

## AHA/ACC/HRS GUIDELINE

# 2017 AHA/ACC/HRS Guideline for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death

A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society

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see page e354

**Key Words:** AHA Scientific Statements  
■ acute coronary syndrome ■  
ambulatory ECG monitoring ■  
antiarrhythmic drug therapy ■  
arrhythmogenic cardiomyopathy ■  
athletes ■ cardiac electrophysiology  
■ cardiac resynchronization therapy ■  
cardiomyopathy ■ catheter ablation  
■ congenital heart disease ■ CT  
imaging ■ ECG ■ echocardiography ■  
electrophysiological testing ■ genetic  
arrhythmias ■ guidelines ■ heart failure  
■ imaging ■ implantable cardioverter-  
defibrillator ■ implantable and external  
cardioverter devices ■ medication-  
induced arrhythmias ■ MR imaging  
■ myocardial infarction ■ premature  
ventricular beats ■ resuscitation ■  
sarcoidosis ■ specific pathology (eg,  
congenital heart disease, myocarditis,  
renal failure) ■ stable coronary artery  
disease ■ sudden cardiac arrest ■  
sudden cardiac death ■ torsades de  
pointes ■ ventricular fibrillation ■  
ventricular tachycardia

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## PREAMBLE

Since 1980, the American College of Cardiology (ACC) and American Heart Association (AHA) have translated scientific evidence into clinical practice guidelines with recommendations to improve cardiovascular health. These guidelines, which are based on systematic methods to evaluate and classify evidence, provide a cornerstone for quality cardiovascular care. The ACC and AHA sponsor the development and publication of guidelines without commercial support, and members of each organization volunteer their time to the writing and review efforts. Guidelines are official policy of the ACC and AHA.

## Intended Use

Practice guidelines provide recommendations applicable to patients with or at risk of developing cardiovascular disease. The focus is on medical practice in the United States, but guidelines developed in collaboration with other organizations may have a global impact. Although guidelines may be used to inform regulatory or payer decisions, their intent is to improve patients' quality of care and align with patients' interests. Guidelines are intended to define practices meeting the needs of patients in most, but not all, circumstances and should not replace clinical judgment.

## Clinical Implementation

Guideline-recommended management is effective only when followed by healthcare providers and patients. Adherence to recommendations can be enhanced by shared decision-making between healthcare providers and patients, with patient engagement in selecting interventions based on individual values, preferences, and associated conditions and comorbidities.

## Methodology and Modernization

The ACC/AHA Task Force on Clinical Practice Guidelines (Task Force) continuously reviews, updates, and modifies guideline methodology on the basis of published standards from organizations including the Institute of Medicine<sup>P-1, P-2</sup> and on the basis of internal reevaluation. Similarly, the presentation and delivery of guidelines are reevaluated and modified on the basis of evolving technologies and other factors to facilitate optimal dissemination

of information at the point of care to healthcare professionals.

Toward this goal, this guideline heralds the introduction of an evolved format of presenting guideline recommendations and associated text called the "modular knowledge chunk format." Each modular "chunk" includes a table of related recommendations, a brief synopsis, recommendation-specific supportive text and, when appropriate, flow diagrams or additional tables. References are provided within the modular chunk itself to facilitate quick review. This format also will facilitate seamless updating of guidelines with focused updates as new evidence is published, and content tagging for rapid electronic retrieval of related recommendations on a topic of interest. This evolved format was instituted when this guideline was near completion; therefore, the current document represents a transitional formatting that best suits the text as written. Future guidelines will fully implement this format, including provisions for limiting the amount of text in a guideline.

Recognizing the importance of cost-value considerations in certain guidelines, when appropriate and feasible, an analysis of the value of a medication, device, or intervention may be performed in accordance with the ACC/AHA methodology.<sup>P-3</sup>

To ensure that guideline recommendations remain current, new data are reviewed on an ongoing basis, with full guideline revisions commissioned in approximately 6-year cycles. Publication of new, potentially practice-changing study results that are relevant to an existing or new medication, device, or management strategy will prompt evaluation by the Task Force, in consultation with the relevant guideline writing committee, to determine whether a focused update should be commissioned. For additional information and policies regarding guideline development, we encourage readers to consult the ACC/AHA guideline methodology manual<sup>P-4</sup> and other methodology articles.<sup>P-5–P-8</sup>

## Selection of Writing Committee Members

The Task Force strives to avoid bias by selecting experts from a broad array of backgrounds. Writing committee members represent different geographic regions, sexes, ethnicities, races, intellectual perspectives/biases, and scopes of clinical practice. The Task Force may also invite organizations and professional societies with related interests and expertise to participate as partners, collaborators, or endorsers.

## Relationships With Industry and Other Entities

The ACC and AHA have rigorous policies and methods to ensure that guidelines are developed without bias or improper influence. The complete relationships with industry and other entities (RWI) policy can be found

online. Appendix 1 of the current document lists writing committee members' relevant RWI. For the purposes of full transparency, writing committee members' comprehensive disclosure information is available [online](#), as is the [comprehensive disclosure information for the Task Force](#).

## Evidence Review and Evidence Review Committees

When developing recommendations, the writing committee uses evidence-based methodologies that are based on all available data.<sup>P-4-P-7</sup> Literature searches focus on randomized controlled trials (RCTs) but also include registries, nonrandomized comparative and descriptive studies, case series, cohort studies, systematic reviews, and expert opinion. Only key references are cited.

An independent evidence review committee (ERC) is commissioned when there are  $\geq 1$  questions deemed of utmost clinical importance that merit formal systematic review. This systematic review will strive to determine which patients are most likely to benefit from a test, medication, device, or treatment strategy and to what degree. Criteria for commissioning an ERC and formal systematic review include: a) the absence of a current authoritative systematic review; b) the feasibility of defining the benefit and risk in a time frame consistent with the writing of a guideline; c) the relevance to a substantial number of patients; and d) the likelihood that the findings can be translated into actionable recommendations. ERC members may include methodologists, epidemiologists, healthcare providers, and biostatisticians. When a formal systematic review has been commissioned, the recommendations developed by the writing committee on the basis of the systematic review are marked with "SR."

## Guideline-Directed Management and Therapy

The term *guideline-directed management and therapy* (GDMT) encompasses clinical evaluation, diagnostic testing, and pharmacological and procedural treatments. For these and all recommended medication treatment regimens, the reader should confirm the dosage by reviewing product insert material and evaluate the treatment regimen for contraindications and interactions. The recommendations are limited to medications, devices, and treatments approved for clinical use in the United States.

## Class of Recommendation and Level of Evidence

The Class of Recommendation (COR) indicates the strength of the recommendation, encompassing the estimated magnitude and certainty of benefit in proportion to risk. The Level of Evidence (LOE) rates the quality of scientific evidence that supports the intervention on the

basis of the type, quantity, and consistency of data from clinical trials and other sources (Table 1).<sup>P-4,P-6,P-8</sup>

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Chair, ACC/AHA Task Force on Clinical Practice Guidelines

## 1. INTRODUCTION

### 1.1. Methodology and Evidence Review

The recommendations listed in this clinical practice guideline are, whenever possible, evidence-based. An initial extensive evidence review, which included literature derived from research involving human subjects, published in English, and indexed in MEDLINE (through PubMed), EMBASE, the Cochrane Library, the Agency for Healthcare Research and Quality, and other selected databases relevant to this guideline, was conducted from April 2016 to September 2016. Key search words included, but were not limited, to the following: sudden cardiac death, ventricular tachycardia, ventricular fibrillation, premature ventricular contractions, implantable cardioverter-defibrillator, subcutaneous implantable cardioverter-defibrillator, wearable cardioverter-defibrillator, and catheter ablation. Additional relevant studies published through March 2017, during the guideline writing process, were also considered by the writing committee, and added to the evidence tables when appropriate. The final evidence tables are included in the [Online Data Supplement](#) and summarize the evidence used by the writing committee to formulate recommendations. Additionally, the writing committee reviewed documents related to ventricular arrhythmias (VA) and sudden cardiac death (SCD) previously published by the ACC, AHA, and the Heart Rhythm Society (HRS). References selected and published in this document are representative and not all-inclusive.

As noted in the Preamble, an independent ERC was commissioned to perform a formal systematic review of 2 important clinical questions for which clear literature and prior guideline consensus were felt to be lacking or limited (Table 2). The results of the ERC review were considered by the writing committee for incorporation into this guideline. Concurrent with this process, writing committee members evaluated other published data relevant to the guideline. The findings of the ERC and the writing committee members were formally presented and discussed, then guideline recommendations were developed. The "Systematic Review for the 2017 AHA/ACC/HRS Guideline for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death" is published in conjunction with this guideline.<sup>S1.4-1</sup>

The ACC and AHA have acknowledged the importance of value in health care and have called for eventual development of a Level of Value for clinical practice recommendations.<sup>S1.4-2</sup> Available cost-effectiveness data were determined to be sufficient to support 2 specific

**Table 1. Applying Class of Recommendation and Level of Evidence to Clinical Strategies, Interventions, Treatments, or Diagnostic Testing in Patient Care\* (Updated August 2015)**

CLASS (STRENGTH) OF RECOMMENDATION	LEVEL (QUALITY) OF EVIDENCE‡
<p><b>CLASS I (STRONG)</b> <span style="float:right">Benefit &gt;&gt;&gt; Risk</span></p> <p>Suggested phrases for writing recommendations:</p> <ul style="list-style-type: none"> <li>■ Is recommended</li> <li>■ Is indicated/useful/effective/beneficial</li> <li>■ Should be performed/administered/other</li> <li>■ Comparative-Effectiveness Phrases†:                             <ul style="list-style-type: none"> <li>○ Treatment/strategy A is recommended/indicated in preference to treatment B</li> <li>○ Treatment A should be chosen over treatment B</li> </ul> </li> </ul>	<p><b>LEVEL A</b></p> <ul style="list-style-type: none"> <li>■ High-quality evidence‡ from more than 1 RCT</li> <li>■ Meta-analyses of high-quality RCTs</li> <li>■ One or more RCTs corroborated by high-quality registry studies</li> </ul>
<p><b>CLASS IIa (MODERATE)</b> <span style="float:right">Benefit &gt;&gt; Risk</span></p> <p>Suggested phrases for writing recommendations:</p> <ul style="list-style-type: none"> <li>■ Is reasonable</li> <li>■ Can be useful/effective/beneficial</li> <li>■ Comparative-Effectiveness Phrases†:                             <ul style="list-style-type: none"> <li>○ Treatment/strategy A is probably recommended/indicated in preference to treatment B</li> <li>○ It is reasonable to choose treatment A over treatment B</li> </ul> </li> </ul>	<p><b>LEVEL B-R (Randomized)</b></p> <ul style="list-style-type: none"> <li>■ Moderate-quality evidence‡ from 1 or more RCTs</li> <li>■ Meta-analyses of moderate-quality RCTs</li> </ul>
<p><b>CLASS IIb (WEAK)</b> <span style="float:right">Benefit ≥ Risk</span></p> <p>Suggested phrases for writing recommendations:</p> <ul style="list-style-type: none"> <li>■ May/might be reasonable</li> <li>■ May/might be considered</li> <li>■ Usefulness/effectiveness is unknown/unclear/uncertain or not well established</li> </ul>	<p><b>LEVEL B-NR (Nonrandomized)</b></p> <ul style="list-style-type: none"> <li>■ Moderate-quality evidence‡ from 1 or more well-designed, well-executed nonrandomized studies, observational studies, or registry studies</li> <li>■ Meta-analyses of such studies</li> </ul>
<p><b>CLASS III: No Benefit (MODERATE)</b> <span style="float:right">Benefit = Risk</span> <i>(Generally, LOE A or B use only)</i></p> <p>Suggested phrases for writing recommendations:</p> <ul style="list-style-type: none"> <li>■ Is not recommended</li> <li>■ Is not indicated/useful/effective/beneficial</li> <li>■ Should not be performed/administered/other</li> </ul>	<p><b>LEVEL C-LD (Limited Data)</b></p> <ul style="list-style-type: none"> <li>■ Randomized or nonrandomized observational or registry studies with limitations of design or execution</li> <li>■ Meta-analyses of such studies</li> <li>■ Physiological or mechanistic studies in human subjects</li> </ul>
<p><b>CLASS III: Harm (STRONG)</b> <span style="float:right">Risk &gt; Benefit</span></p> <p>Suggested phrases for writing recommendations:</p> <ul style="list-style-type: none"> <li>■ Potentially harmful</li> <li>■ Causes harm</li> <li>■ Associated with excess morbidity/mortality</li> <li>■ Should not be performed/administered/other</li> </ul>	<p><b>LEVEL C-EO (Expert Opinion)</b></p> <p>Consensus of expert opinion based on clinical experience</p>

COR and LOE are determined independently (any COR may be paired with any LOE).  
 A recommendation with LOE C does not imply that the recommendation is weak. Many important clinical questions addressed in guidelines do not lend themselves to clinical trials. Although RCTs are unavailable, there may be a very clear clinical consensus that a particular test or therapy is useful or effective.  
 \* The outcome or result of the intervention should be specified (an improved clinical outcome or increased diagnostic accuracy or incremental prognostic information).  
 † For comparative-effectiveness recommendations (COR I and IIa; LOE A and B only), studies that support the use of comparator verbs should involve direct comparisons of the treatments or strategies being evaluated.  
 ‡ The method of assessing quality is evolving, including the application of standardized, widely used, and preferably validated evidence grading tools; and for systematic reviews, the incorporation of an Evidence Review Committee.  
 COR indicates Class of Recommendation; EO, expert opinion; LD, limited data; LOE, Level of Evidence; NR, nonrandomized; R, randomized; and RCT, randomized controlled trial.

recommendations in this guideline (see Sections 7.1.1 and 7.1.2). As a result, a Level of Value was assigned to those 2 recommendations on the basis of the “ACC/AHA Statement on Cost/Value Methodology in Clinical Practice Guidelines and Performance Measures,” as shown in Table 3.<sup>51,4-2</sup> Available quality of life (QoL) data were deemed to be insufficient to support specific recommendations in this guideline.

### 1.2. Organization of the Writing Committee

The writing committee consisted of cardiac electrophysiologists (including those specialized in pediatrics),

general adult and pediatric cardiologists (including those specialized in critical care and acute coronary syndromes [ACS], genetic cardiology, heart failure, and cost-effectiveness analyses), a geriatrician with expertise in terminal care and shared decision-making, and a lay representative, in addition to representatives from the ACC, AHA, HRS, and the Heart Failure Society of America (HFSA).

### 1.3. Document Review and Approval

This document was reviewed by 2 official reviewers nominated by the ACC, AHA, and HRS; 1 official lay re-

**Table 2. Systematic Review Questions on SCD Prevention**

Question Number	Question	Section Number
1	For asymptomatic patients with Brugada syndrome, what is the association between an abnormal programmed ventricular stimulation study and SCD and other arrhythmia endpoints?	7.9.1.3
2	What is the impact of ICD implantation for primary prevention in older patients and patients with significant comorbidities?	10.3

ICD indicates implantable cardioverter-defibrillator; and SCD, sudden cardiac death.

viewer nominated by the AHA; 1 organizational reviewer nominated by the HFSA; and 28 individual content reviewers. Reviewers' RWI information was distributed to the writing committee and is published in this document (Appendix 2).

This document was approved for publication by the governing bodies of the ACC, the AHA, and the HRS; and endorsed by the HFSA.

### 1.4. Scope of the Guideline

The purpose of this AHA/ACC/HRS document is to provide a contemporary guideline for the management of adults who have VA or who are at risk for SCD, including diseases and syndromes associated with a risk of SCD from VA. This guideline supersedes the "ACC/AHA/ESC 2006 Guidelines for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death."<sup>51.4-4</sup> It also supersedes some sections of the "ACC/AHA/HRS 2008 Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities,"<sup>51.4-5</sup> specifically those sections on indications for the implantable cardioverter-defibrillator (ICD); and, it updates the SCD prevention recommendations in the "2011 ACCF/AHA

**Table 3. Proposed Integration of Level of Value Into Clinical Practice Guideline Recommendations\***

Level of Value
High value: Better outcomes at lower cost or ICER <\$50 000 per QALY gained
Intermediate value: \$50 000 to <\$150 000 per QALY gained
Low value: ≥\$150 000 per QALY gained
Uncertain value: Value examined but data are insufficient to draw a conclusion because of no studies, low-quality studies, conflicting studies, or prior studies that are no longer relevant
Not assessed: Value not assessed by the writing committee
Proposed abbreviations for each value recommendation: Level of Value: H to indicate high value; I, intermediate value; L, low value; U, uncertain value; and NA, value not assessed

\*Dollar amounts used in this table are based on US GDP data from 2012 and were obtained from WHO-CHOICE Cost-Effectiveness Thresholds.<sup>51.4-3</sup>

GDP indicates gross domestic product; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-years; and WHO-CHOICE, World Health Organization Choosing Interventions that are Cost-Effective. Reproduced from Anderson, et al.<sup>51.4-2</sup>

Guideline for the Diagnosis and Treatment of Hypertrophic Cardiomyopathy."<sup>51.4-6</sup> Some recommendations from the earlier guidelines have been updated as warranted by new evidence or a better understanding of existing evidence, and irrelevant or overlapping recommendations were deleted or modified.

