,271] In haemodynamically relevant NSVT, amiodarone (300 mg i.v. bolus) should be considered.[1,271]

5.1.3.5 *Sustained VT and VF*

Recurrent sustained VT, especially when polymorphic, or recurrent VF may be an indicator of incomplete reperfusion or recurrence of acute ischaemia. Immediate coronary angiography should therefore be considered.[250,271] Recurrent polymorphic VT degenerating into VF may respond to beta-blockers. In addition, deep sedation may be helpful to reduce episodes of VT or VF. Amiodarone (150–300 mg i.v. bolus) should be considered to acutely suppress recurrent haemodynamically relevant VAs. The use of other anti-arrhythmic drugs in ACS (e.g. procainamide, propafenone, ajmaline, flecainide) is not recommended.[1,269,271]

5.1.3.6 *Catheter ablation of recurrent sustained ventricular tachycardia, recurrent ventricular fibrillation and electrical storm*

In patients with recurrent VT or VF despite complete revascularization and optimal medical treatment, radiofrequency catheter ablation should be considered. Recurrent VF episodes may be triggered by PVCs arising from partially injured Purkinje fibres or ventricular myocardium injured by ischaemia and/or reperfusion. In almost all cases the substrate can be accessed from the endocardium. Precise catheter mapping and successful ablation of triggers for VT or VF, or myocardial substrate sustaining VT or VF, is a complex and demanding procedure. Thus early referral of patients presenting with VT or VF storms to specialized ablation centres should be considered.[261–265]

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5.1.3.7 Extracorporeal support devices

In selected cases with recurrent VT or VF that cannot be managed with the treatment recommendations given above, implantation of LV assist devices or extracorporeal life support should be considered for haemodynamic stabilization. Such interventions may also generate time windows allowing coronary interventions in cardiogenic shock due to recurrent VT or VF. Although haemodynamic stabilization can be achieved with ventricular assist devices, the likelihood of VT or VF recurrence is high and interventional treatment is difficult.[254]

5.1.3.8 Bradycardia and heart block

Bradycardia and heart block can occur and are associated with increased hospital mortality. AV block is most often due to proximal occlusion of the right coronary artery or a dominant circumflex artery. Prompt coronary revascularization most often resolves conduction.[253] When bradycardia results in severe haemodynamic compromise (usually with advanced or complete heart block in the absence of stable junctional escape rhythm) or when it persists despite coronary revascularization, transient ventricular pacing with a pacing lead placed percutaneously to the right ventricle may be necessary.[271] In persistent bradycardia or heart block, permanent pacing may be necessary and should be performed according to current pacing guidelines.[10]

5.1.4 The prognostic role of early ventricular fibrillation

Early VF (i.e. occurring within 48 h) during ACS is associated with an up to five-fold increase in hospital mortality[277] and probably identifies a risk for longer-term mortality. Not all of the later deaths are sudden, and the decision for defibrillator therapy needs to be based on the presence of additional risk factors in addition to VF or VT in the setting of ACS.[278,279]

5.2 Early after myocardial infarction

5.2.1 Risk stratification for sudden cardiac death

Risk stratification for sudden cardiac death early (within 10 days) after myocardial infarction

Recommendations	Class[a]	Level[b]	Ref.[c]
PVS may be considered early after myocardial infarction in patients with reduced LVEF (≤40%) to assess the risk of sudden death.	IIb	B	280–282
Non-invasive tests (e.g. microvolt T-wave alternans, tests for autonomic dysfunction or SA-ECG) are not recommended for risk stratification in the early phase after myocardial infarction.	III	B	283, 284

LVEF = left ventricular ejection fraction; PVS = programmed ventricular stimulation; SA-ECG = signal-averaged electrocardiogram.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

SCD is an important cause of death after acute myocardial infarction and is often due to recurrent infarction. Nonetheless, early defibrillator implantation after an infarction does not improve prognosis, probably due to competing causes of death.[274,275] Optimal revascularization and medical therapy (including beta-blockers, dual antiplatelet therapy and statins) and prevention and treatment of HF are recommended and are the mainstays of prevention of sudden death in this patient group. While several non-invasive risk markers for sudden death have been tested and abandoned in this cohort, some data support the use of an early programmed stimulation in acute myocardial infarction survivors with a reduced LVEF, as those without inducible monomorphic VT have a low risk of subsequent sudden death.[285] Randomized trials are necessary to conclusively define the role of programmed stimulation for risk stratification early after acute myocardial infarction.

5.2.2 Timing of implantable cardioverter defibrillator placement after myocardial infarction—assessment of left ventricular dysfunction before and after discharge

Timing of implantable cardioverter defibrillator placement after myocardial infarction. Assessment of left ventricular ejection fraction

Recommendations	Class[a]	Level[b]	Ref.[c]
Early (before discharge) assessment of LVEF is recommended in all patients with acute myocardial infarction.	I	C	286–288
Re-evaluation of LVEF 6–12 weeks after myocardial infarction is recommended to assess the potential need for primary prevention ICD implantation.	I	C	286–288

ICD = implantable cardioverter defibrillator; LVEF = left ventricular ejection fraction.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

Early (<40 days) ICD implantation or the temporary (<40 days) use of a WCD may be considered in the presence of specific conditions such as pre-existing LVEF impairment, incomplete revascularization and arrhythmia occurring >48 h after the onset of ACS. The type of VA must be assessed (monomorphic, polymorphic, pleomorphic VT or VF) as well as the VT cycle length (non-sustained short runs or non-sustained long runs). If programmed stimulation was performed, inducibility and the type of induced arrhythmia (monomorphic VT, polymorphic VT, VF) should be assessed.[274,275]

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LVEF should be assessed 6–12 weeks after myocardial infarction in stable patients and in those on optimized HF medication to assess a potential indication for a primary preventive defibrillator implantation. This evaluation should be structured and offered to all patients.[271,286–288]

5.3 Stable coronary artery disease after myocardial infarction with preserved ejection fraction

Modern revascularization and secondary prevention therapy allows preservation of LVEF in most patients presenting early with an acute myocardial infarction. Although the risk for SCD in these patients is substantially lower compared with patients with severely impaired LVEF, the absolute number of SCD victims with preserved LVEF is high. Improved SCD risk-detection strategies in the intermediate-risk population are needed.

5.3.1 Risk stratification

Risk stratification in patients with stable coronary artery disease after myocardial infarction with preserved ejection fraction

Recommendations	Class[a]	Level[b]	Ref.[c]
PVS should be considered in survivors of a myocardial infarction with preserved LV function and otherwise unexplained syncope.	IIa	C	280–282

LV = left ventricular; PVS = programmed ventricular stimulation.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

Most studies that have evaluated the usefulness of non-invasive risk stratification have been performed in patients with severely impaired LVEF (<40%) or in mixed populations. In these studies, either the outcome in the subgroup of patients with LVEF >40% has not been reported or the subgroups were too small to allow analysis and interpretation of the data. To date, in patients with remote myocardial infarction and preserved LVEF, no non-invasive risk stratification technique has demonstrated sufficient specificity and sensitivity.

There is limited evidence from subgroups of large-scale studies that programmed ventricular stimulation is helpful for risk stratification in patients after myocardial infarction with intermediate LVEF values or with an LVEF >40%.[280–282] This question is currently being addressed in the ongoing Risk Stratification in Patients With Preserved Ejection Fraction (PRESERVE-EF) trial (NCT02124018).

5.3.2 Recommendations for optimal strategy

Revascularization in patients with stable coronary artery disease after myocardial infarction with preserved ejection fraction

Recommendations	Class[a]	Level[b]	Ref.[c]
Coronary revascularization is recommended to reduce the risk of SCD in patients with VF when acute myocardial ischaemia precedes the onset of VF.	I	B	289, 290

SCD = sudden cardiac death; VF = ventricular fibrillation.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

Guidelines for coronary revascularization have been published recently.[13] They provide clear management information and the reader is referred to the source documents for details.

In patients with CAD and VAs, assessment of obstructive coronary disease and ischaemia is essential. Surgical revascularization may increase survival and prevent SCD. Implantation of an epicardial ICD lead at the time of coronary artery bypass grafting is not associated with an overall mortality benefit. Percutaneous coronary intervention is also associated with a marked decline in cardiac mortality driven by fewer deaths from myocardial infarction or sudden death.

Revascularization may be associated with an increase in LVEF of ≥5–6% in 15–65% of stable patients. This is particularly true for those with evidence of ischaemic or hibernating myocardium on preoperative imaging studies.[291,292] The majority of patients with severely depressed LVEF immediately after STEMI show significantly improved systolic function after 3 months.[286] LVEF should be re-evaluated 6–12 weeks after coronary revascularization to assess potential indications for primary prevention ICD implantation.

In patients who survive SCD, revascularization can reduce the recurrence of life-threatening arrhythmias and SCD and also improve patient outcomes, particularly if there is evidence of ischaemia preceding SCD. Sustained monomorphic VT in patients with previous myocardial infarction is less likely to be affected by revascularization. Myocardial revascularization is unlikely to prevent recurrent SCD in patients with extensive myocardial scarring and markedly depressed LVEF.

5.3.3 Use of anti-arrhythmic drugs

Use of anti-arrhythmic drugs

Recommendations	Class[a]	Level[b]	Ref.[c]
Amiodarone may be considered for relief of symptoms from VAs in survivors of a myocardial infarction but it has no effect on mortality.	IIb	B	293, 294

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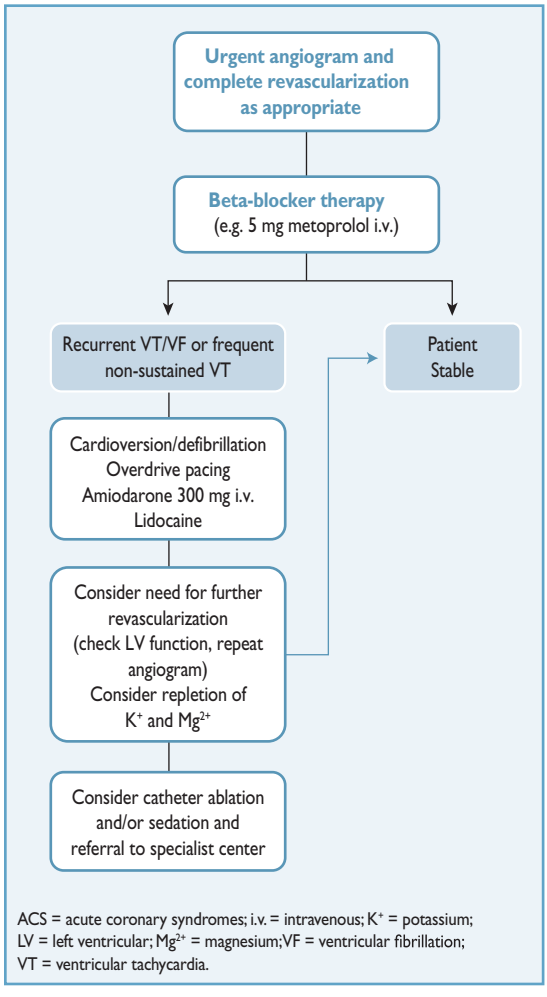
Therapy with sodium channel blockers (class IC) is not recommended to prevent sudden death in patients with CAD or who survived myocardial infarction.	III	B	131

CAD = coronary artery disease; VA = ventricular arrhythmia.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

The role of anti-arrhythmic drugs in the prevention of SCD in post-myocardial infarction patients with preserved ejection fraction is limited. Most of the data come from the CAST study,[129] which showed that sodium channel blockers (class IA and IC agents) increase mortality after myocardial infarction. Class II drugs (beta-blockers) have an established role in reducing mortality in post-myocardial infarction patients with reduced LVEF and this protective role may also persist in patients with preserved LVEF, but their effect on SCD is unproven. Finally, the class III agent amiodarone has not been shown to reduce SCD in post-myocardial infarction patients with preserved LVEF. However, it may have a role in the relief of symptoms and the reduction of arrhythmic episodes in this group of patients.

For symptomatic but not life-threatening arrhythmias (PVCs or short and slow NSVT), amiodarone is the drug of choice since it suppresses arrhythmias without worsening prognosis.[293,294]



ACS = acute coronary syndromes; i.v. = intravenous; K^+ = potassium; LV = left ventricular; Mg^{2+} = magnesium; VF = ventricular fibrillation; VT = ventricular tachycardia.

Figure 3 Diagnostic workup in patients with sustained ventricular arrhythmias and ACS.

5.3.4 Catheter ablation

VT occurs in 1–2% of patients late after myocardial infarction, often after an interval of several years. Recurrent VT can be treated effectively with catheter ablation, which dramatically reduces VT recurrence in small patient series treated in specialized centres. Whether primary ablation of well-tolerated sustained monomorphic VT in patients with an LVEF >40% without a backup ICD is beneficial deserves further study. Until then, ICD implantation should be considered in survivors of a myocardial infarction suffering from sustained VT or VF in the absence of acute ischaemia, even after successful catheter ablation.[261–265]

6. Therapies for patients with left ventricular dysfunction with or without heart failure

VAs are present in most patients with HF, and sudden death is common in this population.[1,8,295,296] The presence and severity of VAs increase along with the severity of HF, but their value to predict sudden death is unclear.[297–300] Indeed, identification of increased risk of sudden death in HF patients has been notoriously difficult, and the only consistent—and independent—association has been reported with the severity of LV dysfunction or LVEF.

6.1 Primary prevention of sudden cardiac death

6.1.1 Drugs

Use of drugs in patients with left ventricular dysfunction

Recommendations	Class[a]	Level[b]	Ref.[c]
Optimal pharmacological therapy with ACE inhibitors (or, when intolerant, ARBs), beta-blockers and MRAs is recommended in patients with HF with systolic dysfunction (LVEF ≤35–40%) to reduce total mortality and SCD.	I	A	301–304

ACE = angiotensin-converting enzyme; ARB = angiotensin II receptor blocker; HF = heart failure; LVEF = left ventricular ejection fraction; MRA = mineralocorticoid receptor antagonist; SCD = sudden cardiac death.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

ACE inhibitors, beta-blockers and MRAs are recommended in patients with HF with systolic dysfunction (LVEF ≤35–40%) since they reduce all-cause mortality and sudden death[8] (see section 5).

ACE inhibitors reduce all-cause mortality by 15–25% and are recommended in all patients with reduced LVEF.[8,305] Beta-blockers

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reduce mortality by ~35% and have anti-ischaemic properties, which lead to specific anti-arrhythmic effects, and these agents specifically reduce the incidence of sudden death.[8] Recent data from the Beta-Blockers in Heart Failure Collaborative Group have challenged the clinical assumption that beta-blockers improve the prognosis in patients with HF and AF and they advocate that clinicians should choose therapy for this subgroup of patients with HF accordingly.[306] To further explore this provocative observation, the authors stated that 'trial data specifically in patients with HF and AF are urgently needed and eagerly anticipated'.[307]

MRAs reduce mortality and reduce rates of sudden death in patients with HF who are already receiving ACE inhibitors and beta-blocker therapy.[143,308,309] In the most recent trial involving eplerenone, 20% of patients also had an implanted device (ICD or CRT), but the drug was equally effective in patients with as in those without device therapy.[309] This beneficial effect of MRAs on the incidence of SCD in patients with LV systolic dysfunction was confirmed by a meta-analysis of six studies showing patients treated with MRAs had 23% lower odds of experiencing SCD compared with controls [OR 0.77 (95% CI 0.66, 0.89), $P = 0.001$].[310] Diuretics and digoxin are still used by many patients with HF, but they do not reduce rates of all-cause mortality or sudden death. Angiotensin receptor blockers and ivabradine are only recommended in subgroups of patients with HF.[8] Amiodarone does not affect outcome in patients with HF,[132] and given its high incidence of drug toxicity,[8] it is not recommended for general use in these patients. However, in cases of symptomatic ventricular (tachy-)arrhythmias in patients with HF (e.g. those suffering from defibrillator shocks or from non-sustained VAs causing symptoms), amiodarone is the anti-arrhythmic agent of choice because it does not worsen outcome.[132] Other anti-arrhythmic drugs are not recommended in patients with HF because of safety concerns.[8]

In the past 10 years there has been increased awareness that many patients who have signs and symptoms of HF have a normal or preserved ejection fraction (HFpEF).[8,311] Many of the therapies that improve survival in HF with reduced ejection fraction (HFrEF) are less effective in HFpEF. A relatively high proportion of these patients have non-cardiovascular co-morbidities, and although sudden death is common,[312] there have been no well-powered studies with ICDs or CRT. Most large-scale drug trials in HF were conducted before the positive results from landmark trials with ICDs[63,64] and CRT[313,314] became available (in 2005); the evidence from these trials led to a powerful recommendation in the HF guidelines and an enormous increase in their use.[7,315]

6.1.2 Implantable cardioverter defibrillators

Implantable cardioverter defibrillator in patients with left ventricular dysfunction

Recommendations	Class[a]	Level[b]	Ref.[c]
ICD therapy is recommended to reduce SCD in patients with symptomatic HF (NYHA class II–III) and LVEF ≤35% after ≥3 months of optimal medical therapy who are expected to survive for at least 1 year with good functional status:			
– Ischaemic aetiology (at least 6 weeks after myocardial infarction).	I	A	63,64
– Non-ischaemic aetiology.	I	B	64,316, 317

HF = heart failure; ICD = implantable cardioverter defibrillator; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; SCD = sudden cardiac death.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

Early studies regarding the value of ICDs in LV dysfunction were conducted in patients with a previous cardiac arrest (i.e. secondary prevention) or in whom additional electrophysiological criteria were required.[1] Two large trials have provided data on the primary prevention of SCD by an ICD in patients with HF and reduced LVEF: the SCD-HeFT trial[64] and the Multicenter Automatic Defibrillator Implantation Trial II (MADIT-II).[63,318] In the SCD-HeFT, use of an ICD was associated with a 23% decreased risk of death [hazard ratio (HR) 0.77 (95% CI 0.62, 0.96), $P = 0.007$] and an absolute decrease in mortality of 7% after 5 years (from 29 to 22%). There was a 60% reduction in sudden death in the ICD arm.[319] The effect on all-cause mortality did not vary according to ischaemic or non-ischaemic causes of HF, but there was a difference according to NYHA class: ICDs were very effective in class II patients but had no apparent effect on mortality in class III. In MADIT-II, patients in the ICD group had a decrease of 31% in all-cause mortality [HR 0.69 (95% CI 0.51, 0.93), $P = 0.016$], and a later analysis from this study showed that the benefit of ICDs in this population was time dependent,[318] with a larger benefit in patients whose index myocardial infarction was more remote from randomization.

While there are more data to support the use of ICDs in survivors of a myocardial infarction (i.e. ischaemic aetiology), in HFrEF patients with non-ischaemic aetiologies a reduction in all-cause mortality and arrhythmic mortality is supported as well. In the DEFibrillator In Non-Ischemic cardiomyopathy treatment Evaluation (DEFINITE) trial,[316] a trend in mortality reduction was observed in the ICD group [HR 0.65 (95% CI 0.40, 1.06), $P = 0.08$], while sudden cardiac death was significantly reduced [HR 0.20 (95% CI 0.06, 0.71), $P = 0.006$]. In the SCD-HeFT trial,[63] a trend in reduction of all-cause death [HR 0.73 (95% CI 0.50, 1.07), $P = 0.06$] was observed in patients without a previous infarction (and non-ischaemic HF). In the same trial also for patients with ischaemic aetiology, there was only a trend in the reduction of all-cause death [HR 0.79 (95% CI 0.60, 1.04), $P = 0.05$], suggesting that the two subgroups were probably too small to reach statistical significance.[63] Accordingly, a meta-analysis by Desai *et al.*[317] of five primary prevention trials enrolling 1854 patients with non-ischaemic HF, use of an ICD was associated with a significant 31% reduction in total mortality [HR 0.69 (95% CI 0.55, 0.87), $P = 0.002$]. ICD therapy is not recommended in patients with end-stage (NYHA class IV) HF and in other patients who have an estimated life expectancy of <1 year.

Currently there are no RCTs demonstrating the value of an ICD in asymptomatic patients (NYHA class I) with systolic dysfunction (LVEF ≤35–40%) or in patients with HF and preserved LVEF >40–45%, so ICDs are not recommended for primary prevention in these patients.

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6.1.3 Implantable cardioverter defibrillators in patients with New York Heart Association class IV listed for heart transplantation

Implantable cardioverter defibrillators in patients with New York Heart Association class IV listed for heart transplantation

Recommendation	Class[a]	Level[b]	Ref.[c]
ICD implantation should be considered for primary and secondary prevention of SCD in patients who are listed for heart transplant.	IIa	C	320, 321

ICD = implantable cardioverter defibrillator; SCD = sudden cardiac death.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

There are no randomized trial data regarding the value of ICDs in patients with NYHA class IV. It is generally accepted that ICD therapy is not recommended in patients with severe, drug-refractory symptoms who are not candidates for CRT, a ventricular assist device or heart transplantation.[8,11] However, the situation for ambulatory class IV patients who are listed for heart transplantation may be different. These patients often have to wait at least 1 year and their risk of sudden death is high. Data from two observational studies that together examined almost 2000 patients, one of them recent[320] and the other older (in which the use of beta-blockers was low),[321] have suggested a survival benefit in patients with an ICD.

6.1.4 Cardiac resynchronization therapy

6.1.4.1 Heart failure with reduced left ventricular ejection fraction and New York Heart Association class III/ambulatory class IV

Table A. Cardiac resynchronization therapy in the primary prevention of sudden death in patients in sinus rhythm and New York Heart Association functional class III/ambulatory class IV

Recommendations	Class[a]	Level[b]	Ref.[c]
CRT is recommended to reduce all-cause mortality in patients with an LVEF ≤35% and LBBB despite at least 3 months of optimal pharmacological therapy who are expected to survive at least 1 year with good functional status:			322–326
– With a QRS duration >150 ms	I	A	313, 314, 327–329
– With a QRS duration of 120–150 ms	I	B	313, 314
CRT should or may be considered to reduce all-cause mortality in patients with an LVEF ≤35% without LBBB despite at least 3 months of optimal pharmacological therapy who are expected to survive at least 1 year with good functional status:			326 323–325
– With a QRS duration >150 ms	IIa	B	313, 314
– With a QRS duration of 120–150 ms	IIb	B	313, 314

CRT = cardiac resynchronization therapy; LBBB = left bundle branch block; LVEF = left ventricular ejection fraction; ms = milliseconds.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

Table B. Cardiac resynchronization therapy in the primary prevention of sudden death in patients with permanent atrial fibrillation in New York Heart Association functional class III/ambulatory class IV

Recommendations	Class[a]	Level[b]	Ref.[c]
CRT should be considered to reduce all-cause mortality in patients with chronic HF, QRS ≥120 ms and LVEF ≤35% who remain in NYHA functional class III/ambulatory class IV despite at least 3 months of optimal pharmacological therapy who are expected to survive at least 1 year with good functional status, provided that biventricular pacing as close as possible to 100% can be achieved.	IIa	B	330, 331
AV junction ablation should be considered in case of incomplete biventricular pacing.	IIa	B	332, 333

AV = atrio-ventricular; CRT = cardiac resynchronization therapy; HF = heart failure; LVEF = left ventricular ejection fraction; ms = milliseconds; NYHA = New York Heart Association.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

For patients in sinus rhythm, recommendations are provided in relation to LBBB vs. non-LBBB morphology and also regarding QRS duration (120–150 ms vs. >150 ms)[10] (*Table A* in this section). For patients with AF, recommendations are provided in *Table B* in this section.

Two large RCTs [the Comparison of Medical Therapy, Pacing, and Defibrillation in Heart failure (COMPANION) Trial[313] and the Cardiac Resynchronization – Heart Failure (CARE-HF) Trial[314]] in patients with moderate to severe (class III–IV) HF and in sinus rhythm have shown that CRT reduces morbidity and mortality in this population.

COMPANION enrolled HFrEF patients with a QRS duration ≥120 ms. When compared with patients on optimal medical therapy alone, a trend in the reduction of all-cause mortality was observed with a CRT pacemaker (CRT-P) [HR 0.76 (95% CI 0.58, 1.01), $P = 0.059$] and a 36% reduction was seen with a CRT-D [HR 0.64 (95% CI 0.48, 0.86), $P = 0.003$]. CRT-D, but not CRT-P, reduced the rate of SCD in this study.

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While the criterion for QRS duration was also ≥120 ms in CARE-HF, additional criteria for dyssynchrony had to be met in patients with a QRS interval of 120–149 ms. CRT-P reduced all-cause mortality by 36% [HR 0.64 (95% CI 0.48, 0.85), $P < 0.002$].[64] In an extended report from the CARE-HF trial (mean follow-up 37 months), CRT-P also reduced sudden death by 46% [HR 0.54 (95% CI 0.35, 0.84), $P = 0.005$], with a reduction in total mortality at that time of 40% [HR 0.60 (95% CI 0.47, 0.77), $P < 0.001$].[335]

COMPANION and CARE-HF together provide strong evidence favouring the use of CRT (CRT-P or CRT-D) in HFrEF patients with moderate to severe symptoms who have a prolonged QRS duration, especially in those with LBBB morphology. Several other studies, registries and a meta-analysis have addressed the issue of the response to CRT based on QRS morphology and the majority supported the view that QRS morphology with LBBB identifies a subgroup of patients with increased benefit; a short outline of key studies, registries, and meta-analysis is reported here.

Data from the Medicare ICD Registry,[326] which included 14 946 patients, showed that CRT-D was not effective in patients with RBBB, as shown by the increased mortality at 3 years of RBBB as compared to LBBB [HR 1.37 (95% CI 1.26, 1.49), $P < 0.001$]. The REsynchronization reVErses Remodeling in Systolic left vEntricular dysfunction (REVERSE) study[336] confirmed the reduction in the composite clinical endpoint only in patients with LBBB (OR 0.53, $P < 0.0032$) and showed no benefit in patients with non-LBBB (OR 0.74, $P = 0.21$). Similarly, analysis of QRS morphology in the MADIT-CRT[322] study showed a reduction in the primary endpoint in patients with LBBB QRS morphology (HR 0.47, $P < 0.001$) but not in patients with non-LBBB QRS morphology (HR 1.24, $P = 0.257$). Also of interest, the risks of VT, VF and death were significantly reduced only in patients with LBBB. A long-term analysis involving patients in MADIT-CRT has been published recently,[148] confirming that after 7 years of follow-up the survival benefit of CRT-D was observed in patients with LBBB QRS morphology [HR 0.59 (95% CI 0.43, 0.80), $P < 0.001$] while patients with non-LBBB morphology showed no effect and possibly harm related to CRT-D [HR 1.57 (95% CI 1.03, 2.39) $P = 0.04$]. When data from the Resynchronization–Defibrillation for Ambulatory Heart Failure Trial (RAFT) were analysed, on the basis of QRS morphology data, CRT therapy showed a greater benefit in patients with LBBB vs. non-LBBB morphology.[323] Interestingly patients with non-LBBB QRS morphology with a QRS >160 ms experienced a modest reduction in the primary outcome [HR 0.52 (95% CI 0.29, 096), $P = 0.033$]. Despite the fact that only 53 patients were present in this group, the potential benefit of CRT in non-LBBB QRS morphology in the presence of a marked QRS prolongation (QRS ≥160 ms) is worth exploring. This observation is supported by the results of the meta-analysis by Cleland *et al.*,[334] involving data from CARE-HF, Multicenter InSync Randomized Clinical Evaluation (MIRACLE), REVERSE, Multicenter InSync ICD Randomized Clinical Evaluation (MIRACLE ICD) and RAFT. Despite an apparent benefit of CRT in patients with LBBB in univariate analysis, the results in the multivariable model suggested that only QRS duration predicted the magnitude of the effect of CRT on outcomes. Nery *et al.*[324] reported a meta-analysis of CRT clinical trials targeted to 485 patients with RBBB QRS morphology and showed no benefit of resynchronization therapy [HR 2.04 (95% CI 1.32, 3.15), $P = 0.001$]; unfortunately no data on QRS duration were provided.

Sipahi *et al.*[325] performed a meta-analysis in which they examined 33 clinical trials investigating the effect of QRS morphology on CRT, but only four (COMPANION, CARE-HF, MADIT-CRT and RAFT) included outcomes according to QRS morphology. When they evaluated the effect of CRT on composite adverse clinical events in 3349 patients with LBBB at baseline, they observed a 36% reduction in risk with the use of CRT [RR 0.64 (95% CI 0.52, 0.77), $P < 0.00001$]. However, such benefit was not observed in patients with non-LBBB conduction abnormalities [RR 0.97 (95% CI 0.82, 1.15), $P = 0.75$].[325] Interestingly, when the analysis was limited to trials without ICD (CARE-HF and COMPANION), the benefit of CRT was still observed only in patients with LBBB ($P < 0.000001$).

In a recent large meta-analysis of six RCTs (COMPANION, CARE-HF, MADIT-CRT, MIRACLE, RAFT and REVERSE),[337] including 6914 participants (1683 with non-LBBB QRS morphology), CRT was not associated with a reduction in death and/or HF hospitalization in patients with non-LBBB QRS morphology [HR 1.09 (95% CI 0.85, 1.39)].[337]

Therefore wide QRS with non-LBBB morphology still remains an area of uncertainty for CRT. Based on these data, despite the fact that most patients in Europe receive a CRT-D,[314] our recommendations are expressed in general for CRT.

Discrepancies exist in previous documents [American College of Cardiology Foundation/AHA guidelines and the consensus document on pacing from the European Heart Rhythm Association (EHRA)/ESC] about the class of recommendation for CRT in patients with QRS between 120 and 150 ms. Based on a meta-analysis by Sipahi *et al.*,[328] CRT significantly reduced all-cause mortality or hospitalization in patients with a QRS duration ≥150 ms [RR 0.60 (95% CI 0.53, 0.67), $P < 0.001$], but not in patients with a QRS duration of 120–150 ms [RR 0.95 (95% CI 0.82, 1.10), $P = 0.49$]. However, methodological concerns due to the multiplicity of analysis in the study by Sipahi *et al.* have been pointed out,[338] and therefore the conclusion that CRT is effective only for patients with a QRS ≥150 ms should at this time be regarded as exploratory only.[338] CRT is not recommended in HF patients with a QRS duration <120 ms.[339]

In patients with AF, CRT should be considered in those with markedly reduced LVEF, but this has not been shown to reduce mortality or sudden death in these patients.[8,340] In the RAFT trial, 229 (or 13% of the total population of 1798) patients had AF or flutter at baseline.[327] Although there was formally no significant interaction between baseline rhythm and treatment effect (ICD vs. CRT-D, $P = 0.14$), the number of patients in this study was small and the effect in patients with AF or atrial flutter appeared less than in those in sinus rhythm. Success of CRT in patients with AF is, for the most part, determined by the degree of biventricular pacing, and this can be achieved only by means of AV junction ablation in many patients.[10]

Although the decision to perform AV junction ablation in these patients is still a matter of some debate, recent data suggest that long-term survival after CRT among patients with AF who have

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undergone AV junction ablation is similar to that observed in patients in sinus rhythm.[333] In summary, CRT can be considered in patients with HF, permanent AF and LVEF ≤35% if (i) ventricular pacing is required or the patient otherwise meets CRT criteria and (ii) near 100% ventricular pacing is achieved with CRT with AV junction ablation or pharmacological rate control (class 2A–B level of recommendation).

6.1.4.2 Heart failure with reduced left ventricular ejection fraction but mild symptoms (New York Heart Association class II)

Table C. Cardiac resynchronization therapy defibrillator[a] in the primary prevention of sudden death in patients in sinus rhythm with mild (New York Heart Association class II) heart failure

Recommendations	Class[b]	Level[c]	Ref.[d]
CRT-D is recommended to reduce all-cause mortality in patients with a QRS duration ≥130 ms, with an LVEF ≤30% and with LBBB despite at least 3 months of optimal pharmacological therapy who are expected to survive at least 1 year with good functional status.	I	A	148, 322, 323, 325, 327, 329
CRT-D may be considered to prevent hospitalization for HF in patients with a QRS duration ≥150 ms, irrespective of QRS morphology, and an LVEF ≤35% despite at least 3 months of optimal pharmacological therapy who are expected to survive at least 1 year with good functional status.	IIb	A	148, 327–329, 334

CRT-D = cardiac resynchronization therapy defibrillator; HF = heart failure; LBBB = left bundle branch block; LVEF = left ventricular ejection fraction; ms = milliseconds.
[a]These recommendations refer specifically to CRT-D, since studies on the effect of resynchronization in patients with NYHA class II only used CRT-D.
[b]Class of recommendation.
[c]Level of evidence.
[d]Reference(s) supporting recommendations.

Two controlled trials randomized 3618 patients with mild HF to optimal pharmacological therapy plus an ICD or optimal pharmacological treatment plus CRT-D.[327,329]

The MADIT-CRT study[329] enrolled 1820 patients who were mildly symptomatic (NYHA class I or II) and who had an LVEF ≤30% with a QRS duration ≥130 ms. The initial report showed a 34% reduction in the primary endpoint of all-cause death or HF events [25.3% vs. 17.2% for ICD vs. CRT-D; HR 0.66 (95% CI 0.52, 0.84), $P = 0.001$]. In a long-term follow-up report from MADIT-CRT (mean follow-up of 7 years),[148] CRT-D significantly reduced mortality [HR 0.59 (95% CI 0.43, 0.80), $P < 0.001$] compared with ICD only, which, however, was confined to patients with LBBB at baseline, while no beneficial effect was observed in those without LBBB ($P < 0.001$ for interaction) (*Table C* in this section).

The RAFT trial[327] enrolled 1798 patients with mild to moderate HF (NYHA class II or III), LVEF ≤30% and a QRS duration ≥120 ms (or a paced QRS duration ≥200 ms). Compared with patients with an ICD alone, the CRT-D group showed a 25% RR reduction in all-cause mortality [HR 0.75 (95% CI 0.62, 0.91), $P = 0.003$], substantiating the systematic use of CRT therapy in HFrEF patients with mild symptoms.

6.2 Premature ventricular complexes in patients with structural heart disease/left ventricular dysfunction

Treatment of patients with left ventricular dysfunction and premature ventricular complex

Recommendations	Class[a]	Level[b]	Ref.[c]
In patients with frequent symptomatic PVC or NSVT:			
– Amiodarone should be considered.	IIa	B	64
– Catheter ablation should be considered.	IIa	B	341–343
Catheter ablation should be considered in patients with LV dysfunction associated with PVCs.	IIa	B	341–343

LV = left ventricular; NSVT = non-sustained ventricular tachycardia; PVC = premature ventricular complex.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

PVCs and runs of NSVT are common in patients with LV dysfunction and may be the consequence or cause of LV dysfunction. PVCs and runs of NSVT in subjects with structural heart disease contribute to an increased mortality risk, and >10 PVCs per hour or runs of NSVT are an acceptable marker of increased risk.[344] If patients are symptomatic due to PVCs or NSVTs, or if PVCs or NSVTs contribute to reduced LVEF ('tachycardia-induced cardiomyopathy'), amiodarone or catheter ablation should be considered.

A high PVC burden (>24%) in patients with LV dysfunction and a rather short coupling interval of the PVCs (<300 ms) suggest PVC-induced cardiomyopathy.[342] In such patients, catheter ablation can suppress PVCs and restore LV function.[341]

6.3 Sustained ventricular tachycardia

6.3.1 Drug therapy

Treatment of patients with left ventricular dysfunction and sustained recurrent monomorphic ventricular tachycardia

Recommendations	Class[a]	Level[b]	Ref.[c]
Optimization of HF medication according to current HF guidelines is recommended in patients with LV dysfunction and sustained VT.	I	C	8

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Amiodarone treatment should be considered to prevent VT in patients with or without an ICD.	IIa	C	64

HF = heart failure; LV = left ventricular; ICD = implantable cardioverter defibrillator; VT = ventricular tachycardia.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

Patients with LV dysfunction with or without HF presenting with sustained VT should be treated according to recently published HF guidelines, similar to patients with LV dysfunction without VT.[8] In addition, medical drug therapy for sustained VT should target maximal sympathetic blockade. In the MADIT-II study, patients with ICD treated with the highest doses of beta-blockers experienced a significant reduction in recurrent episodes of VT or VF necessitating ICD intervention compared with patients not taking beta-blockers [HR 0.48 (95% CI 0.26, 0.89), $P = 0.02$].[8] The Optimal Pharmacological Therapy in Cardioverter Defibrillator Patients (OPTIC) study compared the use of beta-blockers, sotalol and beta-blockers plus amiodarone for the prevention of ICD shocks.[156] Amiodarone plus beta-blocker therapy significantly reduced the risk of shock compared with beta-blocker treatment alone [HR 0.27 (95% CI 0.14, 0.52), $P < 0.001$] and sotalol [HR 0.43 (95% CI 0.22, 0.85), $P = 0.02$]. However, drug discontinuation was more frequent in patients taking sotalol or a combination of amiodarone and a beta-blocker. The rates of study drug discontinuation at 1 year were 18.2% for amiodarone, 23.5% for sotalol and 5.3% for beta-blocker alone.

In the SCD-HeFT trial, patients with LV dysfunction and NYHA class II or III HF received conventional HF therapy, conventional therapy plus amiodarone or conventional therapy and a single-chamber ICD.[64] Compared with conventional HF therapy, the addition of amiodarone did not increase mortality.

6.3.2 Catheter ablation

Prevention of ventricular tachycardia recurrences in patients with left ventricular dysfunction and sustained ventricular tachycardia

Recommendations	Class[a]	Level[b]	Ref.[c]
Urgent catheter ablation in specialized or experienced centres is recommended in patients presenting with incessant VT or electrical storm resulting in ICD shocks.	I	B	183
Amiodarone or catheter ablation is recommended in patients with recurrent ICD shocks due to sustained VT.	I	B	64,156, 184–186
ICD implantation is recommended in patients undergoing catheter ablation whenever they satisfy eligibility criteria for ICD.	I	C	This panel of experts
Amiodarone or catheter ablation should be considered after a first episode of sustained VT in patients with an ICD.	IIa	B	64, 184–186

ICD = implantable cardioverter defibrillator; VT = ventricular tachycardia.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

Depending on the underlying substrate, catheter ablation for sustained VT may result in acute termination and reduction of recurrent VT episodes in patients with structural heart disease.

6.3.2.1 *Patients with left ventricular dysfunction*

In patients with LV dysfunction and sustained VT, scar-mediated re-entry is the common pathophysiological mechanism and ablation targets the critical isthmus within the re-entry circuit. VT is mostly monomorphic. If a 12-lead ECG of the clinical VT is not available in ICD patients, the cycle length of the stored ICD electrograms during VT may facilitate identification of the clinical VT during the electrophysiology study. Irrigated ablation catheters are commonly used, which facilitate deeper lesion formation and reduce the risk of char formation during energy delivery.

At present, the best ablative strategy is unknown. There is a lack of RCTs comparing catheter ablation during VT with a substrate-based approach. In addition, there is no consensus with respect to the ideal procedural endpoint. While elimination of all clinical VTs should be attempted, non-inducibility of any VT after ablation may be the preferred procedural endpoint.

Patients may present with electrical storms. Catheter ablation can acutely terminate this potentially life-threating event and has been shown to decrease the rate of recurrent electrical storm episodes when compared with medical treatment only.[183] Patients with VT related to post-myocardial scar tend to have a better outcome following catheter ablation than patients with VT due to non-ischaemic cardiomyopathy. Five prospective studies have evaluated the role of catheter ablation in the treatment of sustained VT.[184–188] The Multicenter Thermocool study reported an acute success rate, defined as abolishment of all inducible VTs, of 49% and a mid-term freedom from VT of 53% over 6 months of follow-up.[185] In the Cooled RF Multi Center Investigators Group study, acute success, defined as elimination of all inducible VTs, was achieved in 41% of patients.[184] Freedom from recurrent VA was noted in 46% of patients during 8 ± 5 months of follow-up. In the prospective Euro-VT study, ablation was acutely successful in 81% of patients and freedom from recurrent VT was achieved in 51% of patients.[186] The Substrate Mapping and Ablation in Sinus Rhythm to Halt Ventricular Tachycardia Trial (SMASH-VT) evaluated the role of catheter ablation in patients with previous myocardial infarction and reduced LVEF.[187] Patients underwent ICD implantation for VF, haemodynamically unstable VT or syncope with inducible VT during invasive electrophysiology testing. The control arm underwent ICD implantation only. None of the patients received anti-arrhythmic drugs. Catheter ablation was performed using a substrate-guided approach targeting abnormal ventricular potentials during sinus rhythm without the need for VT induction. During a mean follow-up of 23 ± 6 months there was a significant reduction in the incidence of VT episodes, from

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33% in the control group to 12% in the ablation arm. Furthermore, the rate of appropriate ICD shocks decreased from 31% to 9% following catheter ablation.

The Ventricular Tachycardia Ablation in Coronary Heart Disease (VTACH) study prospectively randomized patients with previous myocardial infarction, reduced ejection fraction (≤50%) and haemodynamically stable VT to catheter ablation or no additional therapy, apart from subsequent ICD.[188] The primary endpoint was time to first recurrence of VT or VF. The rate of survival free from recurrent VT over 24 months was higher in the ablation group compared with the control arm [47% vs. 29%, HR 0.61 (95% CI 0.37, 0.99), $P = 0.045$]. The mean number of appropriate ICD shocks per patient per year decreased from 3.4 ± 9.2 to 0.6 ± 2.1 in patients undergoing catheter ablation ($P = 0.018$). Catheter ablation did not affect mortality.

Overall, the success rate of catheter ablation for VT is determined by the amount of infarct-related scar burden, represented as low-voltage areas on electro-anatomic mapping systems,[209] while dedicated units for the treatment of patients undergoing catheter ablation of VT may positively impact outcome.[210]

6.3.2.2 Bundle branch re-entrant tachycardia

Prevention of ventricular tachycardia recurrences in patients with bundle branch re-entrant tachycardia

Recommendation	Class[a]	Level[b]	Ref.[c]
Catheter ablation as first-line therapy is recommended in patients presenting with bundle branch re-entrant tachycardia.	I	C	345, 346

[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

Bundle branch tachycardia is a rare macro-re-entry tachycardia that typically involves the right bundle branch as the anterograde and the left bundle branch as the retrograde limb. On the 12-lead surface ECG, LBBB morphology with left-axis deviation is seen. Bundle branch re-entry is often associated with cardiomyopathy.[347] Catheter ablation of one of the bundle branches is curative, although the right bundle branch is the preferred target, as it is more easily accessible for ablation.[347] As the underlying structural abnormality remains unchanged, concomitant placement of an ICD should be strongly considered.[347]

6.3.3 Implantable cardioverter defibrillator

Implantation of an ICD in patients with sustained VT increases survival compared with anti-arrhythmic drug therapy. To date, no trial has been conducted comparing catheter ablation for sustained VT without ICD implantation and ICD placement only. In view of the scarcity of data and the rather high rate of recurrence following catheter ablation for sustained VT, ICD implantation should be considered in all patients with LV dysfunction (ejection fraction <45%) and sustained VT.

7. Cardiomyopathies

Cardiomyopathies are myocardial disorders defined by structural and functional abnormalities of the ventricular myocardium that are not solely explained by flow-limiting coronary artery stenosis or abnormal loading conditions.[348] They are grouped according to morphological and functional characteristics and subclassified into familial and non-familial forms. Nearly all cardiomyopathies can be associated with VA and an increased risk of SCD that varies with the aetiology and the severity of the disease.

7.1 Dilated cardiomyopathy

7.1.1 Definitions, epidemiology and survival data

DCM is defined as LV dilatation and systolic dysfunction in the absence of abnormal loading conditions or CAD sufficient to cause global systolic impairment.[348] Some genetic defects that cause DCM can also cause systolic dysfunction without LV dilatation or result in myocardial scarring that is only detectable on CMR.

DCM presents in people of all ages and ethnicities. In adults, it is more common in men than in women, with an overall prevalence of 1 in 2500 individuals and a conservative estimated annual incidence of 7 per 100 000.[349] In children, the yearly incidence is 0.57 cases per 100 000.[350]

Potentially pathogenic genetic mutations are found in at least 20% of adults with DCM and between 10 and 20% of relatives have evidence for disease on clinical screening.[351] Sarcomere and desmosomal protein gene mutations are the most common, but mutations in lamin A/C (*LMNA*) and desmin are frequent in patients with conduction diseases.[352,353] A small number of patients have an X-linked disease caused by mutations in the dystrophin gene. A large spectrum of acquired conditions can cause DCM, including inflammatory, infective and systemic diseases, as well as various drugs and toxins. In some cases, patients are genetically predisposed to the development of DCM following exposure to exogenous triggers such as infection, cytotoxic drugs, alcohol and pregnancy.

7.1.2 Approach to risk stratification and management

Risk stratification and management of patients with dilated cardiomyopathy

Recommendations	Class[a]	Level[b]	Ref.[c]
Optimal medical therapy (ACE inhibitors, beta-blockers and MRA) is recommended in patients with DCM to reduce the risk of sudden death and progressive HF.	I	A	8
Prompt identification and treatment of arrhythmogenic factors (e.g. pro-arrhythmic drugs, hypokalaemia) and co-morbidities (e.g. thyroid disease) is recommended in patients with DCM and VA.	I	C	8

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A coronary angiography is recommended in stable DCM patients with an intermediate risk of CAD and new onset VA.	I	B	8
An ICD is recommended in patients with DCM and haemodynamically not tolerated VT/VF, who are expected to survive for >1 year with good functional status.	I	A	151–154
An ICD is recommended in patients with DCM, symptomatic HF (NYHA class II–III) and an ejection fraction ≤35% despite ≥3 months of treatment with optimal pharmacological therapy who are expected to survive for >1 year with good functional status.	I	B	64, 313, 316, 317, 354
Catheter ablation is recommended in patients with DCM and bundle branch re-entry ventricular tachycardia refractory to medical therapy.	I	B	8,208, 345, 346
An ICD should be considered in patients with DCM and a confirmed disease-causing *LMNA* mutation and clinical risk factors.[d]	IIa	B	71
Amiodarone should be considered in patients with an ICD that experience recurrent appropriate shocks in spite of optimal device programming.	IIa	C	229
Catheter ablation may be considered in patients with DCM and VA not caused by bundle branch re-entry refractory to medical therapy.	IIb	C	355
Invasive EPS with PVS may be considered for risk stratification of SCD.	IIb	B	115
Amiodarone is not recommended for the treatment of asymptomatic NSVT in patients with DCM.	III	A	313, 354
Use of sodium channel blockers and dronedarone to treat VA is not recommended in patients with DCM.	III	A	129, 356, 357

ACE = angiotensin-converting enzyme; CAD = coronary artery disease; DCM = dilated cardiomyopathy; EPS = electrophysiological study; HF = heart failure; ICD = implantable cardioverter defibrillator; *LMNA* = lamin A/C; LVEF = left ventricular ejection fraction; MRA = mineralocorticoid receptor antagonists; NSVT = non-sustained ventricular tachycardia; NYHA = New York Heart Association; PVS = programmed ventricular stimulation; SCD = sudden cardiac death; VA = ventricular arrhythmia; VT = ventricular tachycardia.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.
[d]Risk factors in patients with a confirmed *LMNA* mutation: NSVT during ambulatory electrocardiogram monitoring, LVEF <45% at first evaluation, male sex and non-missense mutations (insertion, deletion, truncations or mutations affecting splicing).