In the current guideline, sudden cardiac arrest (SCA) is defined as the "sudden cessation of cardiac activity so that the victim becomes unresponsive, with no normal breathing and no signs of circulation."<sup>51.4-7</sup> If corrective measures are not taken rapidly, this condition progresses to SCD. Cardiac arrest is used to signify an event that can be reversed, usually by cardiopulmonary resuscitation (CPR), administration of medications and/or defibrillation or cardioversion. SCA and SCD can result from causes other than VA, such as bradyarrhythmias, electromechanical dissociation, pulmonary embolism, intracranial hemorrhage, and aortic dissection; however, the scope of this document includes only SCA and SCD due to VA.

This guideline includes indications for ICDs for the treatment of VA and prevention of SCD, but it does not delve into details on individual device selection and programming, including considerations relevant to cardiac resynchronization therapy (CRT), bradycardia pacing, and hemodynamic monitoring. These important aspects of ICD management have been covered in an HRS expert consensus statement.<sup>51.4-8</sup> An AHA science advisory discusses the use of wearable cardioverter-defibrillators.<sup>51.4-9</sup> The findings of that document were reviewed; however, recommendations on this topic were developed independently of that document. This guideline includes indications for catheter ablation of VA, but does not provide recommendations on specific techniques or ablation technologies, which were beyond the scope of this document.

Recommendations for interventional therapies, including ablation and the implantation of devices, apply only if these therapies can be implemented by qualified clinicians, such that outcomes consistent with published literature are a reasonable expectation. The writing committee agreed that a high degree of expertise was particularly important for performance of catheter ablation of VA, and this point is further emphasized in relevant sections. In addition, all recommendations related to ICDs require that meaningful survival of >1 year is expected; meaningful survival means that a patient has a reasonable quality of life and functional status.

Although this document is aimed at the adult population (≥18 years of age) and offers no specific recommendations for pediatric patients, some of the literature on pediatric patients was examined. In some cases, the data from pediatric patients beyond infancy helped to inform this guideline.

The writing committee recognized the importance of shared decision-making and patient-centered care and, when possible, it endeavored to formulate recommenda-

tions relevant to these important concepts. The importance of a shared decision-making process in which the patient, family, and clinicians discuss risks and benefits of diagnostic and treatment options and consider the patients' personal preferences is emphasized (see Section 15).

In developing this guideline, the writing committee reviewed previously published guidelines and related statements. Table 4 contains a list of guidelines and statements deemed pertinent to this writing effort and is intended for use as a resource, obviating repetition of existing guideline recommendations.

During final production review of the guidelines, several recommendations were refined to better reflect

the data and current recommended medical practice. These refinements were reviewed and approved by the writing committee, the Task Force, and ACC, AHA, and HRS organizational leadership. These recommendations were:

- Section 7.1.1., recommendation 1
- Section 7.1.3., recommendation 2
- Section 7.2.1., recommendation 1
- Section 7.9.1.4., recommendation 2
- Section 10.8., recommendation 6

Readers should refer to these sections for the updated text.

**Table 4. Associated Guidelines and Statements**

Title	Organization	Publication Year (Reference)
Guidelines		
Syncope	ACC/AHA/HRS	2017 <sup>§1.4-10</sup>
Heart failure	ACCF/AHA	2017 <sup>§1.4-11</sup> 2016, <sup>§1.4-12</sup> and 2013 <sup>§1.4-13</sup>
Valvular heart disease	AHA/ACC	2017 <sup>§1.4-14</sup> and 2014 <sup>§1.4-15</sup>
Supraventricular tachycardia	ACC/AHA/HRS	2015 <sup>§1.4-16</sup>
Ventricular arrhythmias and the prevention of sudden cardiac death	ESC	2015 <sup>§1.4-17</sup>
Guidelines for cardiopulmonary resuscitation and emergency cardiovascular care	AHA	2015 <sup>§1.4-18</sup>
Atrial fibrillation	AHA/ACC/HRS	2014 <sup>§1.4-19</sup>
Non–ST-elevation acute coronary syndromes	AHA/ACC	2014 <sup>§1.4-20</sup>
Assessment of cardiovascular risk	ACC/AHA	2013 <sup>§1.4-21</sup>
ST-elevation myocardial infarction	ACCF/AHA	2013 <sup>§1.4-22</sup>
Acute myocardial infarction in patients presenting with ST-segment elevation	ESC	2012 <sup>§1.4-23</sup>
Device-based therapies for cardiac rhythm abnormalities	ACCF/AHA/HRS	2012 <sup>§1.4-24</sup>
Coronary artery bypass graft surgery	ACCF/AHA	2011 <sup>§1.4-25</sup>
Hypertrophic cardiomyopathy	ACCF/AHA	2011 <sup>§1.4-6</sup>
Percutaneous coronary intervention	ACCF/AHA/SCAI	2011 <sup>§1.4-26</sup>
Secondary prevention and risk reduction therapy for patients with coronary and other atherosclerotic vascular disease	AHA/ACCF	2011 <sup>§1.4-27</sup>
Scientific Statements		
Wearable cardioverter-defibrillator therapy for the prevention of sudden cardiac death	AHA	2016 <sup>§1.4-9</sup>
Optimal implantable cardioverter defibrillator programming and testing	HRS/EHRA/APHR/SOLAECE	2016 <sup>§1.4-8</sup>
Treatment of cardiac arrest: current status and future directions: strategies to improve cardiac arrest survival	IOM	2015 <sup>§1.4-28</sup>
Eligibility and disqualification recommendations for competitive athletes with cardiovascular abnormalities	ACC/AHA	2015 <sup>§1.4-29</sup>
Ventricular arrhythmias	EHRA/HRS/APHR	2014 <sup>§1.4-30</sup>
Arrhythmias in adult congenital heart disease	PACES/HRS	2014 <sup>§1.4-31</sup>
Implantable cardioverter-defibrillator therapy in patients who are not included or not well represented in clinical trials	HRS/ACC/AHA	2014 <sup>§1.4-32</sup>
Cardiac sarcoidosis	HRS	2014 <sup>§1.4-33</sup>
Inherited primary arrhythmia syndromes	HRS/EHRA/APHR	2013 <sup>§1.4-34</sup>

ACC indicates American College of Cardiology; ACCF, American College of Cardiology Foundation; AHA, American Heart Association; APHR, Asia Pacific Heart Rhythm Society; EHRA, European Heart Rhythm Association; ESC, European Society of Cardiology; HRS, Heart Rhythm Society; PACES, Pediatric and Congenital Electrophysiology Society; SCAI, Society for Cardiovascular Angiography and Interventions; and, SOLAECE, Sociedad Latinoamericana de Estimulacion Cardiaca y Electrofisiologia.

## 1.5. Abbreviations

Abbreviation	Meaning/Phrase
ACS	acute coronary syndromes
AED	automated external defibrillator
AMI	acute myocardial infarction
BNP	B-type natriuretic peptide
CABG	coronary artery bypass graft
CKD	chronic kidney disease
CPR	cardiopulmonary resuscitation
CRT	cardiac resynchronization therapy
CT	computed tomography
ECG	electrocardiogram
ERC	evidence review committee
ESRD	end-stage renal disease
GDMT	guideline-directed management and therapy
HCM	hypertrophic cardiomyopathy
HF	heart failure
HFpEF	heart failure with preserved ejection fraction
HFrEF	heart failure with reduced ejection fraction
ICD	implantable cardioverter-defibrillator
LV	left ventricular
LVAD	left ventricular assist device
LVEF	left ventricular ejection fraction
MI	myocardial infarction
NICM	nonischemic cardiomyopathy
NSVT	nonsustained ventricular tachycardia
PET	positron emission tomography
PCI	percutaneous coronary intervention
PVC	premature ventricular complex
QoL	quality of life
RCT	randomized controlled trial
RV	right ventricular
RVOT	right ventricular outflow tract
SCA	sudden cardiac arrest
SCD	sudden cardiac death
SVT	supraventricular tachycardia
TOF	tetralogy of Fallot
VA	ventricular arrhythmia
VT	ventricular tachycardia

## 2. EPIDEMIOLOGY

### 2.1. General Concepts

VA include a spectrum that ranges from premature ventricular complex (PVC) to ventricular fibrillation (VF), with a clinical presentation that ranges from a total lack of symptoms to cardiac arrest. Most life-threatening VA are associated with ischemic heart disease, particularly in older patients.<sup>S2.2.2-1</sup> The risks of VA and SCD vary in

specific populations with different underlying cardiac conditions, and with specific family history and genetic variants, and this variation has important implications for studying and applying therapies.

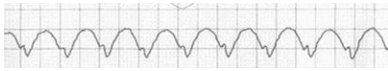

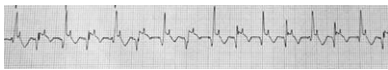

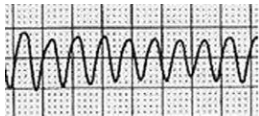
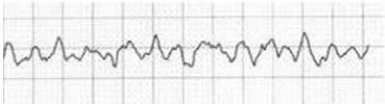
#### 2.1.1. Premature Ventricular Complexes and Nonsustained VT

PVCs are common and increase in frequency with age. Although PVCs were found in a healthy military population in only 0.6% of those <20 years of age and 2.7% of those >50 years of age<sup>S2.2.2-5</sup> on 12-lead ECGs, longer term monitoring shows PVCs in about 50% of all people with or without heart disease.<sup>S2.2.2-6</sup> The presence of PVCs on 2 minutes of monitoring of middle-aged patients in the ARIC (Atherosclerosis Risk In Communities) study was associated with increased risk of both ischemic heart disease events and mortality, with or without prevalent ischemic heart disease.<sup>S2.2.2-7,S2.2.2-8</sup> In the general population, frequent PVCs, which are defined as the presence of at least 1 PVC on a 12-lead ECG or >30 PVCs per hour, are associated with increased cardiovascular risk and increased mortality.<sup>S2.2.2-9</sup> In a study from Taiwan of patients without sustained VT or structural heart disease who had 24-hour Holter monitoring for clinical evaluation, multifocal PVCs were associated with increased risk of death and nonfatal cardiovascular adverse outcomes.<sup>S2.2.2-10</sup> In the same population, nonsustained ventricular tachycardia (NSVT) was independently associated with increased risk of death and other cardiovascular adverse outcomes, including stroke.<sup>S2.2.2-11</sup> An association of PVCs with increased risk of stroke was also seen in the ARIC population.<sup>S2.2.2-8</sup>

Because some studies have shown an association of PVCs with adverse outcomes, the detection of PVCs, particularly if multifocal and frequent, is generally considered a risk factor for adverse cardiovascular outcomes, and such patients are generally evaluated to ensure they do not have underlying conditions (eg, ischemic heart disease, left ventricular [LV] dysfunction) that warrant further treatment to reduce risk. PVC and NSVT in patients with cardiovascular disease are common and have been associated with adverse outcomes.<sup>S2.2.2-12,S2.2.2-13</sup> In CAST (Cardiac Arrhythmia Suppression Trials), treatment of patients with post-myocardial infarction (MI) who took antiarrhythmic medications (eg, flecainide, encainide, moricizine) increased the risk of death despite suppression of VA.<sup>S2.2.2-14,S2.2.2-15</sup> Treatment of PVCs with antiarrhythmic medications has not been shown to reduce mortality and, in the post-MI population, treatment with class I sodium channel–blocking medications (eg, quinidine, flecainide) increases the risk of death.<sup>S2.2.2-15,S2.2.2-16</sup> Likewise, in patients with a reduced LVEF class I, sodium channel–blocking medications and d-sotalol increase the risk of death.<sup>S2.2.2-16,S2.2.2-17</sup> Beta blockers, nondihydropyridines calcium channel block-



**Table 5. Table of Definitions of Commonly Used Terms in this Document**

Term	Definition or Description
Ventricular tachycardia <sup>S2.2.2-2</sup>	<p>Cardiac arrhythmia of <math>\geq 3</math> consecutive complexes originating in the ventricles at a rate <math>&gt;100</math> bpm (cycle length: <math>&lt;600</math> ms). Types of VT:</p> <p>Sustained: VT <math>&gt;30</math> s or requiring termination due to hemodynamic compromise in <math>&lt;30</math> s.</p> <p>Nonsustained/unsustained: <math>\geq 3</math> beats, terminating spontaneously.</p> <p>Monomorphic: Stable single QRS morphology from beat to beat.</p> <p>Polymorphic: Changing or multiform QRS morphology from beat to beat.</p> <p>Bidirectional: VT with a beat-to-beat alternation in the QRS frontal plane axis, often seen in the setting of digitalis toxicity or catecholaminergic polymorphic VT</p> <div style="text-align: center;"> <p>Monomorphic VT</p>  <p>Polymorphic VT</p>  <p>Bidirectional VT</p>  </div>
Torsades de pointes <sup>S2.2.2-2</sup>	<p>Torsades de pointes is polymorphic VT that occurs in the setting of a long QT interval and is characterized by a waxing and waning QRS amplitude. It often has a long-short initiating sequence with a long coupling interval to the first VT beat and may present with salvos of NSVT. The twisting of the points, although characteristic, may not always be seen, especially if the episode is nonsustained or if only a limited number of leads are available. Torsades de pointes can result from bradycardia including high-grade AV block that leads to a long-short sequence initiating torsades de pointes.</p> <div style="text-align: center;">  </div>
Ventricular flutter <sup>S2.2.2-2</sup>	<p>A regular VA <math>\approx 300</math> bpm (cycle length: 200 ms) with a sinusoidal, monomorphic appearance; no isoelectric interval between successive QRS complexes.</p> <div style="text-align: center;">  </div>
Ventricular fibrillation <sup>S2.2.2-2</sup>	<p>Rapid, grossly irregular electrical activity with marked variability in electrocardiographic waveform, ventricular rate usually <math>&gt;300</math> bpm (cycle length: <math>&lt;200</math> ms).</p> <div style="text-align: center;">  </div>
Sudden cardiac arrest <sup>S2.2.2-2</sup>	<p>SCA is the sudden cessation of cardiac activity such that the victim becomes unresponsive, with either persisting gasping respirations or absence of any respiratory movements, and no signs of circulation as manifest by the absence of a perceptible pulse. An arrest is presumed to be of cardiac etiology unless it is known or likely to have been caused by trauma, drowning, respiratory failure or asphyxia, electrocution, drug overdose, or any other noncardiac cause.</p>
Sudden cardiac death <sup>S2.2.2-2</sup>	<p>Sudden and unexpected death occurring within an hour of the onset of symptoms, or occurring in patients found dead within 24 h of being asymptomatic and presumably due to a cardiac arrhythmia or hemodynamic catastrophe.</p>
VT/VF storm <sup>S2.2.2-3</sup>	<p>VT/VF storm (electrical storm or arrhythmic storm) refers to a state of cardiac electrical instability that is defined by <math>\geq 3</math> episodes of sustained VT, VF, or appropriate shocks from an ICD within 24 h.</p>
Primary prevention ICD <sup>S2.2.2-2</sup>	<p>ICD placement with the intention of preventing SCD in a patient who has not had sustained VT or SCA but who is at an increased risk for these events.</p>
Secondary prevention ICD <sup>S2.2.2-2</sup>	<p>ICD placement in a patient with prior SCA, sustained VT, or syncope caused by VA.</p>
Structural heart disease*	<p>This term encompasses IHD, all types of cardiomyopathy, valvular heart disease, and adult congenital heart disease.</p>
Cardiac channelopathy <sup>S2.2.2-4</sup>	<p>Arrhythmogenic disease due to a genetic abnormality that results in dysfunction of a cardiac ion channel (eg, long QT syndrome, catecholaminergic polymorphic VT).</p>

\*The definition of this term may differ across publications. Refer to the entry for the definition used in this document.

AV indicates atrioventricular; ICD, implantable cardioverter-defibrillator; IHD, ischemic heart disease; NSVT, nonsustained ventricular tachycardia; SCA, sudden cardiac arrest; SCD, sudden cardiac death; VA, ventricular arrhythmia; VF, ventricular fibrillation; and VT, ventricular tachycardia.

ers, and some antiarrhythmic medications may relieve symptoms of palpitations.<sup>S2.2.2-18</sup>

PVCs that occur during an exercise test are associated with a higher risk of death.<sup>S2.2.2-19</sup> In 1 study, PVCs that occur during recovery are a stronger predictor of death than PVCs occurring only during exercise.<sup>S2.2.2-20</sup> However, PVCs are common in trained athletes who have palpitations, in whom there does not appear to be increased risk of death based on studies of small numbers of athletes, at least in those without other cardiovascular abnormalities.<sup>S2.2.2-21,S2.2.2-22</sup> Complex PVCs may not represent a benign finding in endurance athletes. An electrophysiological study may be needed to assess patients' arrhythmogenic risk.<sup>S2.2.2-22</sup> Very frequent PVCs, >10 000 to 20 000 a day, can be associated with depressed LV function in some patients that is reversible with control of the PVCs, and has been referred to as PVC-induced cardiomyopathy.<sup>S2.2.2-23,S2.2.2-24</sup> (See also Section 8.5. PVC-Induced Cardiomyopathy.) Very rarely, idiopathic PVCs from the outflow tract may trigger malignant VA in patients without structural heart disease.<sup>S2.2.2-25,S2.2.2-26</sup>

### 2.1.2. VT and VF During ACS

Approximately half of patients with out-of-hospital cardiac arrest with the first rhythm identified as VF and who survive to hospital admission have evidence of acute MI (AMI).<sup>S2.2.2-27</sup> Of all out-of-hospital cardiac arrests, >50% will have significant coronary artery lesions on acute coronary angiography.<sup>S2.2.2-27</sup> Of patients hospitalized with AMI, 5% to 10% have VF or sustained VT prior to hospital presentation, and another 5% will have VF or sustained VT after hospital arrival, most within 48 hours of admission. A study of patients with non-ST-elevation ACS who underwent cardiac catheterization within 48 hours found VT/VF in 7.6% of patients, with 60% of those events within 48 hours of admission.<sup>S2.2.2-28</sup> Accelerated idioventricular rhythm is a common arrhythmia in patients with acute MI, including patients with ST-segment elevation MI undergoing primary percutaneous coronary intervention (PCI). Accelerated idioventricular rhythm is more closely related to the extent of infarction than to reperfusion itself.<sup>S2.2.2-29</sup>

Sustained VA that occurs in the setting of an ACS is more often polymorphic VT or VF than monomorphic VT. Risk factors for VT/VF include prior history of hypertension, prior MI, ST-segment changes at presentation, and chronic obstructive pulmonary disease.<sup>S2.2.2-30</sup> A nationwide Danish study found that 11.6% of patients with ST-segment elevation MI who underwent PCI had VF prior to the PCI, and that VF was associated with alcohol consumption, preinfarction angina, anterior infarct location, and complete coronary occlusion at the time of coronary angiography.<sup>S2.2.2-31</sup> In a select group of patients undergoing primary PCI in a

clinical trial, 5.7% developed sustained VT or VF, with two thirds of these events occurring prior to the end of the catheterization, and 90% within 48 hours from the procedure. VT or VF after primary PCI was associated with lower blood pressure, higher heart rate, poor coronary flow at the end of the procedure, and incomplete resolution of ST elevation.<sup>S2.2.2-32</sup> Importantly, and in contrast to some earlier studies, VT or VF at any time was associated with a substantially higher risk of death within 90 days. Late VT or VF (after 48 hours of hospital presentation) was associated with a higher risk of death than early VT or VF (within 48 hours of hospital presentation).<sup>S2.2.2-33</sup>

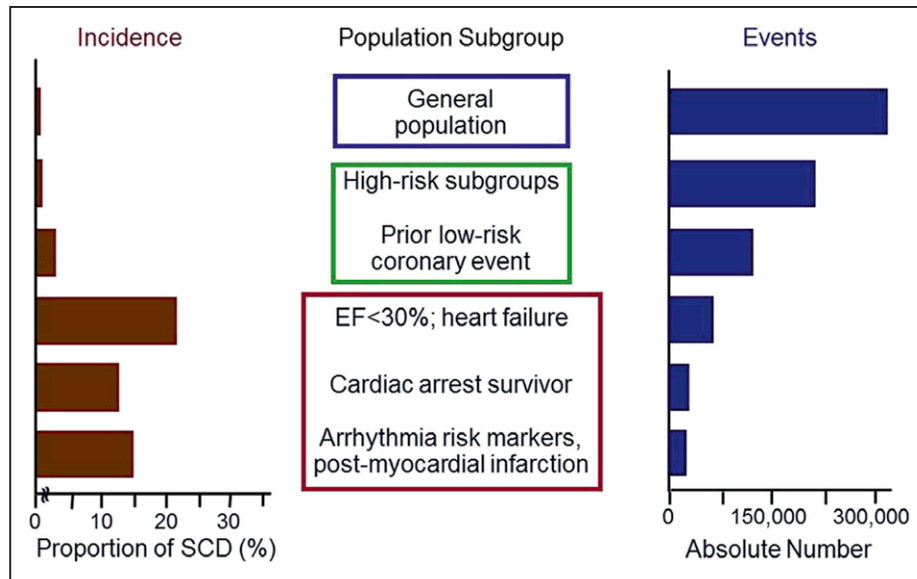
### 2.1.3. Sustained VT and VF Not Associated With ACS

Patients with structural heart disease are at an increased risk for sustained VT and VF. Sustained VT that is not associated with an ACS is often monomorphic as it is usually due to scar-related reentry, but it may degenerate to VF.<sup>S2.2.2-34</sup> The risk and predictors of VT in patients with structural heart disease depend on the type, severity, and duration of structural heart disease, increasing with the severity of ventricular dysfunction and the presence of symptomatic HF. Monomorphic VT occurring in the absence of structural heart disease is commonly referred to as idiopathic VT and is often due to an automatic focus in a characteristic location, giving rise to typical electrocardiographic appearances. Polymorphic VT and VF occurring in the absence of structural heart disease are rare and may be due to a cardiac channelopathy,<sup>S2.2.2-35,S2.2.2-36</sup> medication-induced long QT syndrome,<sup>S2.2.2-36</sup> or they may be idiopathic.<sup>S2.2.2-37,S2.2.2-38</sup>

## 2.2. Sudden Cardiac Death

### 2.2.1. Incidence of SCD

SCA and its most common consequence, SCD, constitute major public health problems, accounting for approximately 50% of all cardiovascular deaths,<sup>S2.2.2-1,S2.2.2-39</sup> with at least 25% being first symptomatic cardiac events.<sup>S2.2.2-1,S2.2.2-40,S2.2.2-41</sup> In addition, analyses of the magnitude of SCD are limited, in part because of the broad range of estimates of the risk based on different epidemiological methods.<sup>S2.2.2-42</sup> During the past 20 to 30 years, SCD accounted for approximately 230 000 to 350 000 deaths per year in the United States, with a range of <170 000 to >450 000, depending on epidemiological methods, data sources, and inclusion criteria.<sup>S2.2.2-41,S2.2.2-43</sup> The lowest of these extremes came from national extrapolation of data from specific local programs, while the highest rates included noncardiac causes of sudden death such as pulmonary embolism or intracranial bleeding. The mid-range numbers were largely based



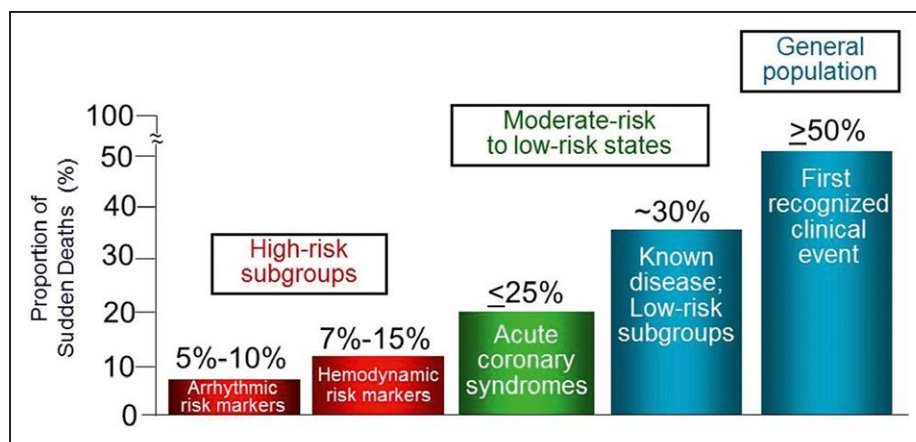
**Figure 1A.** SCD incidence and total events.<sup>S2.2.2-1</sup> EF indicates ejection fraction; and SCD, sudden cardiac death.

on death certificate studies that required a code inclusive of ischemic heart disease.

The 2017 update of cardiovascular statistics from the AHA estimated the total annual burden of out-of-hospital cardiac arrest at 356 500.<sup>S2.2.2-44</sup> An additional 209 000 in-hospital cardiac arrests occur annually.<sup>S2.2.2-45</sup> Among the out-of-hospital cardiac arrest group, approximately 357 000 events trigger emergency rescue response, with 97% occurring in adults >18 years of age.

The survival statistics for out-of-hospital cardiac arrest remain disappointing, with an estimated 10% overall survival rate.<sup>S2.2.2-44</sup> Among the subgroup of 70% of out-of-hospital cardiac arrests that occur in the home, survival is 6%. The best reported outcomes are from locations with highly developed and publicly visible emergency rescue response, along with the com-

bination of public location of cardiac arrest, bystander witnesses willing to provide CPR, first responders arriving quickly, shockable rhythm at initial contact, availability of automated external defibrillators (AEDs), and possibly a benefit from telecommunication-directed CPR.<sup>S2.2.2-46,S2.2.2-47</sup> Survival to hospital discharge after in-hospital cardiac arrests is estimated to be 24%.<sup>S2.2.2-48</sup> In all settings, survival statistics appear to be better when rhythms recorded by responders are shockable (VF, pulseless VT), compared with pulseless electrical activity or asystole.<sup>S2.2.2-49</sup> Although the apparent increase in the incidence of pulseless electrical activity or asystole could be due to the later arrival of medical care, the decrease in the incidence of shockable rhythm has also been attributed, in part, to improvements in diagnosis and treatment of structural heart disease.<sup>S2.2.2-40</sup>



**Figure 1B.** SCD and clinical subsets.<sup>S2.2.2-1</sup> SCD indicates sudden cardiac death.

### 2.2.2. Population Subgroups and Risk Prediction

Risk prediction for SCA and SCD is complex. Risk analysis is divided into 2 general categories: population risk prediction and individual risk prediction.<sup>S2.2.2-41, S2.2.2-50</sup> Conventional epidemiological markers provide insight into probabilities for the development of ischemic heart disease within a general class of subjects, but adequately tested and validated profiles for SCA risk stratification of individuals in the general population do not presently exist. The challenge of defining SCA risk in individuals derives from a population model characterized by large numbers of events diluted into a very large denominator (Figure 1). The overall population can be subgrouped into categories based on integration of age, presence and extent of disease, and identification of small, high-risk subgroups within the large denominator general population.

Increasing age is a strong predictor of risk for SCA, but it is not linear. Risk in the general population, over time, beginning at 35 years of age has been estimated at 1 per 1000 population per year, increasing from a risk <1000 at the younger end of that spectrum to a higher risk in the elderly.<sup>S2.2.2-41</sup> However, an analysis of lifetime risk of SCD, derived from the Framingham data, suggested that the incidence of SCD decreases in later years, especially in people >75 years of age.<sup>S2.2.2-51</sup> The data also suggested that SCD is uniformly more common in men than in women at all age groups. In contrast, the population of children, adolescents, and young adults has an overall annual risk of 1 per 100 000, and there is somewhat a higher risk of SCD at the younger end of that age range.<sup>S2.2.2-41</sup> An age-associated transition range, from the mid-20s to 35 to 40 years of age, is characterized by a steep increase in risk from that of the adolescent group to the middle-aged group, corresponding to the emergence of ischemic heart disease.

Although ischemic heart disease remains the most common underlying substrate associated with SCD, the incidence of ischemic heart disease-related SCD appears to be decreasing,<sup>S2.2.2-52</sup> with various forms of cardiomyopathy associated with myocardial fibrosis and LV hypertrophy increasing.<sup>S2.2.2-53</sup> In addition, a trend over time has suggested that out-of-hospital cardiac arrest patients who are admitted alive to a hospital are becoming more likely to have high-risk clinical profiles, as opposed to manifest disease.<sup>S2.2.2-54</sup> The younger population—children, adolescents, and young adults—is affected by a series of disorders that manifest earlier in life, including the genetic structural disorders and cardiac channelopathies, myocarditis, congenital heart disease, and other rare disorders.<sup>S2.2.2-43</sup> During the transition range, from the mid-20s to the mid-30s, causes of SCA and SCD include a lower proportion of inherited diseases and in-

creasing proportion of ischemic heart disease (>40% of cases).<sup>S2.2.2-43</sup>

Despite the small progress that has been made in risk prediction of SCA and SCD, the greatest challenge is to identify the relatively small, high-risk subgroups concealed within the large general population who have no identified disease but are at risk of SCA as their first cardiac event (Figure 1).<sup>S2.2.2-50</sup>

## 3. MECHANISMS OF VA

### 3.1. Cellular Mechanisms and Substrates

Mechanisms of VA include enhanced normal automaticity, abnormal automaticity, triggered activity induced by early or late afterdepolarizations, and reentry.<sup>S3.4-1–S3.4-3</sup> Reentry requires a trigger to initiate the arrhythmia and a substrate to sustain it. The trigger may be a PVC, which may be due to automaticity. The substrate may be structural remodeling secondary to an underlying disease process, and often includes a scar secondary to a prior MI or surgical repair, or patchy fibrosis in the setting of cardiomyopathy or hypertrophy. Changes in ion channel or transporter function and/or expression and cell to cell coupling secondary to the underlying pathology may alter the initiation or propagation of the cardiac action potential. The electrophysiological substrate is dynamically influenced by a variety of factors including cardiac metabolism, electrolytes, signaling pathways and autonomic effects. Enhanced automaticity or abnormal automaticity causing VA may arise from subordinate pacemaker cells in the His-Purkinje system or ventricular myocardium.

### 3.2. Automaticity

Normal automaticity results from phase 4 spontaneous depolarization of the transmembrane action potential arising from a normal resting potential, reaching threshold and initiating an action potential.<sup>S3.4-1, S3.4-3</sup> An initiating current ( $I_i$ ) is responsible for spontaneous phase 4 depolarization in the sinus node. The rate is determined by the integration of the maximum diastolic potential at the end of repolarization, the slope of phase 4 depolarization, and the threshold potential. In contrast, abnormal automaticity arises from a partially depolarized membrane potential that is usually close to the activation potential for calcium channels in the cell membrane.<sup>S3.4-1, S3.4-3</sup> In the acute phase of an MI or during transient ischemia, increased extracellular potassium causes partial depolarization of the resting membrane potential creating injury currents between the infarcted/ischemic tissue and healthy myocardium. These injury currents may initiate spontaneous activity. In ischemia, abnormal automaticity may occur in both

ventricular myocytes and Purkinje fibers, and may also enhance normal automaticity in Purkinje fibers in the ischemic zone.

### 3.3. Triggered Activity

Early afterdepolarizations occur during late phase 2 or early phase 3 of the action potential,<sup>53.4-3-53.4-5</sup> usually in the setting of action potential prolongation due to an increase in inward currents (the late sodium current, the inward calcium current or the sodium calcium exchange current) or a decrease in repolarizing potassium currents. Under these conditions, early afterdepolarizations may be initiated when reactivation of the inward L-type calcium channel occurs before the membrane has returned to a more negative potential than that required for calcium channel reactivation. Spontaneous calcium release from the sarcoplasmic reticulum may also result in activation of a depolarizing sodium/calcium exchange current. Early afterdepolarizations are the trigger for torsades de pointes VT associated with QT prolongation either induced by medications or other acquired factors or due to mutations of ion channels causing the long QT syndrome. In these cases, it is possible that the early afterdepolarization/triggered activity sequence is the trigger that culminates in polymorphic VT/VF.