All-cause mortality in unselected adult patients with DCM has decreased substantially with the use of neurohormonal antagonists and device therapy.[358] Mortality in children with DCM is relatively high in the first year of life but thereafter many children recover function or remain clinically stable.[359] The major causes of cardiovascular death in DCM are progressive HF and SCD secondary to VA or, less commonly, bradyarrhythmias. Many non-invasive variables have been suggested as predictors of sudden death, but in a recent meta-analysis of 45 studies enrolling 6088 patients, functional and electrocardiographic variables provided only modest discrimination between high- and low-risk patients. The highest OR was for fragmented QRS and T-wave alternans; none of the autonomic tests were significant predictors.[115] The role of CMR imaging has been evaluated in a meta-analysis of nine studies in patients with non-ischaemic cardiomyopathy[360] and suggests that late gadolinium enhancement in patients is associated with increased risk of all-cause mortality, HF hospitalization and SCD. The incremental value of late gadolinium enhancement over other prognostic markers needs to be determined.

Invasive EPS with PVS might play a role in patients with DCM.[115]

7.1.2.1 *Trials of implantable cardioverter defibrillator therapy in dilated cardiomyopathy*

A number of trials have compared ICD therapy alone or in combination with CRT against placebo or amiodarone in patients with DCM.[64,151–154,313,316,317,354] Most were conducted in an era when best medical therapy evolved to include ACE inhibitors, beta-blockers and MRAs.[358] The first RCTs of ICD therapy were underpowered to detect clinically meaningful differences in survival, and in some cases (e.g. DEFINITE) the overall mortality rate was lower than anticipated before enrolment. Follow-up was relatively short in some studies and, as in other settings, the relation of appropriate shocks to prognosis is still uncertain. No study has prospectively investigated the benefit of ICDs in specific aetiological subgroups of DCM.

7.1.2.2 *Primary prophylaxis*

Four randomized trials [CArdiomyopathy Trial (CAT),[361] AMIOdarone Versus Implantable cardioverter-defibrillator: Randomized Trial in patients with non-ischaemic dilated cardiomyopathy and asymptomatic non-sustained ventricular tachycardia (AMIOVIRT),[354] DEFINITE[316] and SCD-HeFT[64]] examined the effect of ICD therapy alone for primary prevention of SCD. A further study, COMPANION,[313] compared CRT-D, CRT-P and amiodarone therapy in patients with advanced HF (NYHA class III or IV) and a QRS interval >120 ms. The studies differ in design: CAT, AMIOVIRT and DEFINITE enrolled only patients with non-ischaemic DCM, whereas SCD-HeFT and COMPANION included patients with ischaemic and non-ischaemic LV dysfunction. Only COMPANION demonstrated a statistically significant reduction in sudden death with ICDs compared with optimal medical therapy. All-cause mortality was lower in the CRT-D group than in the pharmacological therapy group [HR 0.50 (95% CI 0.29, 0.88), $P = 0.015$], but was associated with a significantly higher risk of moderate or severe adverse events from any cause (69% vs. 61% in the medical therapy arm, $P = 0.03$). Pooled analysis of the five primary prevention trials (1854 patients with non-ischaemic DCM) demonstrated a statistically significant 31% reduction in all-cause mortality for ICD relative to medical therapy [RR 0.69 (95% CI 0.55, 0.87), $P = 0.002$].[317] This effect persisted when COMPANION was excluded [RR 0.74 (95% CI 0.58, 0.96), $P = 0.02$].[317] Recommendations for ICD therapy in this guideline are based on these analyses.

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7.1.2.3 Secondary prophylaxis

Three trials (AVID,[153] CASH[152] and CIDS;[151] see *Web Table 5*) examined ICD therapy for secondary prevention in patients with a history of aborted cardiac arrest or symptomatic VT. In the CASH study, patients were initially randomized to receive an ICD or one of three drugs: amiodarone, metoprolol or propafenone, but the propafenone arm was terminated early due to increased mortality. The final analysis pooled data from the amiodarone and metoprolol arms. The three trials enrolled a total of 1963 patients, of whom only 292 (14.8%) had non-ischaemic cardiomyopathy. Neither AVID nor CIDS reported a significant reduction in all-cause mortality with ICD therapy in the subgroup of patients with non-ischaemic cardiomyopathy; outcomes for this subgroup were not reported in CASH. The CASH trial also differed from AVID and CIDS in that the mean LVEF was higher and >50% of patients received epicardial ICD systems. In a subsequent meta-analysis in which data from AVID and CIDS were pooled, there was a non-significant 31% reduction in all-cause mortality relative to medical therapy.[154]

7.1.2.4 Cause-specific mortality

Few studies have examined prognosis or treatment in specific DCM subtypes. The best-characterized are the approximately 5–10% of patients who have disease caused by mutations in the *LMNA* gene.[71,352] *LMNA*-related cardiac disease shows age-related penetrance with early onset atrial arrhythmias followed by development of a conduction disease and a high risk of sudden death, often with only mild LV dilatation and systolic impairment. In a multicentre registry of 269 *LMNA* mutation carriers, multivariable analysis demonstrated that NSVT during ambulatory ECG monitoring, LVEF <45% at first evaluation, male sex and non-missense mutations (insertion-deletion/truncating or mutations affecting splicing) were independent risk factors for malignant VA.[71] Malignant VA occurred only in persons with at least two of these risk factors and there was a cumulative risk for each additional risk factor.

7.1.2.5 Management of ventricular arrhythmia in dilated cardiomyopathy

Patients with DCM and recurrent VA should receive optimal medical therapy with ACE inhibitors, beta-blockers and MRAs in accordance with the ESC guidelines for chronic HF.[8] Obvious precipitating factors for VA (e.g. pro-arrhythmic drugs, hypokalaemia) or co-morbidities (e.g. thyroid disease) for VA should be sought and treated when possible. In previously stable patients with new-onset VA, coronary angiography should be considered in patients with an intermediate to high risk of CAD. Amiodarone should be considered in patients with an ICD that experience recurrent appropriate shocks in spite of optimal device programming,[229] but should not be used to treat asymptomatic episodes of NSVT. The use of sodium channel blockers and dronedarone is not recommended in patients with impaired LV function because of their potential pro-arrhythmic effects.[129,152,357,362,363]

7.1.2.6 Ablation of ventricular tachycardia

The substrate for VT in DCM is highly complex, reflecting the multiple causes of the disease. Studies evaluating different ablation strategies in DCM report, at best, modest success that is not improved when epicardial and endocardial mapping is performed. In a recent registry study comparing 63 patients with non-ischaemic cardiomyopathy and 164 with ischaemic LV dysfunction,[208] ablation of the clinical VT only was achieved in 18.3% of non-ischaemic cardiomyopathy. Thus catheter ablation of VT in DCM patients should be reserved for patients presenting with a clear VT mechanism (e.g. bundle branch re-entry) and performed in experienced centres.

7.2 Hypertrophic cardiomyopathy

7.2.1 Definitions, epidemiology and survival data

HCM is characterized by increased LV wall thickness that is not solely explained by abnormal LV loading conditions.[116] This definition applies to children and adults and makes no assumptions about the aetiology, but for the purposes of this guideline, recommendations on the prevention of SCD apply to patients *without* metabolic, infiltrative or other diseases that have very distinct natural histories and treatment.

Studies in North America, Europe, Asia and Africa report a prevalence of unexplained LV hypertrophy in the range of 0.02–0.23% in adults, with much lower rates in patients <25 years of age.[116] While HCM is most frequently transmitted as an autosomal dominant genetic trait, most studies report a small male preponderance, and the frequency of HCM in different racial groups is similar.[116]

Overall annual cardiovascular mortality and the rate of death or appropriate ICD discharge for VT/VF in unselected adults with HCM is 1–2 and 0.81%, respectively.[364,365] Other major causes of cardiovascular death are HF, thromboembolism and AV block.

7.2.2 Approach to risk stratification and management

Prevention of sudden cardiac death in patients with hypertrophic cardiomyopathy

Recommendations	Class[a]	Level[b]	Ref.[c]
Avoidance of competitive sports[d] is recommended in patients with HCM.	I	C	366
ICD implantation is recommended in patients who have survived a cardiac arrest due to VT or VF or who have spontaneous sustained VT causing syncope or haemodynamic compromise and a life expectancy >1 year.	I	B	116, 367–372
Risk stratification with the HCM Risk-SCD calculator is recommended to estimate the risk of sudden death at 5 years in patients ≥16 years of age without a history of resuscitated VT or VF or spontaneous sustained VT causing syncope or haemodynamic compromise.	I	B	116, 365
It is recommended that the 5-year risk of SCD is assessed at first evaluation and at 1- to 2-year intervals, or when there is a change in clinical status.	I	B	116, 365

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ICD implantation should be considered in patients with an estimated 5-year risk of sudden death ≥6% and a life expectancy >1 year following detailed clinical assessment that takes into account the lifelong risk of complications and the impact of an ICD on lifestyle, socioeconomic status and psychological health.	IIa	B	116, 368
ICD implantation may be considered in individual patients with an estimated 5-year risk of SCD of ≥4 to <6% and a life expectancy >1 year following detailed clinical assessment that takes into account the lifelong risk of complications and the impact of an ICD on lifestyle, socioeconomic status and psychological health.	IIb	B	116, 365, 368
ICD implantation may be considered in individual patients with an estimated 5-year risk of SCD <4% when they have clinical features that are of proven prognostic importance and when an assessment of the lifelong risk of complications and the impact of an ICD on lifestyle, socioeconomic status and psychological health suggests a net benefit from ICD therapy.	IIb	B	116, 365, 368
Invasive EPS with PVS is not recommended for stratification of SCD risk.	III	C	116

ESC = European Society of Cardiology; EPS = electrophysiological study; HCM = hypertrophic cardiomyopathy; ICD = implantable cardioverter defibrillator; PVS = programmed ventricular stimulation; SCD = sudden cardiac death; VF = ventricular fibrillation; VT = ventricular tachycardia.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.
[d]ESC guidelines define competitive sport as amateur or professional engagement in exercise training on a regular basis and participation in official competitions (see relevant ESC guidelines for more detail).

7.2.3 Ventricular arrhythmias in hypertrophic cardiomyopathy

NSVT occurs in ~25% of patients during ambulatory ECG monitoring.[373,374] Its prevalence increases with age and correlates with LV wall thickness and late gadolinium enhancement on CMR.[375] NSVT during ambulatory monitoring is associated with an increased risk of SCD.[373] Documented NSVT during or immediately following exercise is very rare, but may be associated with a higher risk of SCD.[376]

Documented sustained monomorphic VT (≥30 s) is uncommon, but may be more frequent in patients with apical LV aneurysms. The presence of CAD should be excluded in patients with prolonged or symptomatic episodes if risk factors for coronary atherosclerosis are present.[377] Patients with poorly tolerated sustained VT should be considered for ICD therapy and treatment with beta-blockers or amiodarone to suppress further episodes. In patients with evidence for a focal origin of their VT, EPS and ablation may be considered.

7.2.4 Approach to risk stratification and management in adults patients

Historically the risk of SCD in patients with HCM has been estimated using a simple score based on a number of selected clinical parameters.[367,378,379] Other clinical features, such as myocardial fibrosis (determined by contrast-enhanced CMR), LV apical aneurysms and multiple sarcomere protein gene mutations, have been suggested as features that can be used to guide ICD therapy in individuals who are at intermediate risk, with few supportive data. ESC guidelines on HCM recommend the use of a calculator (HCM Risk-SCD) that estimates 5-year risk.[116]

The predictor variables used in the model are all associated with an increased risk of SCD in at least one published multivariable analysis (http://doc2do.com/hcm/webHCM.html). The calculator is designed specifically for use in patients ≥16 years of age and is not intended for use in elite athletes or in individuals with metabolic or infiltrative diseases (e.g. Anderson–Fabry disease) and syndromes (e.g. Noonan syndrome). The model does not use exercise-induced LVOT gradients and has not been validated before and after myectomy or alcohol septal ablation.

Invasive EPS with PVS does not contribute to SCD risk stratification in HCM and its routine use in patients with syncope or symptoms suggestive of arrhythmia is not recommended.[116]

In contrast with the recently released HCM guidelines,[116] we have not incorporated a class III recommendation for patients with an estimated risk <4% at 5 years, in consideration of the degree of uncertainty in estimating risk that calls for caution when excluding a category of patients from the use of ICD.

7.2.5 Approach to risk stratification and management in paediatric patients

In patients <16 years of age, implantation of an ICD (epicardial if necessary) is recommended after a life-threatening VA. Few data are available on the use of clinical risk markers to guide primary prophylaxis, particularly in very young children (<8 years of age). Current ESC guidelines recommend that severe LV hypertrophy (defined as a maximum LV wall thickness ≥30 mm or a Z-score ≥6), unexplained syncope, NSVT and a family history of sudden death should be considered as major risk factors for SCD in children.[116] Implantation of an ICD should be considered in children who have two or more of these major risk factors. In individual patients with a single risk factor, ICD implantation may be considered after careful consideration of the risks and benefits to the child. Single-chamber defibrillators suffice in the majority of cases and reduce the likelihood of complications.[116]

7.2.6 Prevention of sudden cardiac death

7.2.6.1 Drugs and lifestyle advice

Patients with HCM should be advised against participation in competitive sports and discouraged from intense physical activity, especially when they have recognized risk factors for SCD or an LVOT gradient. There are no RCTs of anti-arrhythmics in HCM. Amiodarone possibly reduces the incidence of SCD in patients with NSVT during ambulatory ECG monitoring but often failed to prevent SCD in many studies.[380,381] Disopyramide and beta-blockers are used to treat LVOT obstruction, but there is no evidence that they reduce the risk of SCD.[116] Similarly, current ESC guidelines

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on HCM do not recommend surgical myectomy or alcohol ablation to reduce risk of SCD in patients with LVOT obstruction.[116]

7.2.6.2 Implantable cardioverter defibrillators

Secondary prophylaxis. While there are no trials of ICD therapy in HCM, observational cohort studies and meta-analyses show that aborted cardiac arrest or sustained VT are associated with a high risk of subsequent lethal cardiac arrhythmias.[368] For this reason, ICDs are recommended in this small group of patients.[116]

Primary prophylaxis. It is recommended that patients with HCM undergo a standardized clinical evaluation in line with the ESC guidelines on HCM.[116] This should include a clinical and family history, 48-h ambulatory ECG, transthoracic echocardiography (or CMR in the case of inadequate echo windows) and a symptom-limited exercise test. Recommendations for ICD therapy are based on the 5-year SCD risk calculated using the HCM Risk-SCD model and taking into account the age and general health of the patient.

7.3 Arrhythmogenic right ventricular cardiomyopathy

7.3.1 Definitions, epidemiology and survival

ARVC (or arrhythmogenic cardiomyopathy) is a progressive heart muscle disorder characterized by VA, HF and SCD.[382] The histological hallmark of the disease is replacement of cardiomyocytes by adipose and fibrous tissue.[382,383] Clinically, ARVC is defined by structural and functional abnormalities of the right ventricle, but LV involvement occurs in >50% of patients.[384] Current task force criteria use histological, genetic, electrocardiographic and imaging parameters to classify patients into definite, borderline and possible diagnostic categories.[382]

In most cases ARVC is inherited as an autosomal dominant genetic trait caused by mutations in genes encoding for desmosomal proteins (plakoglobin), desmoplakin, plakophilin-2, desmoglein-2 and desmocollin-2. A minority of cases are caused by mutations in non-desmosomal genes and rare recessive forms (e.g. Carvajal syndrome and Naxos disease) associated with a cutaneous phenotype of palmar and plantar hyperkeratosis.[52]

ARVC has an estimated prevalence of 1 in 1000 to 1 in 5000 of the general population and is an important cause of SCD in athletes and young adults.[385,386] Clinical manifestations, including palpitations, syncope, VT and SCD, usually develop between the second and fourth decade of life. Disease progression may result in right or biventricular HF. The annual mortality rate reported in different studies varies considerably, depending on the characteristics of reported cohorts. Data from one meta-analysis reported an annualized rate for cardiac mortality, non-cardiac mortality and heart transplantation of 0.9, 0.8 and 0.9%, respectively.[387]

7.3.2 Approach to risk stratification and management

Risk stratification and management of patients with arrhythmogenic right ventricular cardiomyopathy

Recommendations	Class[a]	Level[b]	Ref.[c]
Avoidance of competitive sports[d] is recommended in patients with ARVC.	I	C	388
Beta-blockers titrated to the maximally tolerated dose are recommended as the first-line therapy to improve symptoms in patients with frequent PVC and NSVT.	I	C	This panel of experts
ICD implantation is recommended in patients with a history of aborted SCD and haemodynamically poorly tolerated VT.	I	C	389
Amiodarone should be considered to improve symptoms in patients with frequent PVC or NSVT who are intolerant of or have contraindications to beta-blockers.	IIa	C	390, 391
Catheter ablation, performed in experienced centres, should be considered in patients with frequent symptomatic PVC or VT unresponsive to medical therapy to improve symptoms and prevent ICD shocks, respectively.	IIa	B	183, 202, 207, 392, 393
ICD implantation should be considered in ARVC patients who have haemodynamically well-tolerated sustained VT, balancing the risk of ICD therapy, including long-term complications, and the benefit for the patient.	IIa	B	387, 394, 395
ICD implantation may be considered in patients with one or more recognized risk factors for VA in adult patients with a life expectancy >1 year following detailed clinical assessment that takes into account the lifelong risk of complications and the impact of an ICD on lifestyle, socioeconomic status and psychological health.	IIb	C	This panel of experts
Invasive EPS with PVS may be considered for stratification of SCD risk.	IIb	C	113, 114

ARVC = arrhythmogenic right ventricular cardiomyopathy; EPS = electrophysiological study; ESC = European Society of Cardiology; ICD = implantable cardioverter defibrillator; NSVT = non-sustained ventricular tachycardia; PVC = premature ventricular complexes; VA = ventricular arrhythmia; VT = ventricular tachycardia.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.
[d]ESC guidelines define competitive sport as amateur or professional engagement in exercise training on a regular basis and participation in official competitions (see relevant ESC guidelines for more detail).

7.3.3 Ventricular arrhythmias in arrhythmogenic right ventricular cardiomyopathy

Up to two-thirds of patients have VAs on resting or ambulatory ECG monitoring and exercise testing.[396–399] These VAs are usually of RV origin (i.e. show a left bundle branch morphology), but the QRS axis during VT usually differs from the QRS axis in RVOT,[400] and many patients have multiple QRS morphologies. In a recent prospective registry of patients predominantly treated with an ICD, most appropriate therapies were for sustained monomorphic VT.[401]

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7.3.3.1 Treatment of ventricular arrhythmia

Few systematic data are available on the efficacy of anti-arrhythmic drugs in ARVC and the impact of medical therapy on mortality is unknown. Based largely on serial PVS testing, beta-blockers—in particular sotalol—are conventionally recommended as the first approach in patients with frequent ventricular ectopy or NSVA.[391] However, in a recent observational registry neither beta-blockers nor sotalol seemed to reduce VA;[390] amiodarone was superior in preventing VA in a small cohort of patients.[390]

Invasive electrophysiological testing with voltage mapping can be used to identify regions of fibro-fatty replacement and to guide catheter ablation of VA.[202,207,392,402] Acute suppression of VT is more often successful in patients presenting with a single or only a few selected dominant VT morphologies and epicardial ablation may increase success rates. As neither anti-arrhythmic drugs nor catheter ablation provides sufficient protection against SCD, ablation should be used to reduce the frequency of arrhythmia episodes rather than to improve prognosis.

7.3.3.2 Exercise restriction

Endurance training at a competitive level probably exacerbates the phenotype of ARVC.[81,403] Therefore, while there are no controlled trials demonstrating a beneficial effect, avoidance of high-level endurance training is recommended.

7.3.3.3 Implantable cardioverter defibrillators

Most studies on risk stratification and ICD therapy are retrospective and of selected and relatively small high-risk cohorts recruited from single centres. Many also provide little information on the indication for an ICD. In a recent systematic review (24 studies) and meta-analysis (18 studies) of 610 patients followed for a mean period of 3.8 years,[387] the annualized appropriate ICD intervention rate was 9.5%. Difficult ICD lead placement was reported in 18.4% of cases, with lead malfunction, infection and displacement occurring in 9.8, 1.4 and 3.3% of cases, respectively. The annual rate of inappropriate ICD intervention was 3.7%.

Patients with a history of aborted SCD, poorly tolerated VT and syncope have the greatest risk of SCD (up to 10% per annum) and ICD therapy is recommended in this group.[387] Other risk factors for SCD or appropriate ICD discharge reported in different cohorts include documented sustained VT, unexplained syncope, frequent NSVT, a family history of premature sudden death, extensive RV disease, marked QRS prolongation, late gadolinium enhancement on CMR (including LV involvement), LV dysfunction and VT induction during EPS.[113,114,387,389,395,404–406] Compound or digenic heterozygosity occurs in >10% of carriers of the ARVC-causing desmosomal gene mutation and may be a risk factor for major arrhythmic events and SCD.[407] As the studies examining outcomes in ARVC are so diverse, recommendations on ICD therapy for primary prophylaxis are challenging. Based on available data, the consensus is that patients with unexplained syncope should be considered for an ICD. For patients without syncope, an ICD may be considered following detailed clinical assessment that takes into account family history, severity of RV and LV function, lifelong risk of complications and impact of an ICD on lifestyle, socioeconomic status and psychological health.

7.4 Infiltrative cardiomyopathies

7.4.1 Cardiac amyloidosis

Cardiac amyloidosis

Recommendation	Class[a]	Level[b]	Ref.[c]
An ICD should be considered in patients with light-chain amyloidosis or hereditary transthyretin associated cardiac amyloidosis and VA causing haemodynamic instability who are expected to survive >1 year with good functional status.	IIa	C	408–412

ICD = implantable cardioverter defibrillator; VA = ventricular arrhythmia.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

The two main types of cardiac amyloidosis are light-chain amyloidosis, caused by deposition of monoclonal light chains, and hereditary transthyretin-associated amyloidosis, in which normal (wild-type) or mutant transthyretin is deposited in the myocardium.[413,414] Until quite recently, cardiac amyloidosis was associated with a very poor prognosis, with a median survival of <1 year after the onset of HF symptoms, but advances in therapy for light-chain amyloidosis have improved survival.[415]

Up to half of all patients with cardiac amyloidosis die suddenly.[413,416] Death is often attributed to electromechanical dissociation, but case reports describe successful termination of sustained VA with ICDs.[408] VAs during ambulatory monitoring are reported in >25% of patients with cardiac amyloidosis,[409–411] but their presence does not seem to predict SCD. Elevated levels of cardiac troponins and N-terminal pro-B-type natriuretic peptide are sensitive markers of cardiac involvement and predict adverse outcome in patients with light-chain amyloidosis, but there are no data to suggest that these biomarkers can be used to identify patients who might benefit from an ICD. Based on such limited data, ICDs should be considered in patients with light-chain amyloidosis or hereditary transthyretin-associated amyloidosis that experience sustained VA and have a life expectancy >1 year. There are insufficient data to provide recommendations on primary prophylaxis.