Delayed afterdepolarizations occur after complete membrane repolarization and develop under conditions of intracellular calcium overload. Factors contributing to elevated intracellular calcium load include tachycardia, catecholamines, hypokalemia, digoxin toxicity, cardiac hypertrophy, and HF.<sup>53.4-6,53.4-7</sup> Elevated sarcoplasmic calcium content or increased sensitivity of the ryanodine receptor can initiate spontaneous calcium release, which activates a transient inward current driven predominantly by the sodium–calcium exchange current. If the membrane depolarization is sufficiently large, the inward sodium current is activated resulting in a triggered action potential. Delayed afterdepolarizations are the underlying mechanism for VT in the setting of digoxin toxicity, catecholaminergic polymorphic VT, and idiopathic outflow tract VA. Delayed afterdepolarizations are also considered to be an important trigger of VA in the setting of HF. Purkinje cells are more susceptible to spontaneous sarcoplasmic reticulum calcium release than ventricular myocytes suggesting that delayed afterdepolarizations may be an important mechanism for some Purkinje fiber-related VA.<sup>53.4-3,53.4-8,53.4-9</sup>

### 3.4. Reentry

Reentry is the underlying mechanism for most sustained VA in the presence of structural heart disease.<sup>53.4-1-53.4-3,53.4-10-53.4-12</sup> Reentry may occur around

a fixed anatomical obstacle, such as scar after an MI or surgically repaired congenital heart disease. In this setting, an excitable gap separates the excitation wavefront from its tail of refractoriness. The existence of structural reentrant substrates provide the rationale for VT ablation in scar-related VTs.<sup>53.4-11,53.4-12</sup>

Functional reentry around areas of functional block without anatomical obstacles can also occur. Two main models of functional reentry have been proposed.<sup>53.4-2,53.4-3</sup> The leading circle model has a functionally refractory core and no excitable gap. Spiral wave reentry is driven by a rotor with a curved wavefront and wavetail pivoting around an excitable but unexcited core. There remains much debate about the precise mechanism(s) of VF (rotor versus multiple wavelet reentry). Both mechanisms may be operational in different phases of VF.<sup>53.4-10</sup>

Phase 2 reentry may occur due to heterogeneity of ventricular repolarization. Electrotonic currents may flow from endocardial sites with longer action potential durations to the epicardium with shorter action potential durations which can result in reexcitation when these sites have recovered from refractoriness. This is believed to be one potential mechanism of VT/VF in Brugada syndrome<sup>53.4-3</sup> and may also be operative during ischemia.

## 4. GENERAL EVALUATION OF PATIENTS WITH DOCUMENTED OR SUSPECTED VA

### 4.1. History and Physical Examination

#### Recommendation for Syncope\*

Referenced studies that support the recommendation are summarized in Online Data Supplement 1.

COR	LOE	Recommendation
I	B-NR	1. Patients presenting with syncope for which VA is documented, or thought to be a likely cause, should be hospitalized for evaluation, monitoring, and management. <sup>54.1-1-54.1-4</sup>

\*This section covers practices that are well accepted, and a new recommendation was determined to only be warranted for syncope.

### Synopsis

VA can produce a wide spectrum of symptoms, and the severity of symptoms does not necessarily reflect the extent of structural heart disease or the potential risk of SCD. Symptoms of VA include palpitations, either skipped or extra beats or sustained palpitations, shortness of breath, chest pain, dizziness, near syncope, and syncope.<sup>54.1-5,54.1-6</sup> Palpitations may correlate with VA but are frequently reported during normal rhythm.<sup>54.1-7</sup> The differential diagnosis of exercise intolerance, chest pain, dyspnea, presyncope, and syncope includes VA but also includes other etiologies. Nonetheless, more dramatic

**Table 6. Important Considerations in the Evaluation of Patients With Known or Suspected VA**

Component	Assessment and Findings Relevant for VA and/or SCD Risk
History	1. Symptoms/events related to arrhythmia: Palpitations, lightheadedness, syncope, dyspnea, chest pain, cardiac arrest
	2. Symptoms related to underlying heart disease: Dyspnea at rest or on exertion, orthopnea, paroxysmal nocturnal dyspnea, chest pain, edema
	3. Precipitating factors: Exercise, emotional stress
	4. Known heart disease: Coronary, valvular (eg, mitral valve prolapse), congenital heart disease, other
	5. Risk factors for heart disease: Hypertension, diabetes mellitus, hyperlipidemia, and smoking
	6. Medications
	Antiarrhythmic medications
	Other medications with potential for QT prolongation and torsades de pointes
	Medications with potential to provoke or aggravate VA
	Stimulants including cocaine and amphetamines
	Supplements including anabolic steroids
	Medication-medication interaction that could cause QT prolongation and torsades de pointes
	7. Past medical history
	Thyroid disease
	Acute kidney injury, chronic kidney disease, or electrolyte abnormalities
	Stroke or embolic events
	Lung disease
	Epilepsy (arrhythmic syncope can be misdiagnosed as epilepsy)
	Alcohol or illicit drug use
	Use of over-the-counter medications that could cause QT prolongation and torsades de pointes
Unexplained motor vehicle crashes	
Family History	1. SCD, SCA, or unexplained drowning in a first-degree relative
	2. SIDS or repetitive spontaneous pregnancy losses given their potential association with cardiac channelopathies
	3. Heart disease
	IHD
	Cardiomyopathy: Hypertrophic, dilated, ARVC
	Congenital heart disease
	Cardiac channelopathies: Long QT, Brugada, Short QT, CPVT
	Arrhythmias
	Conduction disorders, pacemakers/ICDs
	4. Neuromuscular disease associated with cardiomyopathies
	Muscular dystrophy
5. Epilepsy	

(Continued)

**Table 6. Continued**

Component	Assessment and Findings Relevant for VA and/or SCD Risk
Examination	1. Heart rate and regularity, blood pressure
	2. Jugular venous pressure
	3. Murmurs
	4. Pulses and bruits
	5. Edema
	6. Sternotomy scars

ARVC indicates arrhythmogenic right ventricular cardiomyopathy; CPVT, catecholaminergic polymorphic ventricular tachycardia; IHD, ischemic heart disease; SCA, sudden cardiac arrest; SCD, sudden cardiac death; SIDS, sudden infant death syndrome; and VA, ventricular arrhythmia.

symptoms, particularly in patients with known or discovered structural or electrical heart disease should prompt focused investigation for possible association with VA (Table 6).

The elucidation of precipitating factors, such as exertional or emotional stress, concurrent medications or illness, and alleviating factors is important. The presence of a family history of SCD, ischemic heart disease, valvular heart disease, nonischemic cardiomyopathy (NICM), or HF raises concern for the presence of one of these disorders associated with VA. Obtaining a complete medication history is important. Various antiarrhythmic and other medications can cause QT prolongation and torsades de pointes ([www.crediblemeds.org](http://www.crediblemeds.org))<sup>S4.1-8</sup>; some medications can also induce Brugada type I electrocardiographic pattern and VF ([www.brugadadrugs.org](http://www.brugadadrugs.org)).<sup>S4.1-9,S4.1-10</sup>

Patients with bigeminy and trigeminy can present with effective bradycardia, an apical-radial pulse deficit and relative hypertension with a wide pulse pressure. Effective bradycardia from PVCs can result in inaccurate estimation of the heart rate. Although premature beats on auscultation of the heart can be detected, the physical examination is focused largely on finding evidence of structural heart disease. Carotid bruits or diminished peripheral pulses may be indicators of atherosclerotic disease associated with ischemic heart disease. Jugular venous distention, rales, gallops, and peripheral edema provide evidence of HF. Auscultation may reveal cardiac murmurs consistent with valvular heart disease, such as aortic stenosis or mitral regurgitation, and may be associated with HF and VA. A midsystolic click may indicate mitral valve prolapse that can be associated with VA.<sup>S4.1-11-S4.1-13</sup> Many VA are asymptomatic and detected only on an ECG or telemetry. Such cases highlight the need to search for evidence of underlying heart disease.

**Recommendation-Specific Supportive Text**

1. Rapid, sustained VT may result in syncope secondary to marked reduction in cardiac output,

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followed by spontaneous recovery if VT terminates, or SCA if VT persists and is not treated promptly. Syncope or SCA may be the first manifestation of structural or electrical heart disease,<sup>54.1-14</sup> and some SCA victims have preceding “sentinel” syncope episodes.<sup>54.1-15</sup> Syncope, or its forewarnings of dizziness, lightheadedness, or near-syncope, may constitute a risk factor for SCA and SCD.<sup>54.1-2</sup> The initial evaluation at any age focuses on detection or exclusion of heart disease. Syncope during exercise should prompt thorough evaluation to rule out cardiac causes. Cardiac evaluation with echocardiography, ambulatory monitoring, and exercise testing may be warranted depending on the clinical information elicited.<sup>54.1-3,54.1-4</sup> Cardiac causes of syncope include sustained VT, high-grade atrioventricular block or severe sinus bradycardia or prolonged sinus pauses, supraventricular tachycardia (SVT), malfunction of pacemakers, VA from cardiac channelopathies or structural heart disease syndromes, such as hypertrophic cardiomyopathy (HCM) or congenital heart disease.<sup>54.1-3,54.1-4,54.1-16</sup> Cardiac channelopathies and HCM are particularly important to consider in adolescents and young adults. Arrhythmic causes of syncope are often associated with very short periods of premonitory symptoms, or palpitations, and known preexisting heart disease, especially a history of a low LVEF or HF.<sup>54.1-1</sup> Among nonarrhythmic cardiac causes, considerations should include myocardial ischemia, severe aortic stenosis, HCM, HF, and prosthetic valve malfunction, pulmonary embolism, medications, and illicit drug use.<sup>54.1-3</sup>

## 4.2. Noninvasive Evaluation

### 4.2.1. 12-lead ECG and Exercise Testing

Recommendations for 12-lead ECG and Exercise Testing		
Referenced studies that support the recommendations are summarized in Online Data Supplement 2.		
COR	LOE	Recommendations
I	B-NR	1. In patients with sustained, hemodynamically stable, wide complex tachycardia, a 12-lead ECG during tachycardia should be obtained. <sup>54.2.1-1-54.2.1-3</sup>
I	B-NR	2. In patients with VA symptoms associated with exertion, suspected ischemic heart disease, or catecholaminergic polymorphic ventricular tachycardia, exercise treadmill testing is useful to assess for exercise-induced VA. <sup>54.2.1-4,54.2.1-5</sup>
I	B-NR	3. In patients with suspected or documented VA, a 12-lead ECG should be obtained in sinus rhythm to look for evidence of heart disease. <sup>54.2.1-6</sup>

### Recommendation-Specific Supportive Text

1. A 12-lead ECG during tachycardia is the first diagnostic test that should be done in any patient found to be in a stable wide QRS complex tachycardia on a monitor. VT is the diagnosis in most adults with wide complex tachycardia and underlying structural heart disease.<sup>54.2.1-3</sup> Criteria that support a diagnosis of VT include AV dissociation, a QRS complex >0.14 s, monophasic R wave in aVR, specific QRS morphologies (eg, positively or negatively concordant QRS complexes in the precordial leads), the absence of an RS complex in all precordial leads and an RS interval >100 ms in at least 1 precordial lead.<sup>54.2.1-2</sup> Exceptions occur, particularly in patients with advanced heart disease and with the use of certain antiarrhythmic medications.<sup>54.2.1-1</sup> For patients with preexisting bundle branch block, comparison of the QRS morphology during sinus rhythm with that during wide complex tachycardia is often relevant.
2. For exertion-related arrhythmic symptoms, exercise in a monitored setting may reproduce the symptoms and/or the related arrhythmia, allowing for diagnosis. Exercise testing is particularly important when catecholaminergic polymorphic ventricular tachycardia is a possibility. However, exertion-related symptoms and findings may not be reliably reproducible with exercise testing, and long-term electrocardiographic monitoring with external or implantable recorders may be necessary.
3. A 12-lead ECG may indicate the presence of structural heart disease such as prior MI or chamber enlargement that would increase the likelihood that a patient’s symptoms might be due to VA, or it may provide evidence of the underlying substrate for documented VA. An ECG may also reveal evidence of inherited arrhythmia disorders, such as long QT syndrome, Brugada syndrome, and arrhythmogenic right ventricular cardiomyopathy. In patients with structural heart disease, QRS duration and the presence of conduction abnormalities provide prognostic information.<sup>54.2.1-7-54.2.1-14</sup> Data on the use of microvolt T wave alternans and the signal averaged ECG are inconclusive, as such these tests are not routinely used in clinical practice<sup>54.2.1-15-54.2.1-19</sup>; the one exception is the potential use of signal averaged ECG in patients with arrhythmogenic right ventricular cardiomyopathy (see Section 7.3).

#### 4.2.2. Ambulatory Electrocardiography

Recommendation for Ambulatory Electrocardiography		
Referenced studies that support the recommendation are summarized in Online Data Supplements 3 and 4.		
COR	LOE	Recommendation
I	B-NR	1. Ambulatory electrocardiographic monitoring is useful to evaluate whether symptoms, including palpitations, presyncope, or syncope, are caused by VA. <sup>S4.2.2-1-S4.2.2-4</sup>

#### Recommendation-Specific Supportive Text

- Ambulatory electrocardiographic monitoring is often used to assess the effectiveness of treatments to suppress arrhythmias, but more robust data are needed on the clinical use of this practice. Continuous or intermittent ambulatory electrocardiographic recording with a Holter monitor or an event recorder is helpful in diagnosing suspected arrhythmias, establishing their frequency, relating them to symptoms, and assessing the response to therapy. Although the yield of these tests is relatively low, VT is occasionally documented.<sup>S4.2.2-4</sup> A 24-hour continuous Holter recording is appropriate when symptoms occur at least once a day or when quantitation of PVCs/NSVT is desired to assess possible VA-related depressed ventricular function. For sporadic symptoms, event or "looping" monitors are more appropriate because they can be activated over extended periods of time and increase diagnostic yield.<sup>S4.2.2-2,S4.2.2-3</sup> Adhesive patch electrocardiographic monitors can record for weeks and allow for continuous short-term 1-lead monitoring and patient activation for symptoms. Studies have shown satisfactory patient compliance, and arrhythmia detection; however, with some monitors, detected arrhythmias are not discovered until the patch is returned for analysis.<sup>S4.2.2-1,S4.2.2-4</sup> Serial evaluations with exercise testing and/or 24-hour ambulatory monitoring are also used to assess rhythm burden and response of VA to therapy. Notably, implantable monitors are covered in Section 4.2.3. Importantly, when the suspicion of VA in a patient is high, outpatient ambulatory monitoring is inappropriate as prompt diagnosis and prevention of VA are warranted. It is important to accurately correlate the symptoms with the arrhythmias detected by ambulatory ECG monitoring.

#### 4.2.3. Implanted Cardiac Monitors

Recommendation for Implanted Cardiac Monitors		
Referenced studies that support the recommendation are summarized in Online Data Supplement 5.		
COR	LOE	Recommendation
Ila	B-R	1. In patients with sporadic symptoms (including syncope) suspected to be related to VA, implanted cardiac monitors can be useful. <sup>S4.2.3-1-S4.2.3-4</sup>

#### Recommendation-Specific Supportive Text

- Implanted cardiac monitors provide continuous rhythm monitoring and stored recordings of electrograms based on patient activation or preset parameters, allowing a prolonged monitoring period of a few years. These devices require a minor invasive procedure with local anesthesia for implantation. In patients with sporadic symptoms, including syncope, implantable recorders are useful in diagnosing serious tachyarrhythmias (including VA) and bradyarrhythmias.<sup>S4.2.3-2-S4.2.3-4</sup> They are generally reserved for patients in whom other ambulatory monitoring is nonrevealing due to the infrequency of events. A 25% added yield in diagnosis has been described after an unrevealing external ambulatory monitor.<sup>S4.2.3-5</sup> In a study of patients with syncope, the implantable monitor had a greater diagnostic yield than "conventional" testing with external monitoring, tilt table testing and electrophysiological study.<sup>S4.2.3-2</sup> A systematic review in patients with syncope concluded that use of these devices provide a higher rate of diagnosis and a trend toward reduction in syncope relapse after diagnosis, as compared with conventional management.<sup>S4.2.3-3</sup> A prospective study of patients after MI, with LVEF <40%, demonstrated NSVT (>16 beats long) in 13%, VT (>30 s) in 3% and VF in 3% of patients.<sup>S4.2.3-1</sup> It is important to accurately correlate the symptoms with the arrhythmias detected by implanted cardiac monitors.

#### 4.2.4. Noninvasive Cardiac Imaging

Recommendations for Noninvasive Cardiac Imaging		
Referenced studies that support the recommendations are summarized in Online Data Supplement 6.		
COR	LOE	Recommendations
I	B-NR	1. In patients with known or suspected VA that may be associated with underlying structural heart disease or a risk of SCA, echocardiography is recommended for evaluation of cardiac structure and function. <sup>S4.2.4-1,S4.2.4-2</sup>
Ila	C-EO	2. In patients presenting with VA who are suspected of having structural heart disease, cardiac magnetic resonance imaging (MRI) or computed tomography (CT) can be useful to detect and characterize underlying structural heart disease.

#### Recommendation-Specific Supportive Text

- Assessment of global and regional myocardial function, valvular structure and function, along with assessment for adult congenital heart



disease is required in patients with or at high risk for VA or SCD, including patients with cardiomyopathy, HF, prior MI, family history of cardiomyopathy or SCD, or an inherited structural heart disease associated with SCD. Echocardiography is the most readily available and commonly used imaging technique.<sup>S4.2.4-1,S4.2.4-2</sup> LVEF is a strong, independent predictor of SCD and cardiovascular mortality and a determinant of eligibility for ICD implantation for primary prevention of SCD.<sup>S4.2.4-1</sup> In SCD-HeFT (the Sudden Cardiac Death in Heart Failure Trial),<sup>S4.2.4-2</sup> the benefit of the ICD was not dependent on the modality (ie, echocardiography, radionuclide angiography, or contrast angiograms) by which the LVEF was assessed. In clinical practice, if cardiac CT<sup>S4.2.4-3</sup> or cardiac MRI has been performed and provides sufficient evaluation, echocardiography may be unnecessary. This recommendation for imaging differs from that of the 2017 ACC/AHA/HRS syncope guideline<sup>S4.2.4-4</sup> that applies to patients who may not have VA.

- VA or SCA can be an initial manifestation of ischemic heart disease, cardiomyopathic processes, or myocarditis. Cardiac CT and cardiac MRI allow for evaluation of structural heart disease and assessment of LV and RV function including quantification of LVEF, LV mass and volume, valvular structure and coronary anatomy including anomalous coronary origins. Cardiac MRI can be useful in the evaluation for myocardial scar and infiltrative processes evident as late gadolinium enhancement.<sup>S4.2.4-5-S4.2.4-9</sup> Cardiac MRI also provides high-quality assessment of LV and RV function, size, and degree of fibrosis and is particularly useful in arrhythmogenic right ventricular cardiomyopathy and HCM.

#### 4.2.5. Biomarkers

Recommendation for Biomarkers		
Referenced studies that support the recommendation are summarized in Online Data Supplement 7.		
COR	LOE	Recommendation
Ila	B-NR	1. In patients with structural heart disease, measurement of natriuretic peptides (BNP or N-terminal pro-BNP) can be useful by adding prognostic information to standard risk factors for predicting SCD or SCA. <sup>S4.2.5-1-S4.2.5-4</sup>

#### Recommendation-Specific Supportive Text

- Elevated levels of natriuretic peptides—B-type natriuretic peptide (BNP) or N-terminal pro-BNP—are associated with increased risk of SCA and appropriate ICD therapies, even after adjustment of LVEF and other risk factors.<sup>S4.2.5-1-S4.2.5-4</sup> These biomarkers are also predictive of nonsudden cardiovascular mortality and thus are not specific to SCD risk alone. Natriuretic peptides have also been evaluated for

predicting SCD in the general population.<sup>S4.2.5-5,S4.2.5-6</sup> In the Nurses' Health Study, an elevated N-terminal pro-BNP was an independent risk marker for SCD in presumably healthy women.<sup>S4.2.5-5</sup> In an older adult population, higher baseline levels of N-terminal pro-BNP were associated with SCD over a 16-year follow-up period.<sup>S4.2.5-6</sup> These biomarkers may also have a potential role in facilitating the identification of individuals at increased risk of SCD and VA in the general population, particularly in those at intermediate or high risk of ischemic heart disease, but further studies are needed. Use of biomarkers has not been shown to be useful for selecting patients for ICDs. A study of 4431 patients found high-sensitivity troponin to be only weakly predictive of SCD.<sup>S4.2.5-7</sup> However, there are no data on whether high-sensitivity troponin can improve the current SCD prediction algorithms.

#### 4.2.6. Genetic Considerations in Arrhythmia Syndromes

Recommendation for Genetic Counselling*		
COR	LOE	Recommendation
I	C-EO	1. In patients and family members in whom genetic testing for risk stratification for SCA or SCD is recommended, genetic counseling is beneficial.

\*Please refer to section 7.9 for disease-specific recommendations.

#### Synopsis

The diagnosis of most inherited arrhythmia syndromes is based on clinical features and family history. The availability of genetic testing for inherited arrhythmia syndromes can: 1) provide opportunity to confirm a suspected clinical diagnosis and sometimes provide prognostic information for the proband and 2) offer cascade screening of potentially affected family members when a disease-causing mutation is identified in the proband. The yield of genetic testing varies by disease. The verification of pathogenicity of suspected mutations is an evolving field, and exome sequencing has identified an increasing number of variants of uncertain significance in the general population.<sup>S4.2.6-1-S4.2.6-5</sup> Genotyping can have therapeutic implications for some arrhythmogenic phenotypes such as long QT syndrome and Fabry's disease,<sup>S4.2.6-6-S4.2.6-9</sup> where a monogenic pathogenic mutation has been clearly identified, the risk to mutation positive individuals has been extensively studied, and effective therapy relevant to the mutation can be instituted. In other diseases, such as Brugada syndrome, the role of a clear monogenic disease-causing mutation is less certain, and the genotype does not provide therapeutic or prognostic information for the proband.<sup>S4.2.6-5,S4.2.6-10-S4.2.6-12</sup> In arrhythmogenic right ventricular cardiomyopathy, some

desmosomal mutation positive individuals do not develop disease, indicating that additional mutations and environmental interactions likely influence the clinical development of disease.<sup>S4.2.6-13–S4.2.6-16</sup> Importantly, the absence of an identified disease-causing genetic mutation does not exclude the presence of disease, and as such, ongoing monitoring and decision-making are done based on the clinical phenotype. Genotyping is frequently most useful when a pathogenic mutation is identified in the proband, such that screening can be applied to relatives who are in a preclinical phase, allowing institution of lifestyle changes, therapy, or ongoing monitoring for those who are gene mutation positive.<sup>S4.2.6-7</sup> Refer to Section 7.9 for disease-specific recommendations.

In young patients (<40 years of age) without structural heart disease who have unexplained cardiac arrest, unexplained near drowning, or recurrent exertional syncope, genetic testing may be important to identify an inherited arrhythmia syndrome as a likely cause.<sup>S4.2.6-17–S4.2.6-23</sup>

### Recommendation-Specific Supportive Text

1. The decision to proceed with genetic testing requires discussion regarding the clinical use of genetic information to be obtained for both the proband and family members, as well as consideration of the important psychological, financial, employment, disability, and life insurance implications of positive genotyping.<sup>S4.2.6-17,S4.2.6-18,S4.2.6-20,S4.2.6-24</sup> Balancing privacy of health care information for the proband with the “right to know” for family members, and the ability to provide appropriate communication of information to all potentially affected family members can be challenging on many levels, including family dynamics, geographic proximity, and access to health care.<sup>S4.2.6-25</sup> For these reasons, genetic counseling generally occurs before proceeding with genetic testing, and, from a patient’s perspective, is optimally provided by genetic counselors, if available, in collaboration with physicians.<sup>S4.2.6-26,S4.2.6-27</sup> A combined approach of genetic counseling with medical guidance may appropriately balance the decision as to whether genetic testing would be beneficial on an individual basis.

## 4.3. Invasive Testing

### 4.3.1. Invasive Cardiac Imaging: Cardiac Catheterization or CT Angiography

Recommendation for Invasive Imaging: Cardiac Catheterization		
COR	LOE	Recommendation
I	C-EO	1. In patients who have recovered from unexplained SCA, CT or invasive coronary angiography is useful to confirm the presence or absence of ischemic heart disease and guide decisions for myocardial revascularization.

### Recommendation-Specific Supportive Text

1. Although randomized studies are unavailable, coronary angiography has an important role in establishing or excluding the presence of significant obstructive ischemic heart disease in patients with SCA or those with life-threatening VA.<sup>S4.3.1-1–S4.3.1-4</sup> Recurrent polymorphic VT or VF can be due to ongoing myocardial ischemia that resolves with coronary revascularization. Presence of ST-elevation on preresuscitation or early postresuscitation ECG suggests ischemia and potential ACS warranting urgent angiography and revascularization.<sup>S4.3.1-5</sup> ST-elevation can also result from coronary spasm or DC shocks. The absence of ST-elevation after cardiac arrest does not exclude obstructive or thrombotic coronary lesions. A coronary angiogram may not be warranted if a non-ischemic cause of SCA is established. Coronary and CT angiography also have an important role excluding the presence of anomalous origin of the coronary arteries that may cause SCD.

### 4.3.2. Electrophysiological Study for VA

Recommendations for Electrophysiological Study		
References that support the recommendations are summarized in Online Data Supplements 8 and 9.		
COR	LOE	Recommendations
IIa	B-R	1. In patients with ischemic cardiomyopathy, NICM, or adult congenital heart disease who have syncope or other VA symptoms and who do not meet indications for a primary prevention ICD, an electrophysiological study can be useful for assessing the risk of sustained VT. <sup>S4.3.2-1–S4.3.2-7</sup>
III: No Benefit	B-R	2. In patients who meet criteria for ICD implantation, an electrophysiological study for the sole reason of inducing VA is not indicated for risk stratification. <sup>S4.3.2-8–S4.3.2-11</sup>
III: No Benefit	B-NR	3. An electrophysiological study is not recommended for risk stratification for VA in the setting of long QT syndrome, catecholaminergic polymorphic ventricular tachycardia, short QT syndrome, or early repolarization syndromes. <sup>S4.3.2-12–S4.3.2-16</sup>

## Synopsis

Electrophysiological study can be used to induce sustained VA in patients with known or suspected VA. With the advent of the ICD and its proven benefit in the primary and secondary prevention of SCD, there are fewer indications for programmed stimulation to provoke VA. Patients with HF and LVEF ≤35% generally will have an indication for an ICD and specific induction of VT/VF before implantation is not necessary. Patients with LVEF >35% and unexplained syncope or near-syncope may benefit from an electrophysiological study to determine

if VT/VF is the cause of symptoms and to guide further therapy. Induction of VT/VF is often attempted before catheter ablation of the arrhythmia substrate to guide the procedure and to determine the success of the intervention after ablation is performed. An electrophysiological study can be used to determine the mechanism of a wide complex tachycardia. See Sections 7.3, 7.4, 7.6, 7.9.1.3, and 10.8 for recommendations regarding electrophysiological study for specific disease states.

### Recommendation-Specific Supportive Text

1. A study of electrophysiological testing in patients with symptomatic NICM found inducible VT/VF in 28% of patients which was associated with a higher rate of ICD events during follow-up.<sup>54.3.2-17</sup> In a prospective cohort of 180 patients with ischemic or NICM and syncope, induction of VT or VF at electrophysiological study correlated with cardiac mortality only in patients with ischemic heart disease. In patients with NICM, cardiac mortality correlated with LVEF but not with inducibility on electrophysiological study.<sup>54.3.2-18</sup>
2. In patients who meet criteria for ICD implantation (ie, HF and LVEF  $\leq 35\%$ ), data do not support the routine use of electrophysiological study solely for risk stratification, as such patients have been shown to derive survival benefit from the ICD.<sup>54.3.2-8-54.3.2-11</sup> An electrophysiological study may be helpful, however, in selected patients suspected to have preexcitation or supraventricular arrhythmias as the cause of symptoms or wide complex tachycardias that warrant definitive diagnosis and management. SVT leading to VT/VF or aberrantly conducted SVT may also be suspected in younger patients or those with a preserved LVEF. Induction of SVT and ablation may then be curative, with no need for an ICD. In such cases, failure to induce VT/VF after elimination of the substrate for SVT would be expected.
3. Risk stratification for channelopathies is generally made on the basis of symptoms, the ECG,<sup>54.3.2-13, 54.3.2-19-54.3.2-24</sup> exercise treadmill testing,<sup>54.3.2-25-54.3.2-27</sup> and the results of genetic testing.<sup>54.3.2-28-54.3.2-32</sup> The electrophysiological study (ie, programmed ventricular stimulation) does not have prognostic value for risk stratification in patients with these cardiac channelopathies.<sup>54.3.2-12-54.3.2-15</sup>

## 5. THERAPIES FOR TREATMENT OR PREVENTION OF VA

### 5.1. Medication Therapy

With the exception of beta blockers (eg, metoprolol succinate, carvedilol), there is no evidence from RCTs

that antiarrhythmic medications for VA improve survival when given for the primary or secondary prevention of SCD. However, the use of these medications is essential in some patients to control arrhythmias and improve symptoms. Medication use for VA is discussed, and any recommendations are listed, in subsequent sections. Further, medication-induced proarrhythmia is addressed in Section 10.7.

Antiarrhythmic medications are often categorized by the Vaughan Williams 4-level schema (class I: fast sodium channel blockers; class II: beta blockers; class III: repolarization potassium current blockers; class IV: nondihydropyridines calcium channel blockers).<sup>55.1.5.2-1</sup> This system does not address the complexities in antiarrhythmic medications, since nearly every agent has multiple effects. Table 7 shows uses, electrophysiological effects, pharmacological effects, and common adverse effects of antiarrhythmic medications.

#### 5.1.1. Medications With Prominent Sodium Channel Blockade

Except in specific circumstances, sodium channel blockers (Vaughn-Williams class I agents) have a limited role in the prevention of VT/SCD; this is based on a lack of survival benefit and increased mortality observed during chronic therapy in patients with ischemic heart disease (see Section 10.7). Specific circumstances where sodium channel blockers have been used to treat VT/SCA include: intravenous lidocaine for patients with refractory VT/cardiac arrest (especially witnessed)<sup>55.1.5.2-3</sup>; oral mexiletine for congenital long QT syndrome<sup>55.1.5.2-4</sup>; quinidine for patients with Brugada syndrome; and flecainide for patients with catecholaminergic polymorphic ventricular tachycardia.<sup>55.1.5.2-5</sup> These medications could also be used in ICD patients with drug- and ablation-refractory VT.