7.5 Restrictive cardiomyopathy

Restrictive cardiomyopathy

Recommendations	Class[a]	Level[b]	Ref.[c]
An ICD is recommended in patients with restrictive cardiomyopathy and sustained VA causing haemodynamic instability who are expected to survive >1 year with good functional status to reduce the risk of SCD.	I	C	412, 417–420

ICD = implantable cardioverter defibrillator; SCD = sudden cardiac death; VA = ventricular arrhythmia.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

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The term restrictive cardiomyopathy refers to hearts in which there is restrictive physiology, normal or reduced diastolic volumes of one or both ventricles, normal or reduced systolic volumes and normal ventricular wall thickness. Restrictive cardiomyopathy is the least common of all the cardiomyopathies and is caused by a number of genetic and acquired disorders.[412] In western societies, the most common cause in adults is amyloidosis followed by mutations in sarcomeric protein genes and metabolic disorders.[421]

Patients with restrictive cardiomyopathy typically present with signs and symptoms of biventricular HF and are diagnosed by characteristic features on non-invasive cardiac imaging and cardiac catheterization. Restrictive cardiomyopathy is associated with poor long-term prognosis. In children, freedom from death at 1, 2 and 5 years is 82, 80 and 68%, respectively;[417–420] the corresponding values for transplant-free survival are 48, 34 and 22%, respectively. There are fewer data in adults, but reported survival rates are similar at 5 years. Risk factors for all-cause death include NYHA functional class, left atrial size and male sex.[417–420] In children, the risk of sudden death may be higher, particularly in those with ECG evidence of myocardial ischaemia.

The treatment of restrictive cardiomyopathy is mostly palliative. HF symptoms are treated with diuretics and heart rate control to optimize LV filling. Anticoagulation should be used in all patients with AF. There are no prospective data on prophylactic implantation of ICDs in restrictive cardiomyopathy, so for patients with symptomatic sustained VA, indications for ICD should be similar to those for other heart muscle disease, taking into account the short-term prognosis related to HF. Primary prophylaxis should be determined by the underlying aetiology and the presence of established risk factors for SCD.

7.6 Other cardiomyopathies

7.6.1 Left-ventricular non-compaction

Non-compaction refers to the presence of prominent ventricular trabeculations and deep intertrabecular recesses in the left and/or right ventricle, which are often associated with a thin compacted epicardial myocardial layer.[422] In some patients, non-compaction is associated with ventricular dilatation and systolic dysfunction. LV non-compaction occurs in association with congenital cardiac disorders and in an isolated form. Familial disease occurs in 18–50% of adults with isolated LV non-compaction, mostly with an autosomal dominant pattern of inheritance. Numerous mutations in genes encoding sarcomere proteins, calcium-handling proteins and other cardiomyopathy-related genes such as *LMNA*, LDB3 and Taffazin are reported.[423]

Many patients with LV non-compaction are completely asymptomatic, but some present with HF, thromboembolism, arrhythmias or SCD. Increased age, LV end diastolic diameter at presentation, symptomatic HF, permanent or persistent AF, bundle branch block and associated neuromuscular disease are reported predictors for increased mortality, but there are few data to suggest that LV non-compaction by itself is an indication for an ICD.[422–425] The need for an ICD should be guided by the severity of LV systolic dysfunction and the presence of sustained VA using the same criteria for DCM (see section 7.1).

7.6.2 Chagas cardiomyopathy

Chagas cardiomyopathy

Recommendations	Class[a]	Level[b]	Ref.[c]
An ICD should be considered in patients with Chagas cardiomyopathy and an LVEF <40% when they are expected to survive >1 year with good functional status.	IIa	C	426–430

ICD = implantable cardioverter defibrillator; LVEF = left ventricular ejection fraction.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

Chagas disease is a myocardial disease caused by the parasite *Trypanosoma cruzi*. Worldwide, 8–10 million people are currently estimated to be infected and 20–40% will develop chronic myocardial disease, sometimes many decades after the initial infection. Conduction system abnormalities, including RBBB and left anterior fascicular block, are often the earliest manifestations, followed by segmental LV wall-motion abnormalities, complex VA, sinus node dysfunction and more advanced conduction abnormalities. In the later stages of the disease there is progressive LV dilatation and systolic dysfunction.[426–430]

Reported annual mortality rates for patients with Chagas disease vary from 0.2 to 19.2%, reflecting the characteristics of the different study populations. The most consistent independent predictors of death are LV dysfunction, NYHA functional class and NSVT. The risk associated with the combination of NSVT and LV dysfunction may be as high as 15-fold.

Primarily thanks to the study by Gali *et al.*,[430] examining the effect of ICDs in patients with Chagas disease, evidence has been obtained that the greatest benefit is in patients with an LVEF <40%, although most patients with an ICD received appropriate therapies regardless of their LV systolic function.

8. Inherited primary arrhythmia syndromes

8.1 Long QT Syndrome

8.1.1 Definitions and epidemiology

Diagnosis of Long QT Syndrome (in the absence of secondary causes for QT prolongation)

Recommendations	Class[a]	Level[b]	Ref.[c]
LQTS is diagnosed with either – QTc ≥480 ms in repeated 12-lead ECGs or – LQTS risk score >3.[431]	I	C	This panel of experts

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LQTS is diagnosed in the presence of a confirmed pathogenic LQTS mutation, irrespective of the QT duration.	I	C	This panel of experts
ECG diagnosis of LQTS should be considered in the presence of a QTc ≥460 ms in repeated 12-lead ECGs in patients with an unexplained syncopal episode in the absence of secondary causes for QT prolongation.	IIa	C	This panel of experts

ECG = electrocardiogram; LQTS = long QT syndrome; QTc = corrected QT.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

This panel has modified the diagnostic criteria for LQTS proposed in the EHRA/Heart Rhythm Society consensus document.[14] Specifically, it was felt that a QTc >500 ms—suggested as the threshold for diagnosis of LQTS in asymptomatic patients without a family history of the disease—is very conservative and is identical to the QT duration associated with a high risk for arrhythmic events in SCD.[1,67] Accordingly, we have used a corrected QT (QTc) ≥480 ms or a score >3[431] for clinical diagnosis. In the presence of unexplained syncope, however, a QTc ≥460 ms is sufficient to make a diagnosis.

LQTS is characterized by a prolonged QT interval and VAs mainly triggered by adrenergic activation. The mean age at presentation is 14 years. The annual rate of SCD in patients with untreated LQTS is estimated to be between 0.33[67] and 0.9%,[432] whereas that for syncope is estimated to be ∼5%.[432]

Mutations in 13 genes have been associated with LQTS, most encoding for subunits of potassium, sodium or calcium voltage-dependent ion channels. Genetic screening identifies a disease-causing mutation in 75% of LQTS cases and three main genes (*KCNQ1*, *KCNH2* and *SCN5A*) account for 90% of positively genotyped cases.[52]

The subtypes of LQTS may be grouped into the following three categories:

- Autosomal dominant LQTS (Romano–Ward syndrome; prevalence 1 in 2500), which includes LQT1–6 and LQT9–13 and is characterized by an isolated prolongation of the QT interval;
- Autosomal dominant LQTS with extracardiac manifestation, comprising
  - LQT7 (Andersen–Tawil syndrome), which shows a prolonged QT interval with prominent U wave, polymorphic or bidirectional VT, facial dysmorphisms and hyper-/hypokalaemic periodic paralysis[433] and
  - LQT8 (Timothy syndrome), characterized by prolonged QT, syndactyly, cardiac malformations, autism spectrum disorder and dysmorphisms;
- Autosomal recessive LQTS (Jervell and Lange–Nielsen syndrome), which combines an extremely prolonged QT interval with congenital deafness.

8.1.2 Approach to risk stratification and management

Risk stratification and management in Long QT Syndrome

Recommendations	Class[a]	Level[b]	Ref.[c]
The following lifestyle changes are recommended in all patients with a diagnosis of LQTS: (a) Avoidance of QT-prolonging drugs (http://www.crediblemeds.org). (b) Correction of electrolyte abnormalities (hypokalaemia, hypomagnesaemia, hypocalcaemia) that may occur during diarrhoea, vomiting or metabolic conditions. (c) Avoidance of genotype-specific triggers for arrhythmias (strenuous swimming, especially in LQTS1, and exposure to loud noises in LQTS2 patients).	I	B	434
Beta-blockers are recommended in patients with a clinical diagnosis of LQTS.	I	B	435
ICD implantation with the use of beta-blockers is recommended in LQTS patients with previous cardiac arrest.	I	B	436–438
Beta-blockers should be considered in carriers of a causative LQTS mutation and normal QT interval.	IIa	B	67
ICD implantation in addition to beta-blockers should be considered in LQTS patients who experienced syncope and/or VT while receiving an adequate dose of beta-blockers.	IIa	B	439
Left cardiac sympathetic denervation should be considered in patients with symptomatic LQTS when (a) Beta-blockers are either not effective, not tolerated or contraindicated; (b) ICD therapy is contraindicated or refused; (c) Patients on beta-blockers with an ICD experience multiple shocks.	IIa	C	440
Sodium channel blockers (mexiletine, flecainide or ranolazine) may be considered as add-on therapy to shorten the QT interval in LQTS3 patients with a QTc >500 ms.	IIb	C	441–443
Implant of an ICD may be considered in addition to beta-blocker therapy in asymptomatic carriers of a pathogenic mutation in *KCNH2* or *SCN5A* when QTc is >500 ms.	IIb	C	67

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Invasive EPS with PVS is not recommended for SCD risk stratification.	III	C	117

EPS = electrophysiological study; ICD = implantable cardioverter defibrillator; LQTS = long QT syndrome; LQTS1 = long QT syndrome type 1; LQTS2 = long QT syndrome type 2; LQTS3 = long QT syndrome type 3; PVS = programmed ventricular stimulation; QTc = corrected QT; VT = ventricular tachycardia; SCD = sudden cardiac death.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

Clinical, electrocardiographic and genetic parameters should be considered for the stratification of individual risk.[67] Survivors of a cardiac arrest have a high risk of recurrence, even when receiving beta-blockers (14% within 5 years on therapy): this evidence supports the use of ICDs in survivors of cardiac arrest.[436] The occurrence of syncopal events is associated with an increased risk of cardiac arrest.[439,444] Women with LQTS have an increased risk during the 9-month postpartum period (especially women with the LQT2 genotype).[445] In LQT1 and LQT2 patients, the location and type of mutation may be associated with different risks of cardiac events. However, these findings require further study before application in clinical practice.[14] Silent carriers of pathogenic mutations present a modest risk of cardiac events estimated at ~10% between birth and age 40 years; the use of beta-blockers should be considered in this group of patients.[446]

Prophylactic ICD therapy may be considered, on an individual basis, in high-risk patients such as women with LQT2 and QTc >500 ms, patients with QTc >500 ms and signs of electrical instability and patients with high-risk genetic profiles (carriers of two mutations, including Jervell and Lange–Nielsen syndrome or Timothy syndrome).

There are no data supporting any prognostic value for invasive EPS with PVS in patients with LQTS.[117]

8.2 Short QT syndrome

8.2.1 Definitions and epidemiology

Diagnosis of Short QT Syndrome

Recommendations	Class[a]	Level[b]	Ref.[c]
SQTS is diagnosed in the presence of a QTc ≤340 ms.	I	C	This panel of experts
SQTS should be considered in the presence of a QTc ≤360 ms and one or more of the following: (a) A confirmed pathogenic mutation (b) A family history of SQTS (c) A family history of sudden death at age <40 years (d) Survival from a VT/VF episode in the absence of heart disease.	IIa	C	This panel of experts

QTc = corrected QT; SQTS = short QT syndrome; VF = ventricular fibrillation; VT = ventricular tachycardia.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

SQTS is characterized by a reduced duration of cardiac repolarization, which constitutes the substrate for the development of life-threatening arrhythmias. Five genes have been linked to SQTS (*KCNH2, KCNQ1, KCNJ2, CACNA1C* and *CACNB2b*), but the yield of genetic screening remains low (~20% overall).[119]

The disease appears to be highly lethal in all age groups, including children in their first months of life, and the probability of a first cardiac arrest by the age of 40 years is >40%.[119,447] Given the small size of the populations reported so far, the high lethality may partially reflect a reporting bias related to the underdetection of SQTS in asymptomatic patients.

8.2.2 Approach to risk stratification and management

Risk stratification and management in Short QT Syndrome

Short QT Syndrome			
Recommendations	**Class[a]**	**Level[b]**	**Ref.[c]**
ICD implantation is recommended in patients with a diagnosis of SQTS who (a) Are survivors of an aborted cardiac arrest, and/or (b) Have documented spontaneous sustained VT.	I	C	119, 447
Quinidine or sotalol may be considered in patients with a diagnosis of SQTS who qualify for an ICD but present a contra-indication to the ICD or refuse it.	IIb	C	118, 448
Quinidine or sotalol may be considered in asymptomatic patients with a diagnosis of SQTS and a family history of SCD.	IIb	C	118, 448
Invasive EPS with PVS is not recommended for SCD risk stratification.	III	C	118, 119

EPS = electrophysiological study; ICD = implantable cardioverter defibrillator; PVS = programmed ventricular stimulation; SCD = sudden cardiac death; SQTS = short QT syndrome.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

SQTS patients who survive a previous cardiac arrest should receive an ICD for secondary prevention, because the rate of recurrence of cardiac arrest has been estimated at 10% per year.[119]

The optimal strategy for primary prevention of cardiac arrest in SQTS is unclear, given the lack of independent risk factors for cardiac arrest, including syncope.[119] No data are available to quantify the risk of arrhythmic events during competitive physical activity in SQTS patients.

An ICD might be considered on a case-by-case basis in patients with SQTS with a strong family history of SCD and evidence for abbreviated QTc in at least some of the patients, but there are not enough data to make generalized recommendations.[14]

Reports on small cohorts of patients suggest that quinidine therapy can prolong the QTc interval and possibly reduce arrhythmic events.

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Patients on quinidine should be carefully monitored for QT prolongation and possible pro-arrhythmic events.[118,448] The use of quinidine may be considered in survivors of cardiac arrest who qualify for an ICD but present a contraindication to the ICD or refuse it.[118,448]

So far there are no data supporting the role of PVS for predicting arrhythmic events.

8.3 Brugada syndrome

8.3.1 Definitions and epidemiology

Diagnosis of Brugada Syndrome

Recommendations	Class[a]	Level[b]	Ref.[c]
Brugada syndrome is diagnosed in patients with ST-segment elevation with type 1 morphology ≥2 mm in one or more leads among the right precordial leads V1 and/or V2 positioned in the second, third, or fourth intercostal space, occurring either spontaneously or after provocative drug test with intravenous administration of sodium channel blockers (such as ajmaline, flecainide, procainamide or pilsicainide).	I	C	This panel of experts

[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

The prevalence of Brugada syndrome seems to be higher in Southeast Asia than in western countries; the prevalence ranges from 1 in 1000 to 1 in 10 000.[449]

Brugada syndrome is inherited as a dominant trait and shows age- and sex-related penetrance: clinical manifestations of the disease are more frequent in adults and they are eightfold more frequent in men than in women.[450] VF occurs at a mean age of 41 ± 15 years but it may manifest at any age, usually during rest or sleep.[451] Fever, excessive alcohol intake and large meals are triggers that unmask a type I ECG pattern and predispose to VF.

In a recent meta-analysis, the incidence of arrhythmic events (sustained VT or VF or appropriate ICD therapy or sudden death) in patients with Brugada syndrome was 13.5% per year in patients with a history of sudden cardiac arrest, 3.2% per year in patients with syncope and 1% per year in asymptomatic patients.[452]

At least 12 genes have been associated with Brugada syndrome, but only two (*SCN5A* and *CACN1Ac*) individually account for >5% of positively genotyped patients.[52] Results of genetic screening do not currently influence prognosis or treatment.

8.3.2 Approach to risk stratification and management

Risk stratification and management in Brugada Syndrome

Recommendations	Class[a]	Level[b]	Ref.[c]
The following lifestyle changes are recommended in all patients with a diagnosis of Brugada syndrome: (a) Avoidance of drugs that may induce ST-segment elevation in right precordial leads (http://www.brugadadrugs.org) (b) Avoidance of excessive alcohol intake and large meals (c) Prompt treatment of any fever with antipyretic drugs.	I	C	This panel of experts
ICD implantation is recommended in patients with a diagnosis of Brugada syndrome who (a) Are survivors of an aborted cardiac arrest and/or (b) Have documented spontaneous sustained VT.	I	C	451
ICD implantation should be considered in patients with a spontaneous diagnostic type I ECG pattern and history of syncope.	IIa	C	451
Quinidine or isoproterenol should be considered in patients with Brugada syndrome to treat electrical storms.	IIa	C	453
Quinidine should be considered in patients who qualify for an ICD but present a contraindication or refuse it and in patients who require treatment for supraventricular arrhythmias.	IIa	C	454
ICD implantation may be considered in patients with a diagnosis of Brugada syndrome who develop VF during PVS with two or three extrastimuli at two sites.	IIb	C	120
Catheter ablation may be considered in patients with a history of electrical storms or repeated appropriate ICD shocks.	IIb	C	201, 455

ECG = electrocardiogram; ICD = implantable cardioverter defibrillator; PVS = programmed ventricular stimulation; VF = ventricular fibrillation; VT = ventricular tachycardia.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

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The only treatment able to reduce the risk of SCD in Brugada syndrome is the ICD, therefore the device is recommended in patients with documented VT or VF and in patients presenting with a spontaneous type 1 ECG and a history of syncope.[14,451] The prognostic value of PVS has been debated and most clinical studies have not confirmed either a positive or a negative predictive value for the occurrence of cardiac events at follow-up.[14,456] Quinidine has been proposed as preventive therapy in patients with Brugada syndrome, based on data showing that it reduces VF inducibility during PVS; however, there are no data confirming its ability to reduce the risk of SCD. Recently it has been suggested that epicardial catheter ablation over the anterior RVOT may prevent electrical storms in patients with recurring episodes, but the data require confirmation before entering general clinical practice.[455]

8.4 Catecholaminergic polymorphic ventricular tachycardia

8.4.1 Definitions and epidemiology

Diagnosis of catecholaminergic polymorphic ventricular tachycardia

Recommendations	Class[a]	Level[b]	Ref.[c]
CPVT is diagnosed in the presence of a structurally normal heart, normal ECG and exercise- or emotion-induced bidirectional or polymorphic VT.	I	C	14,52, 457
CPVT is diagnosed in patients who are carriers of a pathogenic mutation(s) in the genes *RyR2* or *CASQ2*.	I	C	14,52

CPVT = catecholaminergic polymorphic VT; ECG = electrocardiogram; VT = ventricular tachycardia.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

CPVT is a rare inheritable arrhythmogenic disorder characterized by adrenergic-induced bidirectional and polymorphic VT. The disease has an estimated prevalence of 1 in 10 000.[14]

Two genetic types of CPVT have been identified: a dominant variant due to mutations in the gene encoding for the cardiac ryanodine receptor gene (*RyR2*) and a rare recessive variant caused by mutation in the cardiac calsequestrin gene (*CASQ2*).[52] Mutations in other genes such as *KCNJ2*, *Ank2*, *TRDN* and *CALM1* have been identified in patients with clinical features similar to CPVT. However, at the present time it is not clear whether they are phenocopies of CPVT.[14]

The clinical manifestations of CPVT usually occur in the first decade of life and are prompted by physical activity or emotional stress.[458] Diagnosis is challenging because patients with CPVT have a normal ECG and echocardiogram, therefore an exercise stress test that elicits atrial arrhythmias and VA (bidirectional or polymorphic VT) is recommended to establish the diagnosis.[14] The use of catecholamine infusion has also been suggested, but its sensitivity is not clearly defined,[14,459] therefore we have not established a recommendation on this specific issue.

8.4.2 Approach to risk stratification and management

Risk stratification and management in Catecholaminergic Polymorphic Ventricular Tachycardia

Recommendations	Class[a]	Level[b]	Ref.[c]
The following lifestyle changes are recommended in all patients with a diagnosis of CPVT: avoidance of competitive sports, strenuous exercise and stressful environments.	I	C	This panel of experts
Beta-blockers are recommended in all patients with a clinical diagnosis of CPVT, based on the presence of documented spontaneous or stress-induced VAs.	I	C	458, 460
ICD implantation in addition to beta-blockers with or without flecainide is recommended in patients with a diagnosis of CPVT who experience cardiac arrest, recurrent syncope or polymorphic/bidirectional VT despite optimal therapy.	I	C	458, 461
Therapy with beta-blockers should be considered for genetically positive family members, even after a negative exercise test.	IIa	C	461, 462
Flecainide should be considered in addition to beta-blockers in patients with a diagnosis of CPVT who experience recurrent syncope or polymorphic/bidirectional VT while on beta-blockers, when there are risks/ contraindications for an ICD or an ICD is not available or rejected by the patient.	IIa	C	463
Flecainide should be considered in addition to beta-blockers in patients with a diagnosis of CPVT and carriers of an ICD to reduce appropriate ICD shocks.	IIa	C	463
Left cardiac sympathetic denervation may be considered in patients with a diagnosis of CPVT who experience recurrent syncope or polymorphic/ bidirectional VT/several appropriate ICD shocks while on beta-blockers or beta-blockers plus flecainide and in patients who are intolerant or have contraindication to beta-blockers.	IIb	C	464, 465
Invasive EPS with PVS is not recommended for stratification of SCD risk.	III	C	14

CPVT = catecholaminergic polymorphic ventricular tachycardia; EPS = electrophysiological study; ICD = implantable cardioverter defibrillator; PVS = programmed ventricular stimulation; SCD = sudden cardiac death; VA = ventricular arrhythmia; VT = ventricular tachycardia.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

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Diagnosis in childhood, the lack of beta-blocker therapy and the persistence of complex arrhythmias during the exercise stress test on a full dose of beta-blockers are independent predictors for arrhythmic events.[461]

Most referral centres treat patients with nadolol, even though comparative data on different types of beta-blockers are not available.

Exercise restriction and beta-blockers without intrinsic sympathomimetic activity are the first-line therapy for patients with CPVT.[14]

Preliminary data suggest that flecainide significantly reduces the VA burden in a limited number of patients with CPVT and should be considered as the first addition to beta-blockers when control of arrhythmias is incomplete.[462,463] Left cardiac sympathetic denervation seems to have some degree of efficacy in the management of patients with CPVT intolerant to beta-blockers, but more data and longer follow-up are needed to quantify its efficacy.[464,465] Survivors of cardiac arrest should receive beta-blockers and an ICD; flecainide should also be considered if arrhythmic control in the exercise stress test is incomplete.[14] An ICD should also be considered in patients with CPVT who do not respond to beta-blockers and flecainide.[14] The ICD should be programmed with long delays before shock delivery, because painful shocks can increase the sympathetic tone and trigger further arrhythmias, leading to a malignant cycle of ICD shocks and even death.[466]

PVS has no diagnostic or prognostic value in CPVT, as neither bidirectional nor polymorphic VT is inducible.[14]

8.5 Early repolarization syndrome

8.5.1 Definitions and epidemiology

The presence of an early repolarization pattern in the inferior and/or lateral leads has been associated with idiopathic VF in case–control studies.[467,468] Owing to the high incidence of the early repolarization pattern in the general population, it seems reasonable to diagnose an 'early repolarization syndrome' only in patients with a pattern who are resuscitated from a documented episode of idiopathic VF and/or polymorphic VT.

The genetics of early repolarization are probable polygenic in many instances. No clear evidence of familial transmission of the early repolarization syndrome exists.

Given the uncertainties in the interpretation of the early repolarization pattern as a predictor of SCD, this panel of experts has decided that there is insufficient evidence to make recommendations for management of this condition at this time.

9. Paediatric arrhythmias and congenital heart disease

9.1 Management of ventricular arrhythmias in children with a structurally normal heart

Management of ventricular arrhythmias in children with a structurally normal heart

Recommendations	Class[a]	Level[b]	Ref.[c]
It is recommended that asymptomatic children with frequent isolated PVCs or an accelerated ventricular rhythm and normal ventricular function be followed-up without treatment.	I	B	469, 470
Medical therapy or catheter ablation is recommended in children with frequent PVCs or VT thought to be causative of ventricular dysfunction.	I	C	This panel of experts
Catheter ablation should be considered when medical therapy is either not effective or undesired in symptomatic children with idiopathic RVOT VT/PVCs or verapamil-sensitive left fascicular VT.	IIa	B	471–474
Catheter ablation by experienced operators should be considered after failure of medical therapy or as an alternative to chronic medical therapy in symptomatic children with idiopathic LVOT, aortic cusps or epicardial VT/PVCs.	IIa	B	473, 474
Sodium channel blockers (class IC agents) should be considered as an alternative to beta-blockers or verapamil in children with outflow tract VT.	IIa	C	471
Catheter ablation is not recommended in children <5 years of age except when previous medical therapy fails or when VT is not haemodynamically tolerated.	III	B	475
The use of verapamil is not recommended in children <1 year of age.	III	C	476

LVOT = left ventricular outflow tract; PVC = premature ventricular complex; RVOT = right ventricular outflow tract; VA = ventricular arrhythmia; VT = ventricular tachycardia.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

In children, VAs may occur in congenital heart diseases (CHDs), inheritable channelopathies or cardiomyopathies, myocarditis and cardiac tumours (neonatal rhabdomyomas), as well as in structurally normal hearts. In otherwise healthy children, isolated monomorphic PVCs are very common, particularly in infants (20%) and teenagers (20–35%), originating primarily from the RVOT. When PVCs occur frequently (5–10% of all beats) or are more complex, cardiac evaluation including CMR and family history taking is recommended to exclude inheritable channelopathies or cardiomyopathies. Follow-up is recommended to identify the development of LV dysfunction, (non-)sustained VT or cardiomyopathies, which seldom occur. Medical treatment or catheter ablation is rarely indicated since most children remain asymptomatic and PVCs often resolve in time.[469,470,477–480] Accelerated idioventricular rhythm can be found in otherwise healthy newborns and infants, usually as a coincidental finding. It is a benign arrhythmia and, similar to PVCs in infants, generally disappears without treatment in the first year of life.[481] The reported incidence of sustained VT in the general paediatric population is 1 per 100 000 children in 10 years. The prevalence of non-sustained and sustained VT is also low, at 2–8 per 100 000 schoolchildren.[482,483]

Most idiopathic VTs first present in older children and teenagers, with similar sites of origin as in adults (RVOT, LVOT or aortic cusps). Verapamil-sensitive left fascicular VT is less common.[471–474]

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Incessant VT, commonly originating from the LV, is associated with intracardiac hamartomas in infancy. These tachycardias often lead to HF and have significant mortality despite aggressive drug therapy, catheter ablation and even surgical therapy.[484] Polymorphic VT or multiform PVC occur infrequently in children with normal hearts and are usually associated with inheritable channelopathies or cardiomyopathies, structural or inflammatory heart disease or metabolic or toxicological abnormalities.

In older children, recommendations regarding treatment of idiopathic VTs are similar to those for adults. In young children, studies on the efficacy and safety of drug treatment of idiopathic VTs are limited mainly to beta-blockers and verapamil, with less data available on sodium channel blockers (class IC) and class III drugs.[471,472] In infants <1 year of age, (i.v.) verapamil should be avoided because it may lead to acute haemodynamic deterioration.[476]

In young children, complication rates of catheter ablation appear to be higher and there is concern regarding the growth of radiofrequency and cryo-energy lesions in the ventricular myocardium.[475,485–487] Idiopathic VTs and complex PVC in children tend to resolve spontaneously within months to years.[471] Therefore, in this age group, catheter ablation, including 'simple' RVOT–VT ablation, is only indicated as second-line therapy and should be performed in experienced centres.

9.2 Sudden cardiac death and ventricular arrhythmias in patients with congenital heart disease

Prevention of sudden cardiac death and management of ventricular arrhythmias in patients with congenital heart disease

Recommendations	Class[a]	Level[b]	Ref.[c]
After evaluation to define the cause of the event and exclude any reversible causes, ICD implantation is recommended for patients with CHD who are survivors of an aborted cardiac arrest.	I	B	488–491
ICD implantation is recommended for patients with CHD with symptomatic sustained VT who have undergone haemodynamic and electrophysiological evaluation.	I	B	488–492
Catheter ablation is recommended as additional therapy or an alternative to ICD in patients with CHD who have recurrent monomorphic VT or appropriate ICD therapies that are not manageable by device reprogramming or drug therapy.	I	C	492
ICD therapy is recommended in adults with CHD and a systemic LVEF <35%, biventricular physiology, symptomatic HF despite optimal medical treatment and NYHA functional class II or III.	I	C	493, 494
ICD implantation should be considered in patients with CHD with syncope of unknown origin in the presence of either advanced ventricular dysfunction or inducible sustained VT or VF on PVS.	IIa	B	488, 490, 491
ICD implantation should be considered in selected patients with tetralogy of Fallot and multiple risk factors for SCD, including LV dysfunction, non-sustained VT, QRS duration >180 ms or inducible sustained VT on PVS.	IIa	B	488, 494–496
Catheter ablation should be considered as an alternative to drug therapy for symptomatic sustained monomorphic VT in patients with CHD and an ICD.	IIa	B	492
ICD therapy may be considered in patients with advanced single or systemic RV dysfunction in the presence of other risk factors such as non-sustained VT, NYHA functional class II or III or severe systemic AV valve regurgitation.	IIb	B	489, 497, 498
PVS may be considered for risk stratification of SCD in patients with tetralogy of Fallot who have one or more risk factors among LV dysfunction, non-sustained VT and QRS duration >180 ms.	IIb	B	496
PVS may be considered in patients with CHD and non-sustained VT to determine the risk of sustained VT.	IIb	C	This panel of experts
Surgical ablation guided by electrophysiological mapping may be considered in patients with CHD undergoing cardiac surgery, with clinical sustained VT and with inducible sustained monomorphic VT with an identified critical isthmus.	IIb	C	This panel of experts
Catheter ablation or prophylactic anti-arrhythmic therapy is not recommended for asymptomatic infrequent PVC in patients with CHD and stable ventricular function.	III	C	This panel of experts
PVS is not recommended to stratify the risk in patients with CHD in the absence of other risk factors or symptoms.	III	B	496

AV = atrio-ventricular; CHD = congenital heart disease; HF = heart failure; ICD = implantable cardioverter defibrillator; LV = left ventricular; LVEF = left ventricular ejection fraction; PVS = programmed ventricular stimulation; PVC = premature ventricular complex; NYHA = New York Heart Association; RV = right ventricular; SCD = sudden cardiac death; VA = ventricular arrhythmia; VF = ventricular fibrillation; VT = ventricular tachycardia.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

CHD is the most common birth defect, with an incidence of 700–800 per 100 000 live births.[499] Patients with CHD represent a heterogeneous group whose life expectancy has improved

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dramatically following advances in diagnosis and surgical techniques. The majority of patients with CHD will live to adulthood.[500] Despite these successes, the repair of CHD in childhood is often followed by the development of HF and arrhythmias, which may cause late cardiac mortality in young adulthood.

The incidence of SCD in the total CHD population is low (0.09% per year) but is higher than in age-matched controls.[501] The risk of SCD is time dependent and progressively increases after the second decade of life. Thus far, no RCTs have been performed to delineate risk factors for SCD or the benefit of primary prevention therapies. Retrospective studies have demonstrated that SCD accounts for 14–26% of all deaths after initial repair.[497,501–503] In a large study of adults with a range of CHDs, SCD related to arrhythmias occurred in 14%. SCD occurred mostly at rest and was not limited to patients with severe defects. In this study, risk factors for SCD were similar to those in ischaemic cardiomyopathy, including supraventricular tachycardia, systemic or pulmonary ventricular dysfunction and prolonged QRS duration.[497]

The congenital heart defects with the highest risk of SCD are tetralogy of Fallot, (congenitally corrected) transposition of the great arteries, left heart obstructed lesions and univentricular hearts.[497,501–503] Most studies on risk assessment have been performed in patients with tetralogy of Fallot, showing a risk of SCD of 2–3% per decade, increasing late after operative correction.[495,501,504] Although many risk factors have been identified, the strongest risk factors for SCD are a QRS duration >180 ms, RV volume overload, LV dysfunction or clinical or inducible sustained VT.[494–496] PVS is reported to be useful for risk assessment.[496] Retrospective studies on ICD therapy in tetralogy of Fallot have reported high appropriate shock rates of 8–10% per year for primary and secondary prevention.[488]

In patients with transposition of the great arteries after the atrial switch operation (Mustard or Senning), the risk of SCD is ~5% per decade.[501,505] The presence of atrial tachyarrhythmia and systemic RV failure are important risk factors for SCD.[498] Underlying mechanisms for SCD are atrial tachyarrhythmia with rapid 1 : 1 AV conduction deteriorating to VF, as well as primary VA. Currently catheter ablation of atrial tachycardia is an effective therapy and relevant for lowering the risk of SCD in this group of patients. PVS does not seem useful for general risk stratification. ICDs for secondary prevention appear to be effective, whereas primary prevention ICD therapy for patients with ventricular dysfunction seems less useful, with a shock rate of 0.5% per year.[489] Nowadays, atrial switch is not used and consequently this population of patients is gradually declining in number.

Adequate repair of congenital aortic stenosis (including the bicuspid valves) substantially reduces the native risk of SCD, often obviating the need for specific anti-arrhythmic therapy.[501,506]

In patients with univentricular hearts after the Fontan operation, long-term morbidity is characterized by complex atrial tachycardia and the development of HF, progressively increasing with age. Arrhythmia-related SCD is not rare in Fontan patients, with a reported incidence of 9% during a mean follow-up of 12 years, but no risk factors have yet been identified.[507] Data on the efficacy of ICD therapy in Fontan patients remain scarce.

In general, ICD therapy in patients with CHD has shifted from secondary to primary prevention in the last two decades.[490,491] Retrospective cohort studies have shown that in addition to VA, an impaired ventricular function, either left or right, has become a consistent risk factor for SCD in patients with different types of CHD.[493–495,497,498] This emphasizes the importance of effectively treating ventricular dysfunction by surgical interventions of residual defects, optimizing medication and, if applicable, CRT. In general, patients with CHD with syncope or non-sustained VT should undergo haemodynamic and electrophysiological evaluation. PVS can be useful to identify patients at risk for SCD. Catheter ablation and surgical therapies should be considered as an alternative or in addition to an ICD in patients with recurrent sustained VT after surgical repair of CHD.[492]

9.3 Implantable cardioverter defibrillator therapy in paediatric patients

Implantable cardioverter defibrillator in paediatric patients

Recommendations	Class[a]	Level[b]	Ref.[c]
ICD implantation is recommended for paediatric patients who are survivors of cardiac arrest in the absence of reversible causes.	I	B	490, 508, 509
ICD implantation in combination with medical therapy is recommended for high-risk paediatric patients with inheritable channelopathies, cardiomyopathies or CHD.	I	B	490, 510, 511
Periodic defibrillation threshold testing of non-transvenous ICD systems should be considered during growth in young children.	IIa	C	512

CHD = congenital heart disease; ICD = implantable cardioverter defibrillator.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

SCD is a rare phenomenon in paediatric patients and the use of ICDs is therefore uncommon, with an annual implantation rate of <1 per million[508,513] for primary or secondary prevention.[490,509] Paediatric patients at risk of SCD form a heterogeneous group with a wide variety of underlying cardiac diseases, including inheritable channelopathies or cardiomyopathies, and the broad spectrum of CHD.[490,509] Current indications for ICD therapy in adults are being applied to paediatric patients. Most recommendations for cardiac diseases relevant for the paediatric population have a level of evidence of B or C.

In contrast to adult guidelines, ICDs are not used routinely in paediatric patients with DCM and advanced LV dysfunction because of the low incidence of SCD in this age group.[514,515] Interpretation and comparison of results of paediatric ICD series remain difficult

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because ICD therapy is often evaluated for a variety of conditions and often includes adults with CHD. Several paediatric ICD series have reported appropriate shocks for secondary prevention in 40–67% of patients. When ICD therapy was used for primary prevention, the appropriate shock rates ranged from 10 to 26% during a mean follow-up of 2–4 years.[490,508,510,511,516–519]

Lead fractures and insulation breaks, vascular problems, infections and late increases in the defibrillation threshold are more common in the paediatric population than in adults, likely due to their higher activity levels, smaller body size and growth.[520] Large studies have reported annual rates of lead fracture of 5.3 and 6.5%, with age <8 years and the Fidelis® lead as independent risk factors.[521,522] In most paediatric series, the reported incidence of inappropriate shocks is remarkably high, ranging from 17 to 30%.[490,508,511,516–519] Inappropriate shocks due to sinus tachycardia, supraventricular arrhythmias and T-wave oversensing are common and can be reduced by individual programming, in particular using higher detection rates. In older paediatric patients, as in adults, transvenous dual-chamber ICD systems are mostly used. In younger patients, single-chamber systems are commonly used to avoid venous obstruction, leaving a loop of the ICD lead in the right atrium to allow for growth. In infants and small children, alternative non-transvenous ICD systems seem safe and effective.[512] These systems are constructed by the insertion of the generator into the abdomen, a subcutaneous array in the left thorax and placement of the ventricular lead epicardially.[508,512] Other variants have also been reported.[508] Late increases in the defibrillation threshold occur more frequently with the use of these alternative systems, and periodic defibrillation threshold testing should be considered.[512]

CRT has become an important adjunct to the treatment of HF in paediatric patients, most commonly when there is an indication for antibradycardia pacing.[523,524] CRT-D therapy may be beneficial in selected patients, in particular in the postoperative CHD population, but data supporting its use are scarce.

10. Ventricular tachycardias and ventricular fibrillation in structurally normal hearts

10.1 Outflow tract ventricular tachycardia

Treatment of outflow tract ventricular tachycardia

Recommendations	Class[a]	Level[b]	Ref.[c]
Catheter ablation of RVOT VT/PVC is recommended in symptomatic patients and/or in patients with a failure of anti-arrhythmic drug therapy (e.g. beta-blocker) or in patients with a decline in LV function due to RVOT-PVC burden.	I	B	525–528
Treatment with sodium channel blockers (class IC agents) is recommended in LVOT/aortic cusp/epicardial VT/PVC symptomatic patients.	I	C	529–531
Catheter ablation of LVOT/aortic cusp/epicardial VT/PVC by experienced operators after failure of one or more sodium channel blockers (class IC agents) or in patients not wanting long-term anti-arrhythmic drug therapy should be considered in symptomatic patients.	IIa	B	195, 531–533

LV = left ventricular; LVOT = left ventricular outflow tract; PVC = premature ventricular complex; RVOT = right ventricular outflow tract; VT = ventricular tachycardia.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

The ventricular OTs are the most common origins of idiopathic VT/PVC.[525,534–536] Approximately 70% originate from the RVOT.[536] Other origins include the aortic sinuses of Valsalva,[537–540] LVOT,[539–541] great cardiac veins,[195,539,541] epicardial myocardium,[195,539,541,542] aorta-mitral continuity[529,543] and rarely the pulmonary artery.[544–546] Idiopathic focal OT–VT usually occurs in patients without structural heart disease, however, subtle wall abnormalities have been demonstrated on CMR imaging in some patients.[547,548] They have a focal mechanism secondary to automaticity, micro-re-entry or triggered activity.[549–552] Idiopathic RVOT–VT typically presents between the ages of 20 and 50 years and more frequently in women.[553] There are two typical forms: exercise/stress-induced VT and repetitive monomorphic VT occurring at rest. Repetitive NSVT occurs in 60–92% of cases while incessant VT occurs only occasionally.[549–552]

Paroxysmal sustained VT separated by long periods of infrequent PVCs is less common. Episodes increase in frequency and duration during exercise and/or emotional stress; exercise tests may provoke focal OT–VT during the exercise or recovery phases. Typical QRS morphology is an inferior axis with dominant LBBB morphology.[525,534–541] PVCs or the first beat of VT generally have relatively long coupling intervals to the preceding QRS complex.[553] VT is monomorphic, however, the QRS morphology may vary slightly. Multiple distinct VT morphologies are very rare and raise the suspicion for scar-related VT, such as in ARVC.[535] Although idiopathic OT–VT follows a benign course, malignant VT may occasionally occur.[551,553] ECG during sinus rhythm is usually normal, however, ~10% have complete or incomplete RBBB.[554] Exercise testing and cardiac imaging should be performed to exclude the presence of underlying structural heart disease, and cardiac catheterization may be warranted in some cases.

Treatment is only warranted if patients are symptomatic. It is worth noting that symptoms may be related to LV dysfunction, considering that idiopathic VT may be a cause of tachycardia-induced cardiomyopathy.[555] In such patients, treatment with sodium channel blockers (class IC agents) or catheter ablation should be considered. In patients with RVOT–VT/PVCs, primary catheter ablation should be recommended, whereas in patients with LVOT–VT/PVCs, catheter ablation should only be considered after failed anti-arrhythmic therapy.

The close anatomical proximity of the RVOT, LVOT and great cardiac veins limits precise localization of the VT origin based on QRS morphology except for classic RVOT tachycardia.

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Precise localization should be guided by activation mapping and/or pacemapping during an EPS[532,537–540] and should begin in the RVOT (including the pulmonary artery sinus), followed by the great cardiac veins, aortic cusps and endocardial LVOT. When ablation at a site with early ventricular activation does not eliminate the clinical arrhythmia, epicardial mapping may be considered.

10.1.1 Right ventricular outflow tract tachycardias

Clinically, RVOT–VTs have shorter cycle lengths and are more likely to be associated with syncope compared with LVOT arrhythmias.[550–552] The typical RVO–VT/PVC ECG has a later R/S transition at V4 compared with LVOT–VT/PVC. In published reports, acute RVOT–VT/PVC catheter ablation success rates are >95% in patients without structural heart disease when performed by experienced operators;[525,534–540] however, only limited long-term follow-up data are available.[527,528] Reported complication rates are low, with only very rare cases of RVOT rupture, particularly at the free wall.[525] Therefore, in symptomatic patients with surface ECGs highly suggestive of RVOT tachyarrhythmia, an EPS is recommended and primary catheter ablation should be performed when the mapping has confirmed an RVOT–VT/PVC origin.

10.1.2 Left ventricular outflow tract tachycardias

LVOT–VT/PVC ablation requires an in-depth understanding and careful mapping, including the LVOT, aortic cusps, pulmonary artery and epicardium.[532,556] The septal LVOT, although primarily muscular, includes the membranous ventricular septum. The posterior quadrant consists of an extensive fibrous curtain. The lateral and anterior LVOT are muscular structures. Epicardially the left anterior descending and left circumflex coronary arteries lie superior to the aortic portion of the LVOT and occupy the most superior portion of the LV, termed the LV summit by McAlpine.[557] This is a major source of idiopathic VT/PVCs. Typically LVOT–VT/PVCs have an inferior axis with early transition at V1/V2 and LBBB or RBBB (70% and 30%, respectively).[195,529,530,532,533,537–543,558]

Complication rates of catheter ablation are not negligible and include major complications such as myocardial rupture and tamponade, stroke, valvular damage and coronary artery damage. As a combined transseptal and retrograde approach for complete mapping and ablation may be required due to anatomical complexity, LVOT ablation should only be performed in highly experienced ablation centres after use of at east one sodium channel blockers (class IC agents) has failed.[532]

10.1.3 Aortic cusp ventricular tachycardias

VT originating within the sinuses of Valsalva accounts for ~20% of idiopathic OT–VTs, most from the left coronary cusp, followed by the right coronary cusp, right coronary cusp/left coronary cusp junction and rarely the fibrous non-coronary cusp.[195,529,537–543] ECGs typically show broad QRS with early transition at V1–V2.[537,538] The main complication from ablation within the aortic cusps is the acute occlusion of the left main coronary artery. It is therefore important to identify the coronary ostium of the left main and/or right coronary artery by angiography, intracardiac echocardiography or CT before ablation. A margin >6 mm from the left main coronary artery should be observed, using conventional energy with power titration. Aortic valve injury has been rarely reported.[559] So far, complication rates have been low and are likely to have been underreported, as these arrhythmias are generally performed in highly experienced centres. Therefore ablation should only be performed after failure of at least one sodium channel blocker (class IC agents).

10.1.4 Epicardial outflow tract ventricular tachycardias

An epicardial approach should be considered only after unsuccessful endocardial ablation of OT–VT/PVCs.[195,530,539–541,558] Most focal epicardial VTs originate adjacent to the great cardiac veins or coronary arteries,[195,539–541] and coronary artery injury is a major concern.[531,560–562] The overlying left atrial appendage and epicardial fat pads can also be anatomical obstacles to ablation.

10.1.5 Others (including pulmonary arteries)

Successful ablation of VT originating from the pulmonary artery has only been described in case reports and series.[544–546] However, there is no myocardium in this region with the exception of that in the pulmonary sinuses.[556] ECG recordings typically show LBBB with tall R waves in the inferior leads and transition in V4/V5.[544–546] Complication rates of catheter ablation, generally performed in highly experienced centres, are unknown due to the small number of patients concerned.