One newer medication of potential benefit, based on very limited data, is ranolazine. This medication, developed and FDA-approved as an antianginal agent, provides relatively specific late sodium channel current blockade in addition to less potent blockade of the phase 3 repolarizing potassium current; that is, the rapid delayed rectifier potassium current; IKr. The potential for clinical antiarrhythmic efficacy is supported by basic studies and experimental models.<sup>55.1.5.2-6</sup> Clinical data are scant. In a study of 12 patients, ranolazine reduced ICD shocks in otherwise medication-resistant VT/VF in 11 patients.<sup>55.1.5.2-7</sup> In MERLIN TIMI-36 (Metabolic Efficiency With Ranolazine for Less Ischemia in Non-ST-Elevation Acute Coronary Syndromes-Thrombolysis In Myocardial Infarction 36), ranolazine did not reduce SCD but did reduce VT in the first few days after a non-ST-segment elevation ACS.<sup>55.1.5.2-8</sup> In 1 RCT, high-risk ICD patients with ischemic or NICM were randomly assigned to ranolazine 1000 mg twice a day versus placebo.<sup>55.1.5.2-9</sup> High risk was defined as: 1) having a primary prevention

**Table 7. Pharmacological Characteristics of Available Antiarrhythmic Medications for Treating VA**

Antiarrhythmic Medication (Class) and Dose	Uses in VA/SCA	Target	Electrophysiological Effects	Pharmacological Characteristics	Common Adverse Effects
Acebutolol PO 200–1200 mg daily or up to 600 mg bid	VT, PVCs	Beta 1, Mild intrinsic sympathomimetic activity	Sinus rate slowed AV nodal refractoriness increased	Active metabolite $t_{1/2}$ : 8–13 h pProlonged with renal impairment) Metab: H Excr: F 60%, U 40%	Cardiac: Bradycardia, hypotension, HF, AVB Other: Dizziness, fatigue, anxiety, impotence, hyper/hypoesthesia
Amiodarone (III) IV: 300 mg bolus for VF/pulseless VT arrest; 150-mg bolus for stable VT; 1 mg/min x 6 h, then 0.5 mg/min x 18 h PO: 400 mg* q 8 to 12 h for 1–2 wk, then 300–400 mg daily; reduce dose to 200 mg daily if possible	VT, VF, PVC,	$I_{Na^+}$ , $I_{Ca^{2+}}$ , $I_{Kr}$ , $I_{K1}$ , $I_{Ks}$ , $I_{to}$ Beta receptor, Alpha receptor nuclear T3 receptor	Sinus rate slowed QRS prolonged QTc prolonged AV nodal refractoriness increased; increased DFT	$t_{1/2}$ : 26–107 d Metab: H Excr: F	Cardiac: Hypotension, bradycardia, AVB, TdP, slows VT below programmed ICD detection rate, increases defibrillation threshold Other: Corneal microdeposits, thyroid abnormalities, ataxia, nausea, emesis, constipation, photosensitivity, skin discoloration, ataxia, dizziness, peripheral neuropathy, tremor, hepatitis, cirrhosis, pulmonary fibrosis or pneumonitis
Atenolol (II) PO: 25–100 mg qd or bid	VT, PVC, ARVC, LQTS	Beta 1	Sinus rate slowed AV nodal refractoriness increased	$t_{1/2}$ : 6–7 h (prolonged with renal impairment) Metab: H Excr: F 50%, U 40%	Cardiac: Bradycardia, hypotension, HF, AVB Other: Dizziness, fatigue, depression, impotence
Bisoprolol (II) PO: 2.5–10 mg once daily	VT, PVC	Beta 1 receptor	Sinus rate slowed AV nodal refractoriness increased	$t_{1/2}$ : 9–12 h Metab: H Excr: U	Cardiac: Chest pain, bradycardia, AVB Other: Fatigue, insomnia, diarrhea
Carvedilol (II) PO: 3.125–25 mg q 12 h	VT, PVC	Beta 1 and 2 receptors, Alpha	Sinus rate slowed AV nodal refractoriness increased	$t_{1/2}$ : 7–10 h Metab: H Excr: F	Cardiac: Bradycardia, hypotension, AVB, edema, syncope Other: Hyperglycemia, dizziness, fatigue, diarrhea
Diltiazem (IV) IV: 5–10 mg qd: 15–30 min Extended release: PO: 120–360 mg/day	VT specifically RVOT, idiopathic LVT	$I_{Ca-L}$	Sinus rate slowed PR prolonged AV nodal conduction slowed	$t_{1/2}$ : Injection 2–5 h, immediate release 4.5–12 h, extended release 12 h, and severe hepatic impairment 14–16 h Metab: H Excr: U	Cardiac: Hypotension, edema, HF, AVB, bradycardia, exacerbation of HFrEF Other: Headache, rash, constipation
Esmolol (II) IV: 0.5 mg/kg bolus, 0.05 mg/kg/min	VT	Beta 1 receptor	Sinus rate slowed AV nodal refractoriness increased	$t_{1/2}$ : 9 min Metab: RBC esterases Excr: U	Cardiac: Bradycardia, hypotension, HF, AVB Other: Dizziness, nausea
Flecainide (IC) PO: 50–200 mg q 12 h	VT, PVC (in the absence of structural heart disease). Has a role in treating patients with CPVT	$I_{Na^+}$ , $I_{Kr}$ , $I_{Kur}$	PR prolonged QRS prolonged; increased DFT	$t_{1/2}$ : 7–22 h Metab: H Excr: U	Cardiac: Sinus node dysfunction, AVB, drug-induced Brugada syndrome, monomorphic VT in patients with a myocardial scar, exacerbation of HFrEF Other: Dizziness, tremor, vision disturbance, dyspnea, nausea
Lidocaine (IB) IV: 1 mg/kg bolus, 1–3 mg/min 1–1.5 mg/kg. Repeat 0.5–0.75 mg/kg bolus every 5–10 min (max cumulative dose 3 mg/kg). Maintenance infusion is 1–4 mg/min although one could start at 0.5 mg/min	VT, VF	$I_{Na}$	No marked effect on most intervals; QTc can slightly shorten	Initial $t_{1/2}$ 7–30 min; terminal 90–120 min. Prolonged in HF, liver disease, shock, severe renal disease Metab: H Excr: U	Cardiac: Bradycardia, hemodynamic collapse, AVB, sinus arrest Other: Delirium, psychosis, seizure, nausea, tinnitus, dyspnea, bronchospasm

(Continued)

Table 7. Continued

Antiarrhythmic Medication (Class) and Dose	Uses in VA/SCA	Target	Electrophysiological Effects	Pharmacological Characteristics	Common Adverse Effects
Metoprolol (II) IV: 5 mg q 5 min up to 3 doses PO: 25–100 mg Extended release qd or q 12 h	VT, PVC	Beta 1 receptor	Sinus rate slowed AV nodal refractoriness increased	$t_{1/2}$ : 3–4 h Metab: H Excr: U	Cardiac: Bradycardia, hypotension, AVB Other: Dizziness, fatigue, diarrhea, depression, dyspnea
Mexiletine (IB) PO: 150–300 mg q 8 h or q 12 h	T, VF, PVC, has a role in patients with LQT3	$I_{Na}$	No marked effect on most intervals; QTc can slightly shorten	$t_{1/2}$ : 10–14 h Metab: H Excr: U	Cardiac: HF, AVB Other: Lightheaded, tremor, ataxia, paresthesias, nausea, blood dyscrasias
Nadolol (II) PO: 40–320 mg daily	VT, PVC, LQTS, CPVT	Beta 1 and 2 receptors	Sinus rate slowed AV nodal refractoriness increased	$t_{1/2}$ : 20–24 h Metab: none Excr: U	Cardiac: Bradycardia, hypotension, HF, AVB Other: Edema, dizziness, cold extremities, bronchospasm
Procainamide (IA) IV: loading dose 10–17 mg/kg at 20–50 mg/min Maintenance dose: 1–4 mg/min PO (SR preparation): 500–1250 mg q 6 h	VT	$I_{Na}^+$ , $I_{Kr}$	QRS prolonged QTc prolonged; increased DFT	Metab: H $t_{1/2}$ : 2–5 h; NAPA 6–8 h $t_{1/2}$ prolonged in renal dysfunction. Anephric: proc 11 h and NAPA 42 h Excr: U	Cardiac: TdP; AVB, hypotension and exacerbation of HFrEF Other: Lupus symptoms, diarrhea, nausea, blood dyscrasias
Propafenone (IC) PO: Immediate release 150–300 mg q 8 h Extended release 225–425 mg q 12 h	VT, PVC (in the absence of structural heart disease)	$I_{Na}^+$ , $I_{Kr}$ , $I_{Kur}$ , Beta receptor, Alpha receptor	PR prolonged QRS prolonged; increased DFT	$t_{1/2}$ : 2–10 h or 10–32 h $t_{1/2}$ : extensive metabolizers 2–10 h; poor metabolizers 10–32 h. Metab: H Excr: U	Cardiac: HF, AVB, drug-induced Brugada syndrome Other: Dizziness, fatigue, nausea, diarrhea, xerostomia, tremor, blurred vision
Propranolol (II) IV: 1–3 mg q 5 min to a total of 5 mg PO: Immediate release 10–40 mg q 6 h; Extended release 60–160 mg q 12 h	VT, PVC, LQTS	Beta 1 and 2 receptors, $I_{Na}$	Sinus rate slowed AV nodal refractoriness increased	$t_{1/2}$ : Immediate release 3–6 h Extended release 8–10 h Metab: H Excr: U	Cardiac: Bradycardia, hypotension, HF, AVB Other: Sleep disorder, dizziness, nightmares, hyperglycemia, diarrhea, bronchospasm
Quinidine (IA) PO: sulfate salt 200–600 mg q 6 h to q 12 h gluconate salt 324–648 mg q 8 h to q 12 h IV: loading dose: 800 mg in 50 mL infused at 50 mg/min	T, VF, (including short QT syndrome, Brugada)	$I_{Na}^+$ , $I_{to}$ , $I_{Kr}$ , M, Alpha receptor	QRS prolonged QTc prolonged; increased DFT	$t_{1/2}$ : 6–8 h longer in HF, liver cirrhosis, and with older age Metab: H Excr: U	Cardiac: Syncope, TdP, AVB Other: Dizziness, diarrhea, nausea, esophagitis, emesis, tinnitus, blurred vision, rash, weakness, tremor; blood dyscrasias
Ranolazine (not classified) PO: 500–1000 mg q 12 h	VT	$I_{Na}^+$ , $I_{Kr}$	Sinus rate slowed Tc prolonged	$t_{1/2}$ : 7 h Metab: H Excr: U 75%, F 25%	Cardiac: Bradycardia, hypotension Other: Headache, dizziness, syncope, nausea, dyspnea
Sotalol (III) IV: 75 mg q 12 h PO: 80–120 mg q 12 h, may increase dose every 3 d; max 320 mg/d	VT, VF, PVC	$I_{Kr}$ , Beta 1 and 2 receptor	Sinus rate slowed QTc prolonged AV nodal refractoriness increased; decreased DFT	$t_{1/2}$ : 12 h Metab: none Excr: U	Cardiac: Bradycardia, hypotension, HF, syncope, TdP Other: Fatigue, dizziness, weakness, dyspnea, bronchitis, depression, nausea, diarrhea

(Continued)

Table 7. Continued

Antiarrhythmic Medication (Class) and Dose	Uses in VA/SCA	Target	Electrophysiological Effects	Pharmacological Characteristics	Common Adverse Effects
Verapamil (IV) IV: 2.5–5 mg q 15–30 min Sustained release PO: 240–480 mg/d	VT (specifically RVOT, verapamil-sensitive idiopathic LVT)	$I_{Ca-L}$	Sinus rate slowed PR prolonged AV nodal conduction slowed	$t_{1/2}$ : 3–7 h Metab: H Excr: U	Cardiac: Hypotension, edema, HF, AVB, bradycardia, exacerbation of HFrEF Other: Headache, rash, gingival hyperplasia, constipation, dyspepsia

\*Although up to 800 mg every 8 h might be used, higher doses of amiodarone are associated with a higher risk of adverse events. Modified from Shleifer JW, et al.<sup>55.1.5.2-2</sup>

Alpha indicates alpha-adrenergic receptor; ARVC, arrhythmogenic right ventricular cardiomyopathy; AV, atrioventricular; AVB, atrioventricular block; Beta, beta-adrenergic receptor; HF, heart failure; CPVT, catecholaminergic polymorphic ventricular tachycardia; DFT, defibrillation threshold; F, feces; H, hepatic;  $I_{Ca}$ , L-type calcium channel current;  $I_{K1}$ , inward rectifier potassium channel;  $I_{KACHr}$ , muscarinic receptor-gated potassium channel;  $I_{KATP}$ , adenosine-activated potassium channel;  $I_{Kr}$ , rapid delayed rectifier potassium current;  $I_{Ksr}$ , slow delayed rectifier potassium current;  $I_{Kur}$ , ultra-rapid delayed rectifier potassium current;  $I_{Na}$ , fast inward sodium current;  $I_{to}$ , transient outward potassium current; LQTS, long QT syndrome; LVT, left ventricular tachycardia; M, muscarinic; Metab, metabolism; NAPA, n-acetyl procainamide; PVC, premature ventricular complex; QTc, corrected QT interval;  $t_{1/2}$ , half-life; RVOT, right ventricular outflow tract; T3, triiodothyronine; TdP, torsades de pointes; U, urine; VT, ventricular tachycardia; and VF, ventricular fibrillation.

ICD without a history of documented VT/VF and with one of the following conditions: BUN  $\geq$ 26 mg/dL, QRS  $>$ 120 msec, atrial fibrillation, or NSVT or  $>$ 500 VPBs on 24-hour Holter recording; 2) having a primary prevention ICD with a history of documented VT/VF appropriately treated with ICD therapy or untreated NSVT; or 3) having a secondary prevention ICD after documented VT/VF or cardiac arrest. Ranolazine did not significantly reduce the primary endpoint of VT/VF requiring appropriate ICD therapy or death. In a prespecified secondary analysis, ranolazine was associated with a significant reduction in VT events treated with anti-tachycardia pacing.<sup>55.1.5.2-9</sup>

### 5.1.2. Beta Blockers

Because of their excellent safety profile and effectiveness in treating VA and reducing the risk of SCD, beta blockers are often first-line antiarrhythmic therapy.<sup>55.1.5.2-10,55.1.5.2-11</sup> Their antiarrhythmic efficacy is related to the effects of adrenergic-receptor blockade on sympathetically mediated triggering mechanisms, slowing of the sinus rate, and possibly inhibition of excess calcium release by the ryanodine receptor.<sup>55.1.5.2-12</sup>

Beta blockers reduce all-cause mortality and SCD in patients with HF with reduced EF (HFrEF).<sup>55.1.5.2-13–55.1.5.2-15</sup> Although beta blockers have long been proven to reduce mortality after MI,<sup>55.1.5.2-16</sup> registry data confirm that early beta blocker use in patients with MI and risk factors for shock ( $>$ 70 years of age, symptoms  $<$ 12 hours [ST-elevation MI patients], systolic blood pressure  $<$ 120 mm Hg, and heart rate  $>$ 110 beat/min on presentation) is associated with an increased risk of shock or death.<sup>55.1.5.2-17</sup> In the setting of polymorphic VT after MI, beta blockers reduce mortality.<sup>55.1.5.2-18</sup> Beta blockers suppress VA in some patients with structurally normal hearts.<sup>55.1.5.2-19</sup> When used in combination with membrane-stabilizing antiarrhythmic medications, beta blockers can enhance antiarrhythmic efficacy.<sup>55.1.5.2-20</sup> Beta blockers (eg, nadolol, propranolol) are also first-

line therapy for some cardiac channelopathies (eg, long QT syndrome, catecholaminergic polymorphic ventricular tachycardia).

### 5.1.3. Amiodarone and Sotalol

Amiodarone possesses a wide spectrum of actions that include blockade of beta receptors and sodium, calcium and potassium currents (ie, a multichannel blocker). Its overall long-term effect on survival is controversial, with most studies showing no clear advantage over placebo. A few studies and a meta-analysis of several large studies have shown a reduction in SCD using amiodarone in patients with LV dysfunction due to prior MI and NICM,<sup>55.1.5.2-21–55.1.5.2-23</sup> but SCD-HeFT showed no survival benefit from amiodarone compared with placebo.<sup>55.1.5.2-24</sup> A secondary analysis of the SCD-HeFT showed increased risk of mortality with amiodarone in patients with New York Heart Association (NYHA) class III symptoms.<sup>55.1.5.2-25</sup> A systematic review of the literature in high-risk patients (LVEF  $<$ 40%, with or without coronary disease), concluded that, for primary prevention, amiodarone, compared with no treatment or placebo, decreased the risk of SCD (Risk ratio: 0.76; 95% CI: 0.66–0.88) and all-cause mortality (Risk ratio: 0.88; 95% CI: 0.78–1.00), but the quality of the supporting evidence was very low.<sup>55.1.5.2-26</sup> For secondary prevention of SCD, the same systematic review identified neither risk nor benefit with amiodarone.<sup>55.1.5.2-26</sup> Compared with beta-blocker therapy and other antiarrhythmic medications (including sotalol), amiodarone appears to reduce the risk of SCD and all-cause mortality.<sup>55.1.5.2-26</sup> Intravenous amiodarone has a role in reducing recurrent VF/VF during resuscitation.<sup>55.1.5.2-3,55.1.5.2-27–55.1.5.2-29</sup>

Chronic administration of amiodarone is associated with complex medication interactions and a host of adverse effects involving the lung, liver, thyroid, skin, and nervous system. As a general rule, the longer the therapy and the higher dose of amiodarone, the greater the likelihood of adverse effects that will require

discontinuance of the medication.<sup>55.1.5.2-26</sup> For this reason, chronic treatment of young patients with amiodarone should be reserved as a bridge to more definitive treatment options such as catheter ablation. Baseline evaluation of patients may include ECG, liver function tests, thyroid function tests, chest x-ray, and pulmonary function tests (including diffusing capacity of the lungs for carbon monoxide). Monitoring for toxicity generally includes periodic history and physical examination, as well as evaluation of the ECG, chest x-ray, and thyroid, liver, and lung function. High-resolution chest CT is generally reserved for suspected pulmonary toxicity.<sup>55.1.5.2-30</sup>

Although sotalol has some efficacy in suppressing VA, it has significant proarrhythmic effects and has not been shown to improve survival.<sup>55.1.5.2-31</sup> D-sotalol was shown in the SWORD (Survival With Oral d-Sotalol) trial to increase the risk of death in patients with heart failure.<sup>55.1.5.2-32</sup> Unlike amiodarone and many other antiarrhythmic agents, sotalol appears to reduce the defibrillation threshold.<sup>55.1.5.2-33</sup> Also, sotalol may lead to HF decompensation, and so its use in patients with an LVEF <20% is generally avoided.