10.2 Ventricular tachycardias of miscellaneous origin

Treatment to prevent recurrence of idiopathic ventricular tachycardia

Recommendations	Class[a]	Level[b]	Ref.[c]
Catheter ablation by experienced operators is recommended as a first-line treatment in symptomatic patients with idiopathic left VTs.	I	B	346, 347, 563–575
When catheter ablation is not available or desired, treatment with beta-blockers, verapamil or sodium channel blockers (class IC agents) is recommended in symptomatic patients with idiopathic left VT.	I	C	This panel of expert
Treatment with beta-blockers, verapamil or sodium channel blockers (class IC agents) is recommended in symptomatic patients with papillary muscle tachycardia.	I	C	This panel of experts
Treatment with beta-blockers, verapamil or sodium channel blockers (class IC agents) is recommended in symptomatic patients with mitral and tricuspid annular tachycardia.	I	C	This panel of experts

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Catheter ablation under echo guidance by experienced operators after failure of one or more sodium channel blockers (class IC agents) or in patients refusing long-term anti-arrhythmic drug therapy should be considered in symptomatic patients with papillary muscle tachycardia.	IIa	B	576–578
Catheter ablation by experienced operators after failure of one or more sodium channel blockers (class IC agents) or in patients not wanting long-term anti-arrhythmic drug should be considered in symptomatic patients with mitral and tricuspid annular tachycardia.	IIa	B	534, 579–581

VT = ventricular tachycardia.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

10.2.1 Idiopathic left ventricular tachycardia

Monomorphic and polymorphic idiopathic left VT may occur in patients with and without underlying structural heart disease. These may be divided into different entities: verapamil-sensitive left fascicular VT, bundle branch re-entry tachycardia, interfascicular VT and focal Purkinje VT.[582]

The most common form is left posterior fascicular VT (>90%), occurring predominantly in young patients without structural heart disease. On the surface ECG, left posterior fascicular VT appears with RBBB morphology, a superior axis and a narrow QRS complex. Catheter ablation in experienced centres is recommended as a first-line treatment since left posterior fascicular VT affects mostly young patients and long-term drug-based treatment with verapamil is not effective.[563–567] Recurrence rates after successful ablation range from 0 to 20%.[564,568–570]

Left anterior fascicular VT and left upper septal fascicular VT are responsible for <10% and <1%, respectively, of left fascicular VTs. On the surface ECG, left anterior fascicular VT is characterized by RBBB morphology and right-axis deviation, whereas left upper septal fascicular VT demonstrates a narrow QRS complex and a normal axis or right-axis deviation. In both types of VT, catheter ablation is recommended as a first-line treatment in experienced ablation centres.[571–573]

Bundle branch re-entry tachycardia is usually found in patients with pre-existing intraventricular conduction defects such as prolonged His-ventricular intervals or bundle branch block.[346,347,574] Bundle branch re-entry tachycardia is amenable to catheter ablation either within the left bundle or (more commonly) by right bundle branch ablation, at least in experienced centres, and commonly results in non-inducibility and can be considered curative.[346,347,575] ICD implantation is generally not indicated in patients with normal hearts.

10.2.2 Papillary muscle ventricular tachycardia

Idiopathic VTs or PVCs may arise from the RV or LV papillary muscles in a small number of patients.[576–578] When originating from the left posterior papillary muscle, they usually present with RBBB morphology and a right or left superior QRS axis and a QRS duration >150 ms.[576] In the case of non-responsiveness to sodium channel blockers (class IC agents) and/or beta-blockers, catheter ablation of PVCs or VTs arising from the papillary muscles is an effective treatment option.[578] However, catheter stability during mapping and ablation in the region of the papillary muscles is challenging. A transseptal approach and guidance by intracardiac echocardiography should be strongly considered. Mitral regurgitation after successful ablation is a potential but rare complication.

10.2.3 Annular ventricular tachycardia (mitral and tricuspid)

The mitral annulus is responsible for ~5% of all idiopathic PVCs and VTs.[534,579–581] The QRS complex usually presents with an RBBB pattern, a persistent S wave in lead V6 and pre-cordial R-wave transition in lead V1 or in some cases between leads V1 and V2. The incidence of a tricuspid annulus origin is described with up to 8% of all idiopathic VTs and PVCs.[581] Tachycardia presents usually with LBBB morphology and left-axis deviation. In the case of an insufficient response to class IC anti-arrhythmic drugs and/or beta-blockers, catheter ablation (performed in experienced centres) at the earliest site of ventricular activation or at a site with a perfect pace map is an effective treatment option for mitral as well as tricuspid annular tachycardias.[581]

10.3 Idiopathic ventricular fibrillation

Treatment of idiopathic ventricular fibrillation

Recommendations	Class[a]	Level[b]	Ref.[c]
ICD implantation is recommended in survivors of idiopathic VF.	I	B	154, 583
Catheter ablation of PVCs triggering recurrent VF leading to ICD interventions is recommended when performed by experienced operators.	I	B	467, 584–587
Catheter ablation of PVCs leading to electrical storm is recommended when performed by experienced operators.	I	B	467, 584–587

ICD = implantable cardioverter defibrillator; SCD = sudden cardiac death; PVC = premature ventricular complex; VF = ventricular fibrillation.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

Idiopathic VF is a diagnosis by exclusion, but may change in the future due to better diagnostics of underlying structural heart disease or new evidence of ion channel defects. ICD implantation is strongly recommended for secondary prevention.

Anti-arrhythmic drug therapy using beta-blockers and/or class III anti-arrhythmic drugs may potentially reduce, but rarely prevent, recurrent VF episodes.[154] In patients with VF and underlying structural heart disease, as well as in patients with idiopathic VF, PVC originating from various locations within the Purkinje system or from the

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RVOT can be identified as triggers and potential targets for catheter ablation.[467,584–588] Catheter ablation of the PVC triggering recurrent VF should be considered in patients with frequent VF episodes, but relies on the presence of such extrasystolic beats during the procedure, mostly after a VF episode or VF storm. In patients without spontaneous PVCs, a pre-interventional 12-lead Holter ECG is recommended to document the morphology of the contractions and guide ablation.

A long-term success rate of 82%, defined as the absence of VF, polymorphic VT or SCD, after a follow-up of >5 years has been reported.[586,588] Irrespective of the results of catheter ablation, all patients with idiopathic VF should undergo ICD implantation.

10.4 Short-coupled torsade de pointes

Treatment of short-coupled torsade de pointes

Recommendations	Class[a]	Level[b]	Ref.[c]
ICD is recommended in patients with conclusive diagnosis of short-coupled TdP.	I	B	589
Intravenous verapamil to acutely suppress/prevent an electrical storm or recurrent ICD discharges should be considered.	IIa	B	590, 591
Catheter ablation for long-term suppression/prevention of an electrical storm or recurrent ICD discharges should be considered.	IIa	B	586

ICD = implantable cardioverter defibrillator; TdP = torsade de pointes.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

Short-coupled TdP is a rare variant of polymorphic VT of unknown aetiology. TdP is characterized by its typical ECG pattern in the form of non-uniform but organized electrical activity with progressive changes in its morphology, amplitude and polarity. Short-coupled TdP is characterized by an extremely short-coupled interval of the first premature ventricular contraction (<300 ms) initiating the tachycardia. This predominantly affects young patients who often present with unclear syncope and a positive family history for SCD.[589–591] In most cases, TdP deteriorates into VF. Although the mechanisms are not yet well understood, there may be a link to an autonomic nervous system imbalance.[592] Intravenous verapamil seems to be the only drug that can suppress the arrhythmia, but it does not reduce the risk of SCD.[590,591] Consequently, ICD implantation is strongly recommended.[589] In cases of recurrence of VA triggered by monomorphic premature ventricular contractions despite drug therapy, catheter ablation should be strongly considered. The ablation target is the PVC initiating TdP.

11. Inflammatory, rheumatic and valvular heart diseases

Management of ventricular arrhythmias in inflammatory heart disease

Recommendations	Class[a]	Level[b]	Ref.[c]
It is recommended that patients with a life-threatening presentation of sustained ventricular tachyarrhythmias in the context of clinically suspected myocarditis are referred to specialized centres with the ability to perform haemodynamic monitoring, cardiac catheterization and endomyocardial biopsy and to use mechanical cardio-pulmonary assist devices and specialized arrhythmia therapies.	I	C	593–596
Temporary pacemaker insertion is recommended in patients with bradycardia and/or heart block triggering VA during the acute phase of myocarditis/pancarditis.	I	C	593, 594
Anti-arrhythmic therapy should be considered in patients with symptomatic non-sustained or sustained VT during the acute phase of myocarditis.	IIa	C	594
The implant of an ICD or pacemaker in patients with inflammatory heart diseases should be considered after resolution of the acute episode.	IIa	C	593, 597
In patients with haemodynamically compromising sustained VT occurring after the resolution of acute episodes, an ICD implantation should be considered if the patient is expected to survive >1 year with good functional status.	IIa	C	8
A wearable defibrillator should be considered for bridging until full recovery or ICD implantation in patients after inflammatory heart diseases with residual severe LV dysfunction and/or ventricular electrical instability.	IIa	C	598, 599
ICD implantation may be considered earlier in patients with giant cell myocarditis or sarcoidosis who had haemodynamically compromising sustained VA or aborted cardiac arrest, due to adverse prognosis of these conditions, if survival >1 year with good functional status can be expected.	IIb	C	600

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Demonstration of persistent myocardial inflammatory infiltrates by immunohistological evidence and/or abnormal localized fibrosis by CMR after acute myocarditis may be considered as an additional indicator of increased risk of SCD in inflammatory heart disease.	IIb	C	601

CMR = cardiac magnetic resonance; ICD = implantable cardioverter defibrillator; LV = left ventricular; SCD = sudden cardiac death; VA = ventricular arrhythmia; VT = ventricular tachycardia.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

11.1 Myocarditis

Myocarditis is the pathological result of myocardial infection and/or autoimmunity that causes active inflammatory destruction of myocytes. Aetiologically, a wide spectrum of infectious agents, including viruses, bacteria, chlamydia, rickettsia, fungi and protozoans, as well as toxic and hypersensitivity reactions might be involved.[609] Enteroviruses (Coxsackie B), adenoviruses, parvovirus B19 and human herpes virus type 6 are among the most common causal agents. Myocarditis can occur also in patients with advanced HIV infections due to cardiotoxicity with cellular apoptosis induced by viral glycoprotein 120, opportunistic infections, autoimmune response, drug-related cardiac toxicity and possibly nutritional deficiencies.[609,610]

The typical microscopic image required for the diagnosis of myocarditis consists of the presence of inflammatory cells together with necrotic myocytes. According to the World Health Organization report, myocarditis is defined as inflammatory disease of the myocardium diagnosed by established histological, immunological and immunohistochemical criteria.[611] In the same document, myocarditis associated with cardiac dysfunction is referred to as inflammatory cardiomyopathy, and both definitions are recommended for use by the relevant ESC recommendations.[593]

Thus endomyocardial biopsy remains the gold standard for the definite diagnosis of myocarditis and should be performed especially in patients with a life-threatening course of the disease. CMR is becoming routine and is a sensitive, non-invasive test for confirmation of acute myocarditis even before endomyocardial biopsy. Essential first-line tests to confirm the diagnosis in patients with a clinical presentation consistent with myocarditis should include 12-lead ECG, transthoracic echocardiogram and assessment of biomarker concentrations (including troponins), erythrocyte sedimentation rate and C-reactive protein. The diagnosis of myocarditis should be based on the criteria summarized by Caforio *et al.*[593]

In the acute stage of disease, myocarditis may be asymptomatic or present with an unrecognized non-specific course. Considering malignant arrhythmias associated with myocarditis, two distinct clinical settings have to be distinguished:

- Acute fulminant myocarditis with refractory malignant ventricular tachyarrhythmias in the context of severe acute HF, and adverse short-term prognosis with early death due to multisystem failure.
- Long-term evolution to inflammatory cardiomyopathy with LV dysfunction and resulting in a high risk of SCD similar to that for DCM.

11.1.1 Acute and fulminant myocarditis

Management of HF and potentially fatal arrhythmias is the main clinical challenge in acute myocarditis. Patients with fulminant myocarditis have a high acute mortality and a severe risk of life-threatening refractory ventricular tachyarrhythmias. In patients who initially present with an HF syndrome suggestive of first DCM manifestation and in whom possible or probable acute myocarditis is suspected, supportive measures with a recommendation to avoid exercise and use of pharmaceutical treatment with neurohormonal blockade with ACE inhibitors and beta-blockers is recommended. Progressive wall motion abnormalities with deteriorating LV function on echocardiography, persistent or fluctuating cardiac troponin concentrations, widening of the QRS complex and frequent non-sustained VA may precede a sustained life-threatening arrhythmia in the setting of acute myocarditis.[594,612]

Patients with VA or heart block in the setting of acute myocarditis need prolonged ECG monitoring and must be admitted to hospital.

Lyme's disease and diphtheria myocarditis are frequently associated with various degrees of heart block, which can also trigger ventricular tachyarrhythmias. Thus temporary pacemaker insertion is recommended in patients with acute myocarditis who present with symptomatic heart block (as with other causes of acute symptomatic heart block). Pacing is recommended in patients with symptomatic sinus node dysfunction or AV block following myocarditis (as with other causes of sinus or AV node dysfunction). Ventricular tachyarrhythmias triggered by high-degree AV block require temporary pacemaker insertion. If persistent AV blocks develop, permanent pacing is recommended. However, device selection should reflect the presence, extent and prognosis (progression or regression) of LV dysfunction in order to appropriately choose a pacemaker or ICD with or without cardiac resynchronization capability. Owing to the adverse prognosis of patients with giant cell myocarditis or sarcoidosis, the implantation of an impulse generator may be considered earlier in these patients.[596]

Fulminant myocarditis is a distinct clinical entity with an adverse short-term but a relatively good long-term prognosis. Refractory sustained arrhythmias are typical for the fulminant form of myocarditis. According to a Japanese registry, the short-term survival rate of patients with fulminant myocarditis was only 58%.[595,613]

Ventricular tachycardia was the most common sustained arrhythmia in 2148 children with acute myocarditis, accounting for 76% of 314 cases with arrhythmias during the course of the disease. Patients with sustained arrhythmias had a very high risk of cardiac arrest, need for mechanical circulatory support and/or death compared with patients without arrhythmias [OR 5.4 (95% CI 3.9, 7.4), $P < 0.001$].[596]

Giant cell myocarditis is a severe form of myocarditis with a dramatic clinical course, frequently affecting young patients. The diagnosis is confirmed by endomyocardial biopsy showing the presence of typical multinucleated giant cells in inflammatory lesions. Patients may develop heart block, requiring placement of temporary or permanent pacemakers. However, refractory electrical

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storms with incessant VT or VF have a particularly adverse prognosis despite the use of aggressive anti-arrhythmic drug therapy.

Surprisingly, in a retrospective study among adult patients after acute myocarditis, those with the fulminant form had a better long-term prognosis than patients with non-fulminant myocarditis. After 11 years, 93% of patients with fulminant myocarditis were alive without heart transplantation compared with only 45% with the non-fulminant form.[614]

Aggressive haemodynamic support using percutaneous cardiopulmonary support or an intra-aortic balloon pump in addition to drug therapy is recommended for patients with acute or fulminant myocarditis to bridge the dramatic but often curable acute stage of the disease. Percutaneous cardiopulmonary support should be initiated if refractory VT or VF does not respond to three to five defibrillation attempts.[594]

The important association between undiagnosed myocarditis and SCD is emphasized by post-mortem data, which have implicated myocarditis in SCD of young adults at rates of 8.6–44%.[615–618]

Data on the causative agents are rare. *Chlamydia myocarditis* was implicated in the sudden death of 5 of 15 young Swedish elite athletes (orienteers) following the identification of chlamydial RNA in their hearts.[619]

During the acute phase of myocarditis, ICD implantation should be deferred until resolution of the acute episode. Because myocarditis may heal completely, the indication for ICD implantation and its timing remain controversial even beyond the acute stage. Bridging the critical period to full recovery by a WCD vest in patients with myocarditis and VT or VF appears to be a promising therapeutic option.[598,599] The presence of malignant VA or heart block in giant cell myocarditis or cardiac sarcoidosis might warrant earlier consideration of an ICD due to the known high risk of arrhythmic death or need for transplantation.[600]

11.1.2 Myocarditis leading to inflammatory cardiomyopathy

Myocarditis has been identified as a cause of DCM in up to 10% of cases in large prospective series. Importantly, inflammatory cardiomyopathy is involved in the pathogenesis of DCM, with a poor prognosis. In long-term follow-up studies of patients after acute myocarditis, DCM developed in 21%.[620]

On the other hand, a viral genome was identified in the myocardium of two-thirds of patients with 'idiopathic' LV dysfunction. Furthermore, persisting cardiac viral infections may constitute a major cause of progressive LV dysfunction in patients with DCM and with a suspicion of prior myocarditis.[621] However, these observations were not confirmed by Kindermann *et al.*,[597] who identified immunohistological evidence of inflammatory infiltrates in the myocardium as the primary factor associated with a three-fold or greater increase in risk of cardiac death or heart transplantation. Over 5 years of follow-up, 61% of patients in NYHA functional class III or IV with positive immunohistology and not receiving beta-blocker therapy died or underwent heart transplantation.[597]

In patients with documented symptomatic sustained VT of unclear aetiology, myocarditis should also be suspected and a CMR scan may reveal abnormal fibrotic myocardial tissue, frequently located in subepicardial and intramural regions. In a cohort of 405 patients with suspected myocarditis, all of the patients who died suddenly or experienced aborted SCD or ICD discharge had abnormal CMR scans.[601] Successful radiofrequency catheter ablation of epicardial arrhythmogenic foci in myocarditis has been described recently.[622]

Drug treatment of arrhythmias in patients with inflammatory heart disease does not differ from generally accepted clinical principles. Arrhythmia management outside the acute phase should be in line with current ESC guidelines on arrhythmia and device implantation in chronic HF management.[8] In general, the indications for an ICD in inflammatory cardiomyopathy are the same as for non-ischaemic DCM. In secondary prevention of SCD, implantation of an ICD in patients with myocarditis is recommended after cardiac arrest due to VF or after symptomatic VT. CRT-D is recommended for primary prevention in patients with impaired LV function (LVEF $<35\%$) and LBBB in NYHA functional classes II–IV.[8] As LV function may improve over time in patients with inflammatory cardiomyopathy due to the natural course of the disease and/or appropriate HF therapy, implantation of an ICD/CRT-D should not be indicated prematurely.

11.2 Endocarditis

VAs in infective endocarditis are predictors of a very poor prognosis.[623] However, there are no specific recommendations for their management beyond the general principles. Abscess formation in the valve annulus (more often aortic than mitral) can result in first- or second-degree heart block. New-onset heart block in a patient with endocarditis should raise the clinical suspicion of an abscess. The acute haemodynamic compromise related to acute aortic regurgitation secondary to endocarditis can result in sustained VT and is an indication for early surgery.[605]

11.3 Rheumatic heart disease

Acute rheumatic fever can cause a pancarditis involving the pericardium, myocardium and endocardium. There are no specific data on VA in rheumatic heart disease and their management should follow general principles.

Complete AV block during acute rheumatic fever is rare and usually transient. Temporary pacing should be considered when symptomatic or when serious VAs are triggered.

11.4 Pericarditis

SCD can occur in the course of pericardial disease resulting from a variety of pathological processes; these include both constrictive and restrictive processes resulting from trauma, inflammation, neoplastic and infectious aetiologies. However, there is no evidence linking specific VAs with pericardial disease. Furthermore, SCD in these patients has mostly a haemodynamic and not an arrhythmic cause.

11.5 Cardiac sarcoidosis

Cardiac sarcoidosis is a rare and difficult-to-diagnose clinical entity with a wide spectrum of manifestations from subtle asymptomatic ECG alterations to HF and SCD. Cardiac sarcoidosis is a rare cause of VT (5% of all non-ischaemic cardiomyopathies referred for VT).

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Studies performed using voltage cardiac mapping have demonstrated the presence of widespread and confluent RV scarring with predominant epicardial location. Left ventricular scarring was patchier in the basal septum, anterior wall and perivalvular regions. Such substrate is capable of sustaining a large number of re-entrant circuits.

Catheter ablation in conjunction with anti-arrhythmic drugs is an effective palliative therapy for terminating VT storm and eliminating one or more inducible VTs in the majority of patients, but recurrences are common and these patients require ICD backup.[624,625]

11.6 Valvular heart disease

Management of ventricular arrhythmias in valvular heart disease

Recommendations	Class[a]	Level[b]	Ref.[c]
The implantation of an ICD is recommended in patients with valvular heart disease who, after surgical repair, satisfy the criteria for primary and secondary prevention of SCD.	I	C	602–604
Surgical treatment of acute aortic regurgitation due to endocarditis associated with sustained VT is recommended, unless otherwise contraindicated.	I	C	605, 606
An EPS with standby catheter ablation should be considered in patients who develop VT following valvular surgery in order to identify and cure bundle branch re-entry VT.	IIa	C	607, 608

EPS = electrophysiological study; ICD = implantable cardioverter defibrillator; SCD = sudden cardiac death; VT = ventricular tachycardia.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

Valvular heart disease, both in the preoperative period and after valvular surgery, predisposes patients to VA. Aetiologically, increased myocardial mass, ventricular dilatation and wall stress and subendocardial ischaemia in the absence of CAD, together with chronic myocardial damage and iatrogenic post-surgical fibrosis, may be responsible for an increased incidence of complex ventricular tachyarrhythmias that may be associated with sustained VT and SCD.[606] Malignant arrhythmogenic substrate may be further enhanced by frequent concomitant structural heart disease, mainly CAD and HF.

In the past, several investigators described an increased incidence of NSVT in patients with aortic and mitral valvular heart disease.[626,627] In older studies on the natural history of valvular heart disease, sudden death occurred in 15–20% of adult patients with aortic stenosis, at an average age of 60 years. Among symptomatic non-operated patients, sudden death occurs with a prevalence of up to 34%.[628,629] In one study, 60% of all cardiac deaths occurring during non-surgical follow-up in patients with severe mitral regurgitation were sudden.[630]

A study of 348 patients with mitral regurgitation due to flail leaflet revealed that sudden death is not rare in conservatively managed older patients. Since correction of this type of mitral regurgitation appears to be associated with a reduced incidence of sudden death, repair should be considered earlier, with a previous, mandatory and careful search for accompanying CAD.[631] After mitral regurgitation repair, more than two episodes of NSVT during ambulatory monitoring were predictive of sudden death during a 9-year follow-up.[632] Overall rates of SCD in patients with prosthetic valves vary considerably, ranging from 15 to 30%, with an estimated annual risk of 0.2–0.9%.[633] In a large series of 1533 patients who underwent aortic or mitral valve replacement, 6% of deaths were caused by arrhythmias.[634] In a US cooperative study, sudden death accounted for 23% of deaths for mitral valve replacement and 16% for aortic valve replacement.[635,636]

Martinez-Rubio *et al.*[607] demonstrated that inducibility of VT, together with LV volume overload, is predictive of malignant arrhythmic events in patients presenting with VT, VF or syncope. An EPS is of considerable clinical importance in patients who develop VT following valvular surgery. In up to 30% of patients, VT (occurring mostly within 1 month of surgery) was due to bundle branch re-entry—an arrhythmia that is potentially curable with catheter ablation.[608]

Valvular heart disease as the presumably dominant aetiology constituted ~7% of patients referred for secondary prevention ICD implantation.[602] This single-centre experience has shown that 31 patients with valvular heart disease and malignant ventricular tachyarrhythmias protected with ICDs had a favourable outcome. Their survival was not inferior to patients with CAD and was more favourable than that in patients with DCM.[602] In the experience of Yang *et al.*,[603] patients with valvular heart disease and residual LV dysfunction following valvular surgery who underwent a tailored approach to primary preventive ICD implantation had similar overall and arrhythmia-free survival as patients with ischaemic cardiomyopathy.