#### 5.1.4. Calcium Channel Blockers

For the treatment of most VA, nondihydropyridines calcium channel blockers have no role. In fact, intravenous verapamil given for sustained VT has been associated with hemodynamic collapse, especially in patients with prior MI.<sup>55.1.5.2-34,55.1.5.2-35</sup> For patients with a structurally normal hearts, verapamil or diltiazem can suppress some outflow tract origin.<sup>55.1.5.2-35–55.1.5.2-39</sup> Oral and intravenous verapamil are effective in treating idiopathic interfascicular reentrant LVT.<sup>55.1.5.2-38</sup> Calcium channel blockers should not be given to patients with VT in the setting of HF/rEF.

### 5.1.5. Nonantiarrhythmic Medications and Therapies

#### 5.1.5.1. Electrolytes

Administration of potassium and magnesium has been proposed as helpful adjuncts in the prevention of VA.<sup>55.1.5.2-40,55.1.5.2-41</sup> Hypokalemia and hypomagnesemia are common consequences of diuretic therapy in HF, both have been associated with VA during an acute MI,<sup>55.1.5.2-41,55.1.5.2-42</sup> and can increase the risk of torsades de pointes in patients on medications or with conditions known to prolong the QT interval.<sup>55.1.5.2-43</sup> In fact, in patients with torsades de pointes, intravenous magnesium is first-line therapy.<sup>55.1.5.2-44</sup> In patients who are deficient in both magnesium and potassium, magnesium should be repleted to facilitate replacement of the potassium.<sup>55.1.5.2-45</sup> In the case of potassium, some recommend keeping the potassium level between 4.5 mmol/L and 5 mmol/L to prevent VA and SCD.<sup>55.1.5.2-46,55.1.5.2-47</sup> A large observational study of patients with an acute MI found that the lowest rates

of death were seen in patients with serum potassium concentrations between 3.5 mmol/L and <4.5 mmol/L.<sup>55.1.5.2-48</sup> Interestingly, the rates of VA did not rise unless the potassium was <3 mmol/L or ≥5 mmol/L. Likewise, a large randomized, double-blind trial of intravenous magnesium in the post-MI period demonstrated no benefit in 30-day mortality.<sup>55.1.5.2-40</sup> It remains quite reasonable to monitor potassium and magnesium during aggressive diuresis and in the post-MI period.

#### 5.1.5.2. n-3 Fatty Acids and Lipids

Both n-3 polyunsaturated fatty acids and statin therapies may have a role in the prevention of SCD, thought to be due to a stabilization of the bilipid myocyte membrane involved in maintaining electrolyte gradients.<sup>55.1.5.2-49</sup>

Early data were promising regarding the effects of n-3 polyunsaturated fatty acids on the reduction of cardiovascular events and SCD. In 2006, a large meta-analysis of 19 observational and RCTs demonstrated a significant association between the consumption of n-3 polyunsaturated fatty acids and prevention of SCD.<sup>55.1.5.2-50</sup> The randomized GISSI (Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto)-Prevenzione trial in people with recent MI, found that fish oil 1 g/d reduced mortality, due to fewer SCD.<sup>55.1.5.2-51</sup> However, subsequent RCTs have not replicated these benefits and have shown n-3 polyunsaturated fatty acids to be ineffective.<sup>55.1.5.2-52–55.1.5.2-56</sup> Because studies showed a consistent lack of harm from n-3 polyunsaturated fatty acids, patients can be reassured of their safety. Longer-term data will hopefully clarify the conflicting results.

In contrast, statin medications clearly reduce mortality and appear to reduce the risk of SCD related to ischemic heart disease.<sup>55.1.5.2-57</sup> The predominant mechanism remains uncertain. Prevention of coronary plaque rupture or a direct cardioprotective effect reducing VA has been suggested. Experimental ischemia/reperfusion models demonstrate a cardioprotective effect of statins, and a large observational analysis observed this effect in humans.<sup>55.1.5.2-42,55.1.5.2-56–55.1.5.2-58</sup> This was explored further in HF in several secondary analyses of patients on statins in ICD prevention trials, including the MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial-Cardiac Resynchronization Therapy), SCD-HeFT, AVID (Antiarrhythmics versus Implantable Defibrillators),<sup>55.1.5.2-59</sup> and DEFINITE (DEFibrillators In Non-Ischemic Cardiomyopathy Treatment Evaluation) trials that showed less SCD risk among the patients on statins.<sup>55.1.5.2-58,55.1.5.2-60–55.1.5.2-62</sup> However, this general effect in HF was not confirmed in 2 prospective RCTs of rosuvastatin in HF; the CORONA (Controlled Rosuvastatin Multinational Trial in Heart Failure) and GISSI-HF (Gruppo Italiano per lo Studio della Sopravvivenza nell'Insufficienza Cardiaca-Heart Failure).<sup>55.1.5.2-63,55.1.5.2-64</sup> It appears that the beneficial effects of statins are con-

fined to the population with or at risk for atherosclerotic cardiovascular disease and/or ischemia, and not HF generally.

## 5.2. Preventing SCD With HF Medications

Recommendation for Pharmacological Prevention of SCD		
References that support the recommendation are summarized in Online Data Supplement 10.		
COR	LOE	Recommendation
I	A	1. In patients with HFrEF (LVEF $\leq$ 40%), treatment with a beta blocker, a mineralocorticoid receptor antagonist and either an angiotensin-converting enzyme inhibitor, an angiotensin-receptor blocker, or an angiotensin receptor-neprilysin inhibitor is recommended to reduce SCD and all-cause mortality. <sup>S5.2-1–S5.2-8</sup>

### Recommendation-Specific Supportive Text

1. For patients with HF and depressed LV function, appropriate medical therapy is important to reduce SCD. These therapies have various beneficial effects on arrhythmia mechanisms. Beta blockers reduce myocardial oxygen demand and electrical excitability, and counter arrhythmogenic effects of sympathetic stimulation. Angiotensin-converting enzyme inhibitors and angiotensin-receptor blockers decrease preload and afterload, decreasing myocardial oxygen demand, blocking the formation of angiotensin II, and slowing the progression of ventricular remodeling and fibrosis. Mineralocorticoid receptor antagonists limit potassium loss, decrease fibrosis, and increase the myocardial uptake of norepinephrine.<sup>S5.2-7</sup>

RCTs in patients with HFrEF have consistently demonstrated that chronic therapy with beta blockers reduces all-cause mortality, VA, and SCD.<sup>S5.2-2,S5.2-4,S5.2-5,S5.2-9</sup> Three beta blockers (ie, bisoprolol, carvedilol, sustained-release metoprolol succinate) have been proven to reduce mortality in patients with current or prior symptoms of HFrEF without beta-blocker contraindications. Angiotensin-converting enzyme inhibition also reduces mortality and SCD.<sup>S5.2-3</sup> Angiotensin-receptor blockers added to angiotensin-converting enzyme inhibitor showed additional benefit to angiotensin-converting enzyme inhibitors in some<sup>S5.2-10</sup> but not other RCTs.<sup>S5.2-8,S5.2-11</sup> Therapy with the mineralocorticoid-receptor antagonists, spironolactone and eplerenone, have also demonstrated reductions in both all-cause mortality and SCD.<sup>S5.2-6,S5.2-12,S5.2-13</sup> Recent studies of the angiotensin receptor-neprilysin inhibitor (sacubitril/valsartan) versus

angiotensin-converting enzyme inhibitor demonstrated a reduction in SCD and cardiac mortality.<sup>S5.2-14</sup>

## 5.3. Defibrillators for Treatment of VA and SCD

See Sections 7, 10.2, 10.3, 10.8, and 10.9.

Defibrillation is highly effective in terminating life-threatening VA. This therapy can be delivered by a transvenous ICD, a subcutaneous implantable cardioverter-defibrillator, a wearable cardioverter-defibrillator or an external defibrillator. These devices monitor the heart rhythm continuously and deliver therapy in response to a tachycardia that meets preprogrammed detection rates and arrhythmia duration. The vast majority of transvenous ICDs are implanted in the subclavicular area under fluoroscopy guidance. subcutaneous implantable cardioverter-defibrillators are implanted in the left side of the chest over the sixth rib between the left midaxillary and left anterior axillary lines. ICDs with epicardial sensing and pacing leads are still being implanted in some patients especially those with certain forms of congenital heart disease.

The transvenous ICD has been in clinical use for >3 decades, and robust data from high-quality RCTs support its use in various patient populations including survivors of cardiac arrest, patients with VT and structural heart disease, and patients with significant LV dysfunction.

## 5.4. Catheter Ablation

### 5.4.1. General Considerations

Catheter ablation is an important treatment option for patients with VA when antiarrhythmic medications are ineffective, not tolerated, or not desired by the patient. Monomorphic VA usually have an origin or substrate that can be targeted for ablation. Ablation is an option for selected patients with polymorphic VT/VF only if an initiating PVC focus or substrate can be identified. The ablation strategy, risks and outcomes are related to the mechanism and location of the VA. Most VA originate close to the subendocardium and are approached through a transvenous (for the right ventricle) or transaortic/transeptal (for the left ventricle) catheterization. Some diseases give rise to VA from the subepicardium, which may be approached by epicardial mapping and ablation. Pericardial access is usually achieved by a percutaneous subxiphoid puncture. The catheter ablation procedure usually involves attempts to induce VT by programmed electrical stimulation to confirm the diagnosis and guide ablation. Problems limiting success include inability to induce an arrhythmia for mapping (common with idiopathic VA), or origin of the arrhythmia from an inaccessible location in the myocardium (common in some cardiomyopathies).



### 5.4.2. VA in Patients With No Apparent Structural Heart Disease

See Section 8.

VA that are not associated with underlying structural heart disease or a genetic arrhythmia syndrome are commonly referred to as idiopathic. Most idiopathic VA are monomorphic and based on a focal mechanism of triggered activity or abnormal automaticity; a few are due to reentry. For patients who are symptomatic, and in whom antiarrhythmic medications are ineffective, not tolerated, or not desired by the patient, catheter ablation is a treatment option. The ablation strategy is to identify the site of origin manifested by the earliest site of electrical activation, or when this is not practical, by pace mapping. Catheter ablation of idiopathic VA is usually accomplished with endocardial catheterization, though an epicardial approach through the coronary venous circulation or a subxiphoid pericardial puncture may occasionally be required. Ablation failure for idiopathic VA is often due to inability to provoke the arrhythmia to allow mapping in the electrophysiological laboratory or origin from an inaccessible region.

### 5.4.3. Scar-Related VT

See Section 8.

For most patients with structural heart disease, sustained monomorphic VT is due to reentry through regions of surviving myocardial fibers associated with areas of fibrous scar. The ablation strategy for these reentry circuits is to identify and eliminate channels of surviving myocardium within the scar that are often associated with slow conduction facilitating reentry. For most VTs that are related to prior MI, the substrate is on the subendocardial surface of the left ventricle. In NICM, the reentrant circuits are more variable in location, often involve the epicardial surface of either ventricle and frequently extending into the midmyocardium where ablation may be difficult to achieve from either surface. In tetralogy of Fallot specific reentry paths have been defined.<sup>55.4.3-1</sup> Electroanatomical mapping that helps clarify the relation of electrophysiological abnormalities to cardiac anatomy is commonly employed. Areas of scar can be appreciated as regions of relatively low electrogram voltage. For scar-related VTs, hemodynamic intolerance often limits mapping during VT. Ablation is then often guided by substrate mapping, in which areas of scar and potential reentry circuit substrate are delineated in electroanatomic maps based on electrocardiographic and pacing characteristics assessed during hemodynamically stable sinus or paced rhythm. Catheter ablation of scar-related VT requires an advanced level of experience by the operator, electrophysiological laboratory staff, and anesthesiologists as well as availability of surgical back-up and specialized mapping, imaging, and ablation equipment.<sup>55.4.3-2,55.4.3-3</sup>

## 5.5. Surgery and Revascularization Procedures in Patients With Ischemic Heart Disease

### Recommendations for Surgery and Revascularization Procedures in Patients With Ischemic Heart Disease

References that support the recommendations are summarized in Online Data Supplement 11.

COR	LOE	Recommendations
I	B-NR	1. Patients with sustained VA and survivors of SCA should be evaluated for ischemic heart disease, and should be revascularized as appropriate. <sup>55.5-1-55.5-4</sup>
I	C-EO	2. In patients with anomalous origin of a coronary artery suspected to be the cause of SCA, repair or revascularization is recommended.

### Recommendation-Specific Supportive Text

1. Myocardial ischemia is a cause of sustained polymorphic VT/VF, and revascularization is an effective treatment to prevent myocardial ischemia. For patients with life-threatening VA, observational studies show that patients undergoing coronary artery bypass graft (CABG) had substantially better survival after accounting for other predictors.<sup>55.5-1,55.5-5</sup> The risk of SCD appears comparable for patients with complex ischemic heart disease randomized to treatment with PCI versus CABG.<sup>55.5-6</sup> For patients with low LVEF and ischemic heart disease amenable to CABG, the risk of SCD is lower with CABG than medical therapy.<sup>55.5-2,55.5-7</sup> Observational studies show an association between a lower likelihood of death with revascularization for survivors of SCA and CABG<sup>55.5-3</sup> or PCI.<sup>55.5-4</sup> Revascularization alone is usually insufficient to prevent recurrence of sustained monomorphic VT; further evaluation for inducible VT is generally considered if ventricular function is depressed and/or scar is present.
2. Anomalous aortic origin of the coronary arteries is detected in approximately 1% of patients undergoing routine coronary angiography, and <0.2% of children and adolescents undergoing echocardiography.<sup>55.5-8</sup> Although ischemic heart disease is detected in as many as 24% to 55% of SCD cases in young patients <35 years of age,<sup>55.5-9,55.5-10</sup> anomalous aortic origin of the coronary arteries is an important cause of SCD in the young, reported in 10% to 17% of patients included in postmortem studies.<sup>55.5-10,55.5-11</sup> Anomalous origin of the coronary arteries can be identified by echocardiography, invasive coronary angiography, CT angiography or cardiac MRI. In patients with SCA or life-threatening VA presumed

related to ischemia caused by anomalous origin of a coronary artery, repair or revascularization is performed to alleviate ischemia and reduce the recurrence of VA.<sup>S5.5-6,S5.5-7,S5.5-12-S5.5-14</sup>

### 5.5.1. Surgery for Arrhythmia Management

Recommendation for Surgery for Arrhythmia Management		
References that support the recommendation are summarized in Online Data Supplement 12.		
COR	LOE	Recommendation
IIb	C-LD	1. In patients with monomorphic VT refractory to antiarrhythmic medications and attempts at catheter ablation, surgical ablation may be reasonable. <sup>S5.5.1-1-S5.5.1-7</sup>

### Recommendation-Specific Supportive Text

- Cardiac surgery as a standalone procedure for VT is rarely performed, but has a role in some highly symptomatic patients, when antiarrhythmic medications and catheter ablation fails or are not possible, particularly if the failure of ablation is due to an arrhythmia arising from an area that is inaccessible to catheter ablation, such as deep in the myocardium, beneath epicardial fat, or near the coronary arteries. Surgical ablation of tachycardia can also be performed at the time of other cardiac surgical interventions, such as during surgical resection of large aneurysms due to prior MI in which the border zone is often a substrate for VT, or placement of an LV assist device (LVAD).<sup>S5.5.1-5-S5.5.1-7</sup> The procedure requires detailed characterization of the arrhythmia usually with preoperative imaging and mapping, therefore, surgical ablation is best undertaken at tertiary referral centers and with collaboration between experienced surgeons and electrophysiologists.