More recently, it has been demonstrated that patients with valvular heart disease who undergo ICD implantation for primary or secondary SCD prevention have similar appropriate ICD discharge rates and mortality as those with CAD or DCM.[604]

12. Arrhythmic risk in selected populations

12.1 Psychiatric patients

Arrhythmic risk in psychiatric patients

Recommendations	Class[a]	Level[b]	Ref.[c]
Dosage adjustment or interruption of the offending agent is recommended when, after treatment with antipsychotic drugs, the QTc interval reaches a length >500 ms or increases by >60 ms compared with baseline.	I	C	637

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Monitoring of plasma potassium levels to avoid hypokalaemia is recommended during treatment with antipsychotic drugs.	I	C	638
Avoidance of treatment with more than one drug prolonging the QT interval is recommended.	I	C	639, 640
Evaluation of the QT interval before initiation of treatment and during titration of dose with antipsychotic drugs should be considered.	IIa	C	638, 641, 642

QTc = corrected QT.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

12.1.1 Epidemiology

Patients with schizophrenia, anorexia nervosa and other mental health disorders have a higher than expected incidence of sudden death,[643] believed to be related to both these diseases and to their treatment. For instance, patients with schizophrenia have a three-fold increase in the risk of SCD compared with the general population.[644] Moreover, a number of antipsychotic and antidepressant drugs are known to increase the risk of VA and SCD,[639] with the principal mechanism believed to be TdP.[645]

Ray *et al.*[646] studied the association between the use of antipsychotic drugs (mostly conventional antipsychotics) and sudden death in >480 000 patients and found evidence for a dose-dependent effect, with a higher risk in patients with cardiovascular disease. In another recent large study by Ray *et al.*,[647] the association with sudden death was also demonstrated for atypical antipsychotics, with a dose-dependent effect.

A recent study by Wu *et al.*[639] enrolled 17 718 patients with incident VA and/or SCD to examine the effects of antipsychotic drugs on the risk of VA/SCD. Antipsychotic drug use was associated with a 1.53-fold increased risk of VA and/or SCD (95% CI 1.38, 1.70; $P < 0.005$) and antipsychotics with a high potency of the human ether-a-go-go-related gene potassium channel blockade had the highest risk of VA and/or SCD (see *Table 6*).

12.1.2 Diagnosis

Drugs such as tricyclic antidepressants are associated with a greater increase in QTc and TdP than selective serotonin reuptake inhibitors. Severe sodium channel blockade and baseline risk factors, including previous arrhythmias, impaired LV function, concurrent digoxin therapy and hypokalaemia (diuretics), are frequently involved.[638,642,648,649] The association of different drugs must be carefully monitored even if these drugs are not known to prolong the QT interval.

12.1.3 Treatment

An assessment of cardiac risk profile is recommended, and in the case of positive findings, assessment by a cardiologist. After initiating drugs, a heart check-up is recommended, and in the event of QTc prolongation >500 ms or new cardiac symptoms, treatment should be re-evaluated.[641] Use of concomitant drugs interacting with the metabolism

Table 6 Risk of ventricular arrhythmia and/or sudden cardiac death in relation to current antipsychotic use among 17,718 patients. With permission from Wu *et al.*[639]

Antipsychotic class and agent	Case period, N	Control period, N	Crude OR	95% CI	Adjusted OR	95% CI
Use of Antipsychotics	5625	5117	1.84	1.67 to 2.03	1.53	1.38 to 1.70
First-generation Antipsychotics	2070	1770	2.02	1.76 to 2.33	1.66	1.43 to 1.91
Chlorpromazine	248	218	1.98	1.28 to 3.05	1.45	0.93 to 2.27
Clopenthixol	30	25	2.66	0.71 to 10.04	2.40	0.46 to 12.48
Clothiapine	135	117	2.68	1.33 to 5.39	2.16	1.03 to 4.53
Flupentixol	400	382	1.28	0.92 to 1.78	1.07	0.77 to 1.51
Haloperidol	833	730	1.83	1.47 to 2.27	1.46	1.17 to 1.83
Loxapine	14	14	1.00	0.14 to 7.10	0.49	0.04 to 5.87
Prochlorperazine	272	172	2.04	1.60 to 2.61	1.69	1.32 to 2.17
Thioridazine	194	173	2.17	1.24 to 3.79	1.78	1.01 to 3.15
Trifluoperazine	87	73	1.88	1.02 to 3.44	1.37	0.73 to 2.57
Second-generation antipsychotics	4017	3736	1.63	1.45 to 1.84	1.36	1.20 to 1.54
Amisulpride	90	88	1.14	0.56 to 2.34	0.94	0.45 to 1.96
Aripriprazole	35	34	1.14	0.41 to 3.15	0.90	0.31 to 2.59
Clozapine	141	130	2.64	1.09 to 6.38	2.03	0.83 to 4.94
Olanzapine	245	221	2.01	1.23 to 3.29	1.64	0.98 to 2.72
Quetiapine	1421	1326	1.51	1.26 to 1.82	1.29	1.07 to 1.56
Risperidone	1163	1066	1.67	1.36 to 2.05	1.39	1.13 to 1.72
Sulpiride	1015	930	1.59	1.29 to 1.95	1.26	1.02 to 1.56
Ziprasidone	27	26	1.20	0.37 to 3.93	0.80	0.24 to 2.67
Zotepine	154	142	1.86	0.97 to 3.56	1.50	0.77 to 2.91

n = number; CI = confidence interval; OR = odds ratio.

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of a QT-prolonging drug should be avoided. It is important to know all co-medications, including those purchased over the counter.[641]

12.2 Neurological patients

12.2.1 Sudden unexplained death in epilepsy

Sudden unexplained death in epilepsy (SUDEP) is defined as a non-accidental death in a person with epilepsy. Most cases occur at night or during sleep and are not witnessed.[650] The greatest risk factor for SUDEP is frequent seizures, especially generalized tonic–clonic seizures.[651–660]

Patients with epilepsy should undergo ECG screening to rule out diseases that mimic epilepsy. Furthermore, epilepsy may also be due to neurological channelopathy, providing potential interaction between ion channel abnormalities in the heart and the brain.[658,661–664] The best way to prevent SUDEP is to maximize seizure control.

12.2.2 Neuromuscular disorders

Arrhythmic risk in patients with neuromuscular disorders

Recommendations	Class[a]	Level[b]	Ref.[c]
Annual follow-up is recommended in patients with muscular dystrophies, even in the concealed phase of the disease when patients are asymptomatic and the ECG is normal.	I	B	665–668
It is recommended that patients with neuromuscular disorders who have VAs are treated in the same way as patients without neuromuscular disorders.	I	C	This panel of experts
Permanent pacemaker implantation is recommended in patients with neuromuscular diseases and third-degree or advanced second-degree AV block at any anatomical level.	I	B	669
Permanent pacemaker implantation may be considered in patients with myotonic dystrophy type 1 (Steinert disease), Kearns–Sayre syndrome or limb-girdle muscular dystrophy with any degree of AV block (including first-degree) in consideration of the risk of rapid progression.	IIb	B	666, 669–672
The use of an ICD may be considered in myotonic dystrophy type 1 (Steinert disease), Emery–Dreifuss and limb-girdle type 1B muscular dystrophies when there is an indication for pacing and evidence of ventricular arrhythmias.	IIb	B	71,669, 672–674

AV = atrio-ventricular; ECG = electrocardiogram; ICD = implantable cardioverter defibrillator; VA = ventricular arrhythmia.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

Muscular dystrophies are a group of inherited diseases affecting skeletal and cardiac muscle. Cardiac involvement occurs as a degenerative process with fibrosis and fatty replacement of the myocardium[666] and the most frequent manifestations are dilated cardiomyopathy and conduction defects, which may coexist. In all the muscular dystrophies, respiratory muscle involvement can impact quality and quantity of life and needs to be factored in when considering a prophylactic device.

Cardiac involvement is frequent in most patients with Duchenne and Becker dystrophies, myotonic dystrophy type 1 (Steinert disease), Emery–Dreifuss and limb-girdle type 1B dystrophies[666] (*Table 7*). The development of a dilated cardiomyopathy is common in Duchenne and Becker muscular dystrophies.[666] Arrhythmias (ventricular premature beats and NSVT) and conduction disease occur after the development of the dilated cardiomyopathy and therefore arrhythmia management should be aligned with recommendations issued for patients with DCM. In Duchenne muscular dystrophy, sudden death occurs primarily in patients with both respiratory and cardiac failure. The proportion of deaths due to arrhythmias is uncertain, but VA and sudden death are believed to play a similar role in these disorders as in other non-ischaemic dilated cardiomyopathies. Prophylactic ICD implantation should follow the same criteria as in the other forms of non-ischaemic dilated cardiomyopathies.[666]

Myotonic dystrophy type 1 (Steinert dystrophy) presents with conduction disease often requiring pacing with or without dilated cardiomyopathy (*Table 7*); up to one-third of deaths in these patients are sudden and unexpected.[666] In a review of 18 studies (1828 patients) by Petri *et al.*,[667] first-degree AV block was reported in almost 30% of patients, QRS duration >120 ms in 20%, frequent PVCs in 15% and NSVT in 4%. LV systolic dysfunction was reported in 7.2% of the patients and AF or atrial flutter in 5%. Based on the high incidence of conduction disease, it has been speculated that SCD in Steiner disease is primarily caused by progressive conduction disease; however, evidence of sudden death in patients with pacemaker[673] and spontaneous or inducible VTs suggests that VAs account of some of the sudden deaths.

Lallemand *et al.*[668] studied patients with Steiner disease and performed serial invasive measurements of HV intervals showing that the appearance of a new conduction disease is followed within 5 years by lengthening of infra-hissian conduction. Similarly, a study by Laurent *et al.*[673] suggested that prolongation of the HV interval >70 ms at invasive EPS is predictive of complete AV block within 6 years. Groh *et al.*[669] investigated 406 adult patients with genetically confirmed myotonic dystrophy type 1, showing that the severity of AV and/or intraventricular conduction defect and the presence of atrial arrhythmias were independent risk factors for sudden death. In a large retrospective observational study by Wahbi *et al.*,[672] the use of an electrophysiology study followed by implantation of a pacemaker in patients with an HV interval >70 ms reduced sudden death compared with patients followed by ECG assessment.

In patients with Emery–Dreifuss and limb-girdle type 1B muscular dystrophies associated with lamin A or C mutations, sudden death is responsible for 30% of all deaths.[71]

Some series of patients with the two lamin A/C dystrophies suggested that the development of AV block is associated with poor

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Table 7 Cardiac involvement in muscular dystrophies. Adapted with permission from Groh *et al.*[666]

Myopathy	Gene	Heart involvement	Frequency of heart involvement	Ventricular arrhythmia	Atrial arrhythmia	Sudden death reported
Duchenne	Dystrophin	DCM	>90%	PVC	Only at late stage	Yes
Becker	Dystrophin	DCM	60–75%	VT associated with DCM	Associated with DCM	Yes
Myotonic, type 1	CGT repeat expansion	Conduction disease and DCM	60–80%	VT, ICD indicated	Age dependent	Yes, 30% of death
Myotonic, type 2	CGT repeat expansion	Conduction disease	10–25%	Uncommon	Uncommon	Yes
Emery-Dreifuss	Emerin, lamin A and C	Conduction disease and DCM	>90%	VT, ICD indicated	Common, atrial standstill	Yes, 30% of death
Limb-girdle type 1B	Lamin A and C	Conduction disease and DCM	>90%	VT, ICD indicated	Common	Yes, 30% of death
Limb-girdle type 2C–2F	Sarcoglycans	DCM	<25%	Uncommon	Limited data	Unknown
Limb-girdle type 2I	Fukutin-related protein	DCM	20–80%	Uncommon	Not reported	Unknown
Facioscapulohumeral	D4Z4 repeat contraction	Conduction disease	5–15%	Rare VTs	Rare	No

DCM = dilated cardiomyopathy; ICD = implantable cardioverter defibrillator; PVC = premature ventricular complex; VT = ventricular tachycardia.

outcomes and pacing therapy is insufficient to prevent SCD, thus supporting the use of prophylactic ICDs rather than pacemakers when cardiac involvement is present.[674] Risk factors for sudden death and appropriate ICD therapy include non-sustained ventricular tachycardia, left ventricular ejection fraction <45%, male sex and lamin A or C non-missense mutations.[71] Management of the rare X-linked recessive Emery–Dreifuss muscular dystrophy associated with mutations in the emerin gene is complicated by a lack of clinical data; in the absence of gene-specific information it seems reasonable to adopt the management strategy used in the dominant form of Emery–Dreifuss.[666,671]

12.3 Pregnant patients

12.3.1 Arrhythmias not related to peripartum cardiomyopathy

Management of arrhythmic risk during pregnancy

Recommendations	Class[a]	Level[b]	Ref.[c]
Implantation of an ICD is recommended if an indication emerges during pregnancy.	I	C	675
Beta-blocking agents are recommended during pregnancy and also post-partum in patients with LQTS or CPVT.	I	C	675, 676
Oral metoprolol, propranolol or verapamil is recommended for long-term management of idiopathic sustained VT.	I	C	675, 677
Immediate electrical cardioversion is recommended for sustained VT, especially if haemodynamically unstable.	I	C	675, 677
Sotalol or procainamide i.v. should be considered for acute conversion of haemodynamically stable monomorphic sustained VT.	IIa	C	675
Amiodarone i.v. should be considered for acute conversion of sustained, monomorphic VT when haemodynamically unstable, refractory to electrical cardioversion or not responding to other drugs.	IIa	C	675, 677, 678
Catheter ablation may be considered for management of drug-refractory and poorly tolerated tachycardias.	IIb	C	675

CPVT = catecholaminergic polymorphic ventricular tachycardia; i.v. = intravenous; ICD = implantable cardioverter defibrillator; LQTS = long QT syndrome; VT = ventricular tachycardia.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

12.3.1.1 *Epidemiology*

Pregnancy contributes a significant risk in women with structural heart disease.[675,679–681] There is a substantial increase in the risk of cardiac events in women with the congenital LQTS in the post-partum period (the 40-week period after delivery), and beta-blocker therapy should be continued[676,682] throughout pregnancy and post-partum. Women with Brugada syndrome can have a safe pregnancy and peripartum period.[683,684]

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12.3.1.2 Diagnosis

Palpitations may be caused by atrial or ventricular extrasystoles or even sinus tachycardia, and most are benign.[677,685–688] Symptomatic exacerbation of paroxysmal supraventricular tachycardia occurs during pregnancy in many patients. New-onset VT may present during pregnancy[677,686–688] and may be related to elevated catecholamines.[689] Risk of recurrent VT is higher in patients with previous VT and structural heart disease.[676,690,691]

12.3.1.3 Treatment

When benign arrhythmias are found, patients need reassurance and should avoid stimulants such as caffeine, smoking and alcohol. Symptomatic tachyarrhythmia should be treated by catheter ablation before pregnancy, if the pregnancy was previously planned. If drug therapy is recommended, it is advised to begin as late in pregnancy as possible and to use the lowest effective dose.

Arrhythmias in the absence of structural heart disease during pregnancy are usually sensitive to beta-blocker therapy.[675,692,693] Sotalol or sodium channel blockers (class IC agents) may be considered in the absence of structural heart disease if beta-blocking agents are ineffective.

While the first trimester is associated with the greatest teratogenic risk, drug exposure later in pregnancy may confer adverse effects on foetal growth and development as well as increase the risk of pro-arrhythmia. The Food and Drug Administration has defined five categories for the use of anti-arrhythmic drugs during pregnancy:[694]

- A: controlled studies show no risk (no anti-arrhythmic drug)
- B: chance of foetal harm is remote (sotalol, lidocaine)
- C: potential benefits outweigh the risk (quinidine, adenosine, metoprolol, propranolol, verapamil, diltiazem, digoxin, flecainide, propafenone)
- D: positive evidence of risk (phenytoin, amiodarone)
- X: contraindicated.

The pharmacological treatment of idiopathic VT from the RVOT is verapamil or beta-blockers (metoprolol or sotalol) as prophylaxis, if they are associated with severe symptoms or haemodynamic compromise. Idiopathic fascicular left VT usually does not respond to beta-blockers and may be treated with verapamil; the mechanism of this tachycardia depends on the slow entry of calcium in partially depolarized Purkinje fibres.[1] Catheter ablation may be necessary in the case of drug-refractory and poorly tolerated tachycardias. Patients with ICDs can have a successful pregnancy with no foetal compromise.[695–697] If indications for an ICD emerge during pregnancy, the use of subcutaneous ICD may be considered, to avoid fluoroscopy, but weighted against the limited experience available.

12.3.2 Arrhythmias related to peripartum cardiomyopathy

Management of arrhythmias related to pregnancy-induced cardiomyopathy

Recommendations	Class[a]	Level[b]	Ref.[c]
Electrical cardioversion or defibrillation is recommended in pregnant women developing haemodynamically unstable VT or VF.	I	B	698
Standard management of HF with avoidance of drugs contraindicated in pregnancy (ACE inhibitors, ARB and renin inhibitors) is recommended in pregnant women.	I	C	698, 699

ACE = angiotensin-converting enzyme; ARB = angiotensin II receptor blocker; HF = heart failure; VF = ventricular fibrillation; VT = ventricular tachycardia.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

Peripartum cardiomyopathy is defined as HF caused by LV systolic dysfunction presenting towards the end of pregnancy or in the months following delivery.[700] The cause of peripartum cardiomyopathy is uncertain, and infections, inflammation and autoimmune processes may play a role.[1,701] The incidence has been estimated at 50 in 100 000 live births.[702] The estimated mortality rate associated with peripartum cardiomyopathy in the US ranges from 6 to 10%.[703] Recent studies indicate that peripartum cardiomyopathy can be a manifestation of familial DCM associated with gene mutations.[704]

Peripartum cardiomyopathy usually presents with HF secondary to LV systolic dysfunction towards the end of pregnancy or in the months following delivery. The LV may not be dilated, but the ejection fraction is nearly always reduced (<45%).[698] With this recent definition, the time window is not strictly defined.[705] Complex VA and sudden cardiac arrest may occur as a result. Post-partum cardiomyopathy should be ruled out in women presenting with new-onset VT during the last 6 weeks of pregnancy or in the early post-partum period.[706]

Guidelines for the management of acute HF should be applied.[8] During pregnancy, ACE inhibitors, ARBs and renin inhibitors are contraindicated.[699,707] Beta-blocker treatment is recommended for all patients with HF, if tolerated; beta-blockers with beta1-adrenoceptor preferential properties (i.e. metoprolol) should be preferred. Atenolol should not be used.[708] MRAs should be avoided.[709] Potentially life-threatening ventricular tachyarrhythmias should be terminated by electrical cardioversion. Implantation of an ICD in patients with VA or low ejection fraction should follow

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standard guidelines. However, the relatively high rate (50%) of spontaneous recovery of dilated cardiomyopathy after delivery must be considered when decisions are made.[710]

12.4 Obstructive sleep apnoea

12.4.1 Bradyarrhythmias and tachyarrhythmias

Management of ventricular arrhythmias and bradyarrhythmias in sleep apnoea

Recommendations	Class[a]	Level[b]	Ref.[c]
Sleep apnoea syndrome should be considered in the differential diagnosis of bradyarrhythmias.	IIa	B	711
The presence of sleep apnoea and reduced oxygen saturation may be considered as a risk factor for SCD in subjects with sleep disordered breathing.	IIb	C	712

SCD = sudden cardiac death.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

12.4.1.1 Epidemiology

Data on the prevalence of obstructive sleep apnoea in the general population are not univocal due to the high heterogeneity of the populations studied; however, according to a rigorous population-based study determining the epidemiological features of obstructive sleep apnoea, the prevalence of the disease in 602 adults between 30 and 60 years of age was 9% for women and 24% for men.[713] The prevalence of arrhythmias largely depends on the co-morbidities present in the different populations. Data from the Busselton Health Study[714] and the Wisconsin Sleep Cohort[715] suggest that obstructive sleep apnoea is associated with increased mortality. The existence of a link with SCD has been debated.

Recently Gami *et al.*[712] showed that obstructive sleep apnoea associated with a reduced mean nocturnal oxygen saturation <93% and a lowest nocturnal oxygen saturation <78% were independent risk factors for SCD ($P < 0.0001$). Therefore the presence of obstructive sleep apnoea should be included in panels of investigations for risk stratification for SCD.

The frequency of cardiac arrhythmias, mainly nocturnal, increases with the increased severity of sleep apnoea–hypopnea syndrome.[716–718]

12.4.1.2 Diagnosis

The most common cardiac rhythm abnormalities seen in patients with sleep apnoea–hypopnea syndrome are sinus bradycardia, sinus pause, first-degree and Mobitz I second-degree AV block and an increased rate of PVCs.[719–724] A circadian pattern of VA[712,725–729] and a higher rate of SCD during sleep time (midnight to 6 A.M.) have been demonstrated.

12.4.1.3 Treatment

At the present time there is no evidence suggesting a deviation from the standard management of VA in patients with sleep apnoea–hypopnea syndrome; furthermore, the value of continuous positive airway pressure for the prevention of VA and SCD is still undefined.[711,730–733]

Whether the appropriate treatment of obstructive sleep apnoea could modify clinical manifestations and avoid the need for pacemaker therapy in patients in whom arrhythmias are solely related to obstructive respiratory events is unknown.[733–739]

Newer innovative pacing therapies for the treatment of central sleep apnoea–hypopnea syndrome using phrenic nerve stimulation and upper airway stimulation for the obstructive form are under investigation.[740]

12.5 Drug-related pro-arrhythmia

Management of drug-related pro-arrhythmia

Recommendations	Class[a]	Level[b]	Ref.[c]
Withdrawal of offending agents is recommended whenever drug-induced arrhythmias are suspected and the presence of other arrhythmogenic substrates has been excluded.	I	B	362
Despite a possible correctable cause for VA, the need for prophylactic ICD implantation should be considered based on an individual evaluation of the future risk of life-threatening VA.	IIa	C	741, 742

VA = ventricular arrhythmia.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

12.5.1 Drug–substrate interaction due to underlying disease substrate

When drug-induced arrhythmias are suspected, any offending drug should be interrupted. In addition, a full assessment to exclude cardiovascular risk factors that could contribute to an arrhythmic episode should be performed. Drug-induced arrhythmias should be suspected if an inherited or acquired arrhythmogenic substrate has been excluded and the patient is being treated with agents known to alter the electrical properties of the heart (e.g. inducing QT prolongation) or causing electrolyte abnormalities.

In patients with LV hypertrophy, the use of sotalol has been associated with pro-arrhythmia.[743] Similarly, there is some concern about using flecainide and propafenone in these patients, particularly when significant hypertrophy (LV wall thickness >1.4 cm) and/or underlying CAD is present.[744]

Sodium channel-blocking drugs should not be used in patients with a history of myocardial infarction[129] or sustained VT due to

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structural heart disease. Other drugs with sodium channel-blocking activity, such as tricyclic antidepressants, should also be avoided in these circumstances. If ventricular function is abnormal, evaluation and treatment should be similar to that for patients experiencing VA in the absence of anti-arrhythmic drugs.

12.5.2 Drug–drug interaction (due to specific drugs and combinations)

Many non-cardiac medications inhibit potassium channels (http://www.crediblemeds.org) and are associated with a risk for TdP tachycardias in susceptible patients. Treatment with several antibiotics, such as quinolones or azithromycin, significantly increases the risk of death and cardiac arrhythmia.[125,745–747] Other macrolide antibiotics, including erythromycin and clarithromycin (metabolized also by the cytochrome P450 3A4 enzyme), have been shown to increase the risk of polymorphic VT and cardiac death, especially in women.[748] The combination of inhibitors of the renin–angiotensin system and antibiotics such as co-trimoxazole with unrecognized hyperkalaemia has been associated recently with an increased risk of sudden death.[749]

Sodium channel-blocking drugs, such as tricyclic antidepressants, may produce QRS prolongation and the typical Brugada syndrome ECG.[750] Anthracycline cardiotoxicity is dose dependent, with higher cumulative doses increasing the risk of cardiomyopathy and lethal arrhythmias.[751,752] 5-fluorouracil may cause VF due to coronary spasm.[753–755] Toad venom may produce clinical toxicity resembling that of digoxin;[756] herbal products such as foxglove tea have been reported to produce similar effects.[757,758] Many others drugs may produce coronary spasm.[759–761]

Almost independent of the specific drug that caused TdP, treatment should focus on avoiding drug treatment in high-risk patients for drug-induced arrhythmia. Intravenous magnesium can suppress episodes of TdP without necessarily shortening QT, even when serum magnesium concentration is normal.[762] Temporary pacing is highly effective in managing TdP. Isoproterenol can also be used. Withdrawal of any offending drugs and correction of electrolyte abnormalities are recommended in these patients.

12.5.3 Pro-arrhythmic risk of anti-arrhythmic drugs

Anti-arrhythmic drugs have direct effects on cardiac ion channels. Flecainide, propafenone and quinidine have sodium channel-blocking effects.[763] In large clinical trials such as CAST and CASH, sodium channel-blocking drugs increased mortality among patients with previous myocardial infarction.[129,764] Similar trends were seen in earlier trials of mexiletine[363] and disopyramide.[362] In patients treated for sustained VT, these agents may provoke more frequent, and often more difficult to cardiovert, episodes of sustained VT.[765,766]

D-sotalol, the QT-prolonging agent (a pure class III anti-arrhythmic), slightly increased mortality in a large RCT in patients with remote infarction.[137] In the Danish Investigators of Arrhythmia and Mortality on Dofetilide (DIAMOND) trial, 3.3% of patients with severe HF had TdP during the first 72 h of dofetilide therapy.[767] Amiodarone may cause TdP much less commonly than other QT-prolonging anti-arrhythmics.[768]

Bradyarrhythmias are common pharmacological effects of digoxin, verapamil, diltiazem and beta-blockers. Some arrhythmias are typical of digitalis toxicity: enhanced atrial, junctional or ventricular automaticity often combined with AV block.

In most cases, management includes discontinuing the drug, monitoring rhythm and maintaining normal serum potassium. Intravenous magnesium and temporary pacing can be useful.[762] Isoproterenol can also be used to increase heart rate and shorten ventricular action potential duration, to eliminate depolarizations and TdP.[762,769–771]

12.5.4 Pro-arrhythmia due to triggering factors

Several triggering factors, such as hypokalaemia (<3.5 mM), a rapid rise in extracellular potassium and hypomagnesaemia, are associated with VA and SCD.[772,773] Hypomagnesaemia is classically associated with polymorphic VT or TdP, which may respond to i.v. magnesium.[774,775] Hypokalaemia with or without hypomagnesaemia may be responsible for VAs in subjects with hypertension and congestive cardiac failure (precipitated by the use of thiazide and loop diuretics).[774] Multiple factors, such as bradycardia, ischaemia, coronary spasm, thrombosis, acute starvation[776] and acute alcohol toxicity/withdrawal,[777,778] may facilitate development of VAs and SCD. ICDs may also cause the appearance of VA.[779–781]

Withdrawal of any offending drugs and correction of electrolyte abnormalities are recommended in these patients.

12.6 Sudden cardiac death after heart transplantation

Many clinical studies have demonstrated that sudden death is frequent after heart transplantation (>10% of cardiac transplant recipients).[782] Some patients may have sudden death after a history of several episodes of severe rejection.

In patients with acute rejection, the conduction system may be damaged, leading to VA and sudden death. These hearts may be at increased risk of developing arrhythmias during the haemodynamic stresses of haemodialysis or plasmapheresis.[783] Coronary disease is found in most of the heart transplant patients with sudden death; it may be due to hyperkalaemia, haemodialysis or plasmapheresis as triggers of the event, but it may also be a primary arrhythmic death.

The use of an ICD after heart transplantation may be appropriate in selected high-risk patients.[784]

12.7 Sudden cardiac death in athletes

Prevention of sudden cardiac death in athletes

Recommendations	Class[a]	Level[b]	Ref.[c]
Careful history taking to uncover underlying cardiovascular disease, rhythm disorder, syncopal episodes or family history of SCD is recommended in athletes.	I	C	This panel of experts

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Upon identification of ECG abnormalities suggestive of structural heart disease, echocardiography and/or CMR imaging is recommended.	I	C	This panel of experts
Physical examination and resting 12-lead ECG should be considered for pre-participation screening in younger athletes.	IIa	C	This panel of experts
Middle-aged individuals engaging in high-intensity exercise should be screened with history, physical examination, SCORE and resting ECG.	IIa	C	785
Staff at sporting facilities should be trained in cardiopulmonary resuscitation and on the appropriate use of automatic external defibrillators.	IIa	C	179, 786

CMR = cardiac magnetic resonance; ECG = electrocardiogram; SCD = sudden cardiac death; SCORE = Systematic Coronary Risk Evaluation.[787]
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

Athletes appear at excessive risk of SCD compared with similar-aged non-athletes:[26] the annual incidence of SCD in young athletes (<35 years) is estimated to range from 0.7 to 3.0 per 100 000 athletes.[788] In older athletes the incidence is higher and is expected to increase with age.[789] The intensity of the activity and the age of the athlete are core risk factors.

The most frequent causes of sudden death in younger athletes are inherited arrhythmogenic disorders (cardiomyopathies and channelopathies) and CAD (both congenital and acquired). In the US, the National Registry of Sudden Death in Athletes was established at the Minneapolis Heart Institute in the 1980s and has reported on 1866 sudden deaths in individuals <40 years of age during a 27-year observational period. Their data show that 36% of all sudden deaths in this registry are attributed to confirmed cardiovascular causes, of which the most frequent are HCM (36%), congenital anomalies of the coronary arteries (17%), myocarditis (6%), ARVC (4%) and channelopathies (3.6%).[27] In Italy, investigators in the Veneto region conducted a prospective cohort study enrolling individuals <36 years of age involved in competitive sports between 1979 and 1999. ARVC was found as a cause of SCD in 24% of these athletes, followed by atherosclerotic CAD (20%), anomalous origin of coronary arteries (14%) and mitral valve prolapse (12%).[26] In older athletes (>35–40 years), as in the general population, coronary atherosclerotic disease accounts for more than half of cases.[29]

Pre-participation screening appears efficient[790] in preventing SCD, but the screening programmes vary greatly in European countries and between Europe and the US.[791] Cardiac screening should be adapted to the age of the athlete to account for age-specific risk factors. In young athletes (≤35 years of age), screening should focus on inheritable cardiomyopathies and channelopathies (see Sections 8 and 9). In older athletes, CAD is the most common cause of SCD and screening should also be targeted to detect signs of ischaemia.[792]

The European Association of Cardiovascular Prevention and Rehabilitation has issued recommendations for cardiovascular evaluation of middle-aged/senior active individuals engaged in leisure time sport activities.[792] The risk-assessment scheme for active middle-aged individuals is outlined in *Figure 4*.

Recently Menafoglio *et al.*[785] assessed the implications on the workload, yield and economic costs of this preventive strategy in 785 athletes ages 35–56 years engaged in high-intensity sport. A new cardiovascular abnormality was established in 2.8% of athletes and the cost was $199 per athlete. The authors concluded that the overall evaluation seems to be feasible with a reasonable cost.[785]

It is important that coaches and staff at sporting facilities are trained to face emergency situations, perform cardiopulmonary resuscitation and use automatic external defibrillators.[179,786]

12.8 Wolff–Parkinson–White syndrome

Management of patients with Wolff-Parkinson-White Syndrome

Recommendations	Class[a]	Level[b]	Ref.[c]
Ablation is recommended in patients with WPW syndrome resuscitated from sudden cardiac arrest due to AF and rapid conduction over the accessory pathway causing VF.	I	B	793
Ablation should be considered in patients with WPW syndrome who are symptomatic and/or who have accessory pathways with refractory periods ≤240 ms in duration.	IIa	B	793

AF = atrial fibrillation; VF = ventricular fibrillation; WPW: Wolff–Parkinson–White.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

Wolff–Parkinson–White (WPW) syndrome is a fairly uncommon cause of SCD, with an estimated incidence of between 0.05 and 0.2% per year.[794] SCD may occur due to the development of AF with a rapid ventricular response that degenerates to VF.[795] The principal risk factor for SCD is the presence of an accessory pathway with short antegrade refractoriness. In a recent 8-year prospective registry of 2169 patients with WPW syndrome, SCD occurred primarily in patients with accessory pathway antegrade refractory periods ≤240 ms and AV re-entrant tachycardia initiating AF.[793]

An EPS with ablation is recommended in patients with WPW syndrome resuscitated from aborted cardiac arrest due to AF and rapid conduction over the accessory pathway causing VF.[796] An EPS should be considered and ablation performed if the patient is symptomatic (e.g. with syncope or palpitations) and/or the refractory period of the accessory pathway is ≤240 ms.[793] The EPS should include measurement of the shortest pre-excited RR interval during induced AF (or the shortest pre-excited RR interval during rapid atrial pacing), determination of the number and location of accessory pathways, the anterograde and retrograde characteristics of the accessory pathways and AV node and the effective refractory period

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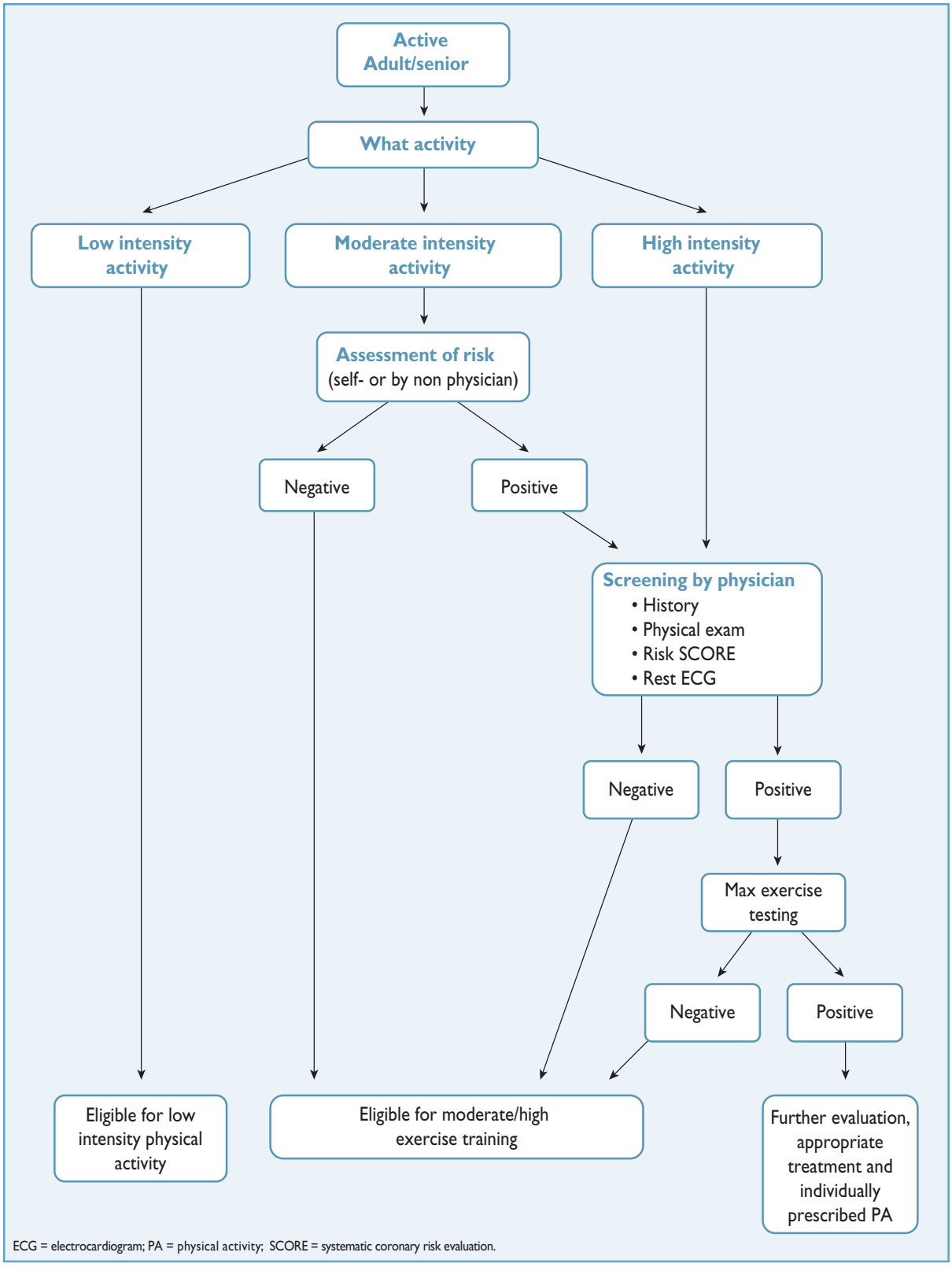

Figure 4 Proposed pre-participation evaluation protocol for asymptomatic active adult or senior individuals. Adapted with permission from Borjesson *et al.*[792]

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of the accessory pathways and of the ventricle at multiple cycle lengths.

Treatment with calcium antagonists (verapamil) or digoxin should be avoided in patients with WPW because these medications may enhance antegrade conduction through the accessory pathway by increasing the refractory period in the AV node.

12.9 Prevention of sudden cardiac death in the elderly

The use of anti-arrhythmic drugs in elderly patients should be adjusted to account for decreased renal and hepatic clearance, changes in body composition and the presence of co-morbidities. The risk of drug interactions should also be taken into consideration and dose adjustment may be required. In the absence of specific contraindications, beta-blockers should be considered in elderly patients after acute myocardial infarction, as they have been shown to prevent SCD in patients >65 years of age.[797]

ICDs are used extensively in the elderly: subgroup analyses in both the AVID and MADIT-II trials demonstrated equivalent benefits from ICD in older and younger patients.[63,153] A meta-analysis combining data from trials on primary prevention of SCD [Multicenter UnSustained Tachycardia Trial (MUSTT), MADIT-II, DEFINITE and SCD-HeFT] found that ICD therapy reduces all-cause mortality in patients ≥75 years of age in the absence of ICD-related complications [HR 0.73 (95% CI 0.51, 0.974), $P = 0.03$].[798] Interestingly, however, a different meta-analysis suggested that ICD therapy might be less beneficial in elderly patients with severe LV dysfunction [HR 0.75 (95% CI 0.61, 0.91)].[799] Pooled data from secondary prevention trials (AVID, CASH and CIDS) revealed that ICD therapy significantly reduced all-cause and arrhythmic death in patients ≤75 years old, but not in patients ≥75 years [all-cause death HR 1.06 (95% CI 0.69, 1.64), $P = 0.79$; arrhythmic death HR 0.90 (95% CI 0.42, 1.95), $P = 0.79$].[800] Observational studies and registry data from everyday clinical practice in primary prevention demonstrate that age alone should not preclude device implantation.[801,802]

The decision to implant an ICD should consider the consequences of the device on quality of life: in a MADIT-II substudy, no significant decrease in quality-adjusted life-years for patients ≥65 years was established.[803] In general, age is not among the criteria considered for appropriate use of the ICD, as octogenarians who die suddenly can be highly functional even in the month before their death.[804] Clinical judgement coupled with the wishes of the patient and/or family may contribute to the decision to deviate from standard recommendations for the use of the ICD.

12.10 End-of-life issues

Management of end-of-life issues

Recommendations	Class[a]	Level[b]	Ref.[c]
Discussion of end-of-life issues with patients who qualify for the implant of an ICD should be considered before implantation and at significant points along the illness trajectory.	IIa	C	805, 806
ICD deactivation should be considered when clinical conditions deteriorate.	IIa	C	805, 806

ICD = implantable cardioverter defibrillator.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

Terminally ill patients frequently develop conditions predisposing to arrhythmias (hypoxia, pain and electrolyte disturbances) and up to 20% of those with an ICD receive shocks in the last weeks of their life.[805,807,808]

Discussing deactivation of the ICD with the patient and family to prevent undue distress and pain to a person who is dying is an important but often neglected necessity. Individual consideration should be given to the patient's desires, honouring both informed consent and informed refusal. When patients are unable to make this decision themselves, a family member or surrogate decision maker should be heard or the living will of the patient should be complied with, if such exists.[805,808,809]

Owing to the complexity of the issue, exhaustive information on how to implement the recommendations can be found in two consensus documents by the EHRA[805] and the Heart Rhythm Society.[809] In addition, local rules and legislation should be taken into account.

Deactivation can be done by device programming or, if this is not available, by application of a magnet directly over the device. It may be preferable to suspend only antitachycardia therapies and maintain pacing for bradycardia to avoid symptomatic deterioration.

13. Gaps in evidence

- The first clinical manifestation of sudden death is often lethal. Therefore identification of patients at risk for sudden death remains the philosopher's stone of sudden death prevention. Risk stratification for primary prevention of SCD with invasive and non-invasive techniques is still unsatisfactory. Novel approaches including genetic profiling, ECG screening and imaging techniques need to be assessed. Research into the best methods to detect asymptomatic populations at risk for sudden death is urgently needed. Simple and cheap methods appropriate for mass screening are needed.
- Ensuring an effective and rapid chain of care is of utmost importance to improve survival of sudden death victims. More research is needed to evaluate the optimal design of such survival chains including pre-hospital care and in-hospital protocols.
- The successes in preventing CAD and HF due to myocardial infarctions have substantially reduced sudden death rates. Further research into the other causes of sudden death is needed to further reduce sudden death rates.
- More than half of sudden death victims have a preserved LV function. Specific research programmes to understand the mechanisms causing sudden death in patients with preserved LV function is urgently needed, probably requiring interdisciplinary

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approaches including cardiologists, geneticists, epidemiologists, and basic and translational scientists. Such research should encompass better detection of patients with inherited cardiomyopathies and inherited arrhythmogenic disorders, sudden death risk stratification in patients with HF and preserved EF and sudden death risk assessment in patients with AF.

- Wearable defibrillators may be an interesting therapeutic option in selected patients but require larger randomized trials before clear indications can be fully defined.
- Randomized trials on the feasibility of risk stratification with invasive electrophysiological study early after myocardial infarction are warranted.
- More than a decade has passed since the publication of landmark RCTs on primary prevention of SCD, which have served until the present as the basis for ICD use in patients with LV systolic dysfunction and HF. Patient profiles and medical treatments have changed significantly since then: today's patients are older and have more co-morbidities such as AF, chronic kidney disease and others. Thus new clinical trials are needed to assess the potential benefit of primary prevention of SCD with an ICD for today's patient population. As no relevant new RCTs are under way, data from prospective registries might shed more light on this clinically very important issue.
- More research is needed to establish evidence-based interventions to reduce the psychosocial impact and optimize care and support for patients and families at risk of SCD.
- Many patients with reduced ejection fraction will experience an improvement in LVEF over time. Some of these patients will receive a defibrillator without a clear need, while others may remain at risk for sudden death despite recovery of LV function. More research into the best assessment of these patients is needed to allow better, personalized sudden death management.
- The use of CRT(-D) in patients with AF and the place of AV nodal ablation has not been well defined outside of observational datasets. There is a clear need for adequately powered randomized trials in this common patient group.
- The field of inherited arrhythmias and cardiomyopathies has faced major advances in the last 20 years, mainly due to the widespread availability of genetic diagnosis and the availability of clinical data from large registries. However, key gaps in evidence still exist. A large number of patients with primary inherited arrhythmias and cardiomyopathies still die before a diagnosis is made, thus suggesting the need for improved diagnostic approaches. Knowledge gaps also exist in risk-stratification schemes for diseases such as Brugada syndrome, SQTS, ARVC and most of the non-ischaemic dilated cardiomyopathies.
- VTs worsen the prognosis of patients with a variety of structural heart diseases. New anti-arrhythmic or other medical therapy is urgently needed to allow a broader population to be protected from first or recurrent life-threatening VAs. It remains to be tested whether specific anti-arrhythmic treatment can improve that prognosis. While catheter ablation of recurrent VT in patients with structural heart disease has been shown to significantly reduce the number of VT recurrences, the impact of VT catheter ablation on mortality is unclear and warrants investigation.

14. To do and not to do messages from the guidelines

General population	Class[a]	Level[b]
The analysis of blood and other adequately collected body fluids for toxicology and molecular pathology is recommended in all victims of unexplained sudden death.	I	C
It is recommended that public access defibrillation be established at sites where cardiac arrest is relatively common and suitable storage is available (e.g. schools, sports stadiums, large stations, casinos, etc.) or at sites where no other access to defibrillation is available (e.g. trains, cruise ships, airplanes, etc.).	I	B
Patients with ICD indications		
Discussion of quality-of-life issues is recommended before ICD implant and during disease progression in all patients.	I	C
Ischaemic heart disease		
Re-evaluation of LVEF 6–12 weeks after myocardial infarction is recommended to assess the potential need for primary prevention ICD implantation.	I	C
Patients with heart failure		
ICD therapy is recommended to reduce SCD in patients with symptomatic HF (NYHA class II or III) and LVEF ≤35% after ≥3 months of optimal medical therapy who are expected to survive at least 1 year with good functional status:		
– Ischaemic aetiology and at least 6 weeks after myocardial infarction	I	A
– Non-ischaemic aetiology	I	B
To reduce all-cause mortality, CRT-D is recommended in patients with a QRS duration ≥130 ms, with an LVEF ≤30% and with an LBBB despite at least 3 months of optimal pharmacological therapy who are expected to survive at least 1 year with good functional status.	I	A
To reduce all-cause mortality, CRT is recommended in patients with an LVEF ≤35% and LBBB despite at least 3 months of optimal pharmacological therapy who are expected to survive at least 1 year with good functional status:		
– With a QRS duration >150 ms	I	A
– With a QRS duration of 120–150 ms	I	B
Inherited arrhythmogenic diseases		
Avoidance of competitive sports is recommended in patients with ARVC.	I	C

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Emerging recommendations		
Flecainide should be considered in addition to beta-blockers in patients with a diagnosis of CPVT who experience recurrent syncope or polymorphic/bidirectional VT while on beta-blockers when there are risks/ contraindications for an ICD or an ICD is not available or is rejected by the patient.	IIa	C
An ICD should be considered in patients with DCM and a confirmed disease-causing *LMNA* mutation and clinical risk factors.	IIa	B

ARVC = arrhythmogenic right ventricular cardiomyopathy; CPVT = catecholaminergic polymorphic ventricular tachycardia; CRT-D = cardiac resynchronization therapy defibrillator; DCM = dilated cardiomyopathy; HF = heart failure; ICD = implantable cardioverter defibrillator; LBBB = left bundle branch block; *LMNA* = lamin A/C; LVEF = left ventricular ejection fraction; ms = milliseconds; NYHA = New York Heart Association; SCD = sudden cardiac death; VT = ventricular tachycardia.
[a]Class of recommendation.
[b]Level of evidence.

15. Web addenda

All Web figures and Web tables are available in the online addenda at: http://www.escardio.org/Guidelines-&-Education/Clinical-Practice-Guidelines/Ventricular-Arrhythmias-and-the-Prevention-of-Sudden-Cardiac-Death

16. Appendix

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