### 5.6. Autonomic Modulation

Recommendations for Autonomic Modulation		
References that support the recommendations are summarized in Online Data Supplements 13 and 14.		
COR	LOE	Recommendations
IIa	C-LD	1. In patients with symptomatic, non-life-threatening VA, treatment with a beta blocker is reasonable. <sup>S5.6-1</sup>
IIb	C-LD	2. In patients with VT/VF storm in whom a beta blocker, other antiarrhythmic medications, and catheter ablation are ineffective, not tolerated, or not possible, cardiac sympathetic denervation may be reasonable. <sup>S5.6-2-S5.6-4</sup>

### Synopsis

Sympathetic activation is proarrhythmic and parasympathetic activation is generally antiarrhythmic in VT/VF.

Modulating the autonomic nervous system for the purpose of preventing arrhythmias is an emerging therapeutic modality. For the prevention of VA, autonomic modulation can be done either through interruption of sympathetic outflow to the heart, pharmacological beta blockade, or through stimulation of the parasympathetic pathway (eg, vagal nerve stimulators, spinal cord stimulators). Although autonomic modulation has proven efficacy for certain conditions such as long QT syndrome and catecholaminergic polymorphic ventricular tachycardia (see Section 7.9), evidence is limited for its applicability to the broader group of VA, but studies are ongoing. Currently, there are limited data on the role of vagal nerve stimulators and spinal cord stimulators for the prevention of VA/SCD in humans, and thus no formal recommendation could be supported.<sup>S5.6-5</sup>

### Recommendation-Specific Supportive Text

- Many patients with non-life-threatening VA require only reassurance, but others have symptoms that warrant therapy. A small RCT of patients with symptomatic VA demonstrated a significant reduction in the arrhythmic burden with atenolol.<sup>S5.6-1</sup>
- VT/VF storm causes significant morbidity and is associated with increased mortality. For VT/VF storm refractory to treatment (medications, catheter ablation), cardiac sympathetic denervation has been shown in several small, observational studies<sup>S5.6-3,S5.6-6</sup> and 1 RCT<sup>S5.6-4</sup> to reduce the arrhythmia burden. This has been shown for left or bilateral cardiac sympathetic denervation, and it has been suggested that bilateral cardiac sympathetic denervation may be superior.<sup>S5.6-3</sup> Although data are limited, the significant morbidity and limited options in these patients make cardiac sympathetic denervation a reasonable option in selected patients.

## 6. Acute Management of Specific VA

Recommendations for Management of Cardiac Arrest		
References that support the recommendations are summarized in Online Data Supplements 15 and 16.		
COR	LOE	Recommendations
I	A	1. CPR should be performed in patients in cardiac arrest according to published basic and advanced cardiovascular life support algorithms. <sup>S6-1-S6-3</sup>
I	A	2. In patients with hemodynamically unstable VA that persist or recur after a maximal energy shock, intravenous amiodarone should be administered to attempt to achieve a stable rhythm after further defibrillation. <sup>S6-1,S6-4-S6-6</sup>

Recommendations for Management of Cardiac Arrest (Continued)		
COR	LOE	Recommendations
I	A	3. Patients presenting with VA with hemodynamic instability should undergo direct current cardioversion. <sup>56-1-56-3</sup>
I	B-NR	4. In patients with polymorphic VT or VF with ST-elevation MI, angiography with emergency revascularization is recommended. <sup>56-7-56-10</sup>
I	C-EO	5. Patients with a wide-QRS tachycardia should be presumed to have VT if the diagnosis is unclear.
IIa	A	6. In patients with hemodynamically stable VT, administration of intravenous procainamide can be useful to attempt to terminate VT. <sup>56-11-56-13</sup>
IIa	B-R	7. In patients with a witnessed cardiac arrest due to VF or polymorphic VT that is unresponsive to CPR, defibrillation, and vasopressor therapy, intravenous lidocaine can be beneficial. <sup>56-1,56-4,56-5,56-14,56-15</sup>
IIa	B-R	8. In patients with polymorphic VT due to myocardial ischemia, intravenous beta blockers can be useful. <sup>56-16,56-17</sup>
IIa	B-NR	9. In patients with a recent MI who have VT/VF that repeatedly recurs despite direct current cardioversion and antiarrhythmic medications (VT/VF storm), an intravenous beta blocker can be useful. <sup>56-17,56-18</sup>
IIb	A	10. In patients in cardiac arrest, administration of epinephrine (1 mg every 3 to 5 minutes) during CPR may be reasonable. <sup>56-1,56-19-56-24</sup>
IIb	B-R	11. In patients with hemodynamically stable VT, administration of intravenous amiodarone or sotalol may be considered to attempt to terminate VT. <sup>56-5,56-13,56-25,56-26</sup>
III: No Benefit	A	12. In patients with cardiac arrest, administration of high-dose epinephrine (>1 mg boluses) compared with standard doses is not beneficial. <sup>56-19,56-21</sup>
III: No Benefit	A	13. In patients with refractory VF not related to torsades de pointes, administration of intravenous magnesium is not beneficial. <sup>56-27,56-28</sup>
III: Harm	B-R	14. In patients with suspected AMI, prophylactic administration of lidocaine or high-dose amiodarone for the prevention of VT is potentially harmful. <sup>56-16,56-29</sup>
III: Harm	C-LD	15. In patients with a wide QRS complex tachycardia of unknown origin, calcium channel blockers (eg, verapamil and diltiazem) are potentially harmful. <sup>56-30,56-31</sup>

## Recommendation-Specific Supportive Text

1. The most common electrical mechanisms for cardiac arrest are VF and pulseless VT, but substantial numbers of cardiac arrests begin as severe bradyarrhythmias or asystole. Survival is better for patients presenting with VT or VF than for those with bradyarrhythmic or asystolic mechanisms.<sup>56-32</sup> Rapid arrival of paramedical personnel is the

major determinant of survival. A number of strategies for responding to unexpected cardiac arrest, including rapid defibrillation and initiation of CPR for a witnessed cardiac arrest, have improved survival probabilities for cardiac arrest victims.<sup>56-2,56-3</sup> Nonetheless, the absolute number and proportion of survivors remain low, except in unique circumstances where there is an extraordinarily rapid response time to victims in VF or VT such as in monitored intensive care units, where survival is >90%.<sup>56-33-56-36</sup> Survival decreases rapidly after the initial 2 minutes from the onset of cardiac arrest, so that by 4 to 5 minutes, survival may be ≤25%, and by 10 minutes it is 0%.<sup>56-33,56-35,56-36</sup> Advanced life support activities, other than those directly related to cardioversion and defibrillation for control of tachyarrhythmias, have led to the generation of comprehensive protocols to guide responders. These AHA documents cover the broad expanse of clinical circumstances and considerations of mechanisms.<sup>56-1,56-37</sup>

2. Paramedic administration of amiodarone after at least 3 failed shocks and administration of epinephrine improved hospital admission rates when compared with placebo<sup>56-6</sup> or 1.5 mg/kg lidocaine<sup>56-1,56-4</sup> in RCTs in adults with out-of-hospital cardiac arrest due to refractory VF or polymorphic VT, although survival to hospital discharge and survival with favorable neurologic outcome were not improved with amiodarone or lidocaine.<sup>56-5</sup> However, in the subset of patients with witnessed cardiac arrest due to initial shock-refractory VF or pulseless VT, survival to hospital discharge after amiodarone administration was higher than with placebo.<sup>56-5</sup> The administration of procainamide in out-of-hospital cardiac arrest due to VF or pulseless VT has been associated with more shocks, more pharmacologic interventions, longer resuscitation times, and lower survival.<sup>56-38</sup>
3. VA with hemodynamic instability, including VF and pulseless monomorphic or polymorphic VT, causes loss of consciousness and leads to death if untreated. A short time to direct current cardioversion is the major determinant of survival, and defibrillation should be performed as quickly as possible. CPR is used until a perfusing rhythm is restored. If defibrillation is unsuccessful in returning spontaneous circulation, responders follow advanced cardiovascular life support activities.<sup>56-1-56-3</sup>
4. Quickly identifying and treating patients with out-of-hospital cardiac arrest related to acute coronary occlusion is associated with improved survival and better functional recovery.<sup>56-37</sup> Coronary occlusion as a cause of cardiac arrest is not reliably predicted by clinical and electrocardiographic

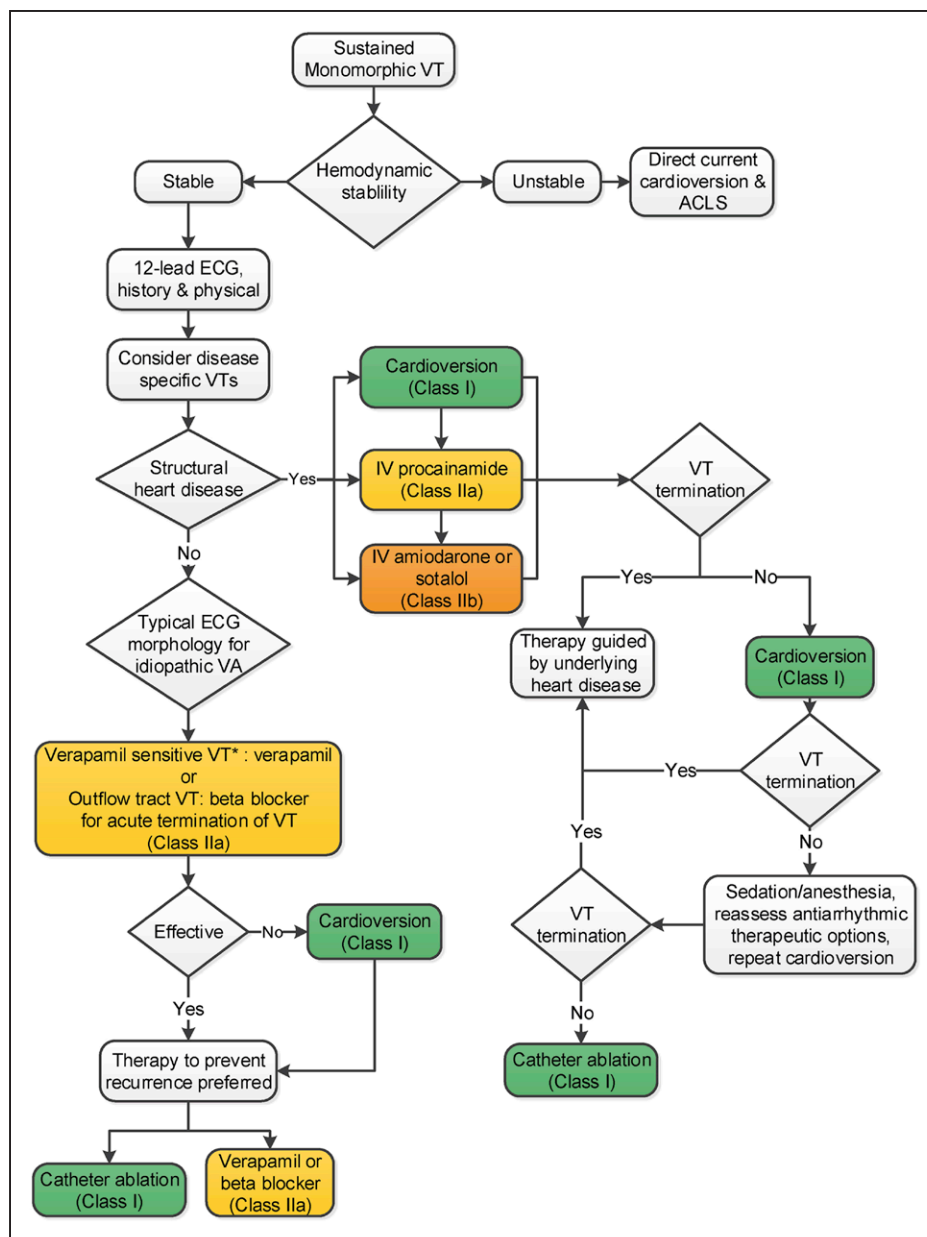
findings,<sup>56-7</sup> and emergency coronary angiography should be considered (rather than later in the hospital stay or not at all) for unstable patients with a suspected cardiac etiology regardless of whether the patient is comatose or awake.<sup>56-9,56-39</sup>

In 1 observational study of patients resuscitated from SCA who did not have ST elevation and had angiography, one third were found to have a culprit lesion and coronary intervention appeared to be associated with a greater likelihood of favorable neurologic outcome.<sup>56-10</sup>

5. The initial management of any tachycardia should proceed according to published AHA advanced cardiovascular life support guidelines.<sup>56-40</sup> Immediate cardioversion should be performed for hemodynamic instability at presentation or if it develops subsequently. An ECG should be obtained for stable rhythms. Wide-complex tachycardias, defined by a QRS duration  $\geq 0.12$  s,<sup>56-37</sup> can be due to VT, SVT with aberrancy, preexcited tachycardia, or a paced rhythm such as pacemaker-mediated tachycardia. An irregular wide-complex tachycardia may be AF with aberrancy, preexcited AF (ie, AF using an accessory pathway for anterograde conduction), atrial flutter, or VT.<sup>56-37</sup> A diagnosis should be established, and consultation with an arrhythmia expert considered.<sup>56-37</sup>
6. In 1 study, amiodarone was more effective than lidocaine in terminating incessant VT with improved survival at 24 hours.<sup>56-26</sup> For patients with recurrent, stable VT not in the setting of an AMI, intravenous procainamide has been shown to be superior to lidocaine for terminating the arrhythmia.<sup>56-11</sup> One randomized trial of 62 patients found procainamide superior to amiodarone for termination of stable VT.<sup>56-13</sup> Adverse events, including hypotension were more common with amiodarone, but the difference was not statistically significant. Procainamide and its metabolite n-acetylprocainamide have potassium channel blocking properties that may prolong the QT interval. In patients who already have QT prolongation, administration of procainamide may further prolong the QT interval and lead to torsades de pointes.<sup>56-11,56-12,56-26</sup>
7. Intravenous lidocaine is an alternative antiarrhythmic medication of long-standing and widespread familiarity. Compared with no antiarrhythmic medication, lidocaine did not consistently increase a return of spontaneous circulation after defibrillation and was not associated with improvement in survival to hospital discharge.<sup>56-4,56-14,56-41</sup> In prospective, blinded, RCTs, lidocaine was less effective than amiodarone in improving hospital admission rates after out-of-hospital cardiac arrest due to shock-refractory VF or

polymorphic VT; but there were no differences between the 2 medications in survival to hospital discharge.<sup>56-4,56-5</sup> However, in the subset of patients with witnessed SCA due to initial shock-refractory VF or pulseless VT, a subgroup analysis showed that survival to hospital discharge with lidocaine was better than with placebo.<sup>56-5,56-42</sup>

8. In a large meta-analysis of antiarrhythmic medications in the setting of AMI, beta blockers were associated with a significant reduction in mortality.<sup>56-16</sup> Beta blockers can be effective in suppressing recurrent VF in patients with recent MI, with an associated improvement in survival.<sup>56-17</sup>
9. In patients with recurrent VT/VF (VT/VF storm) in the setting of a recent MI that is refractory to amiodarone and/or lidocaine and repeated cardioversion, administration of a beta blocker has been shown to improve survival at 1 week. For those who did not survive, mortality was mostly due to recurrent VF. Survival at 1 year was also better in those treated with a beta blocker.<sup>56-17,56-18</sup> Other measures to reduce sympathetic tone including sedation and general anesthesia are also often used.
10. Epinephrine produces beneficial effects in patients during cardiac arrest, primarily because of its alpha-adrenergic (ie, vasoconstrictor) effects.<sup>56-1</sup> These alpha-adrenergic effects can increase coronary and cerebral perfusion pressure during CPR. The value and safety of the beta-adrenergic effects of epinephrine are controversial because they may increase myocardial work and reduce subendocardial perfusion.<sup>56-1</sup> One trial assessed short-term and longer-term outcomes when comparing standard-dose epinephrine to placebo.<sup>56-23</sup> Standard-dose epinephrine was defined as 1 mg given intravenously or intraosseously every 3 to 5 minutes. For both survival to discharge and survival to discharge with good neurologic outcome, there was no benefit with standard-dose epinephrine; however, the study was underpowered for analysis of either of these outcomes. There was, nevertheless, improved survival to hospital admission and improved return of spontaneous circulation with the use of standard-dose epinephrine. A number of trials have compared outcomes of standard-dose epinephrine with those of high-dose epinephrine. These trials did not demonstrate any benefit for high-dose epinephrine over standard-dose epinephrine in relation to survival to discharge with a good neurologic recovery, survival to discharge, or survival to hospital admission.<sup>56-1,56-19,56-21,56-22</sup>
11. Amiodarone was more effective than lidocaine in terminating incessant VT with improved survival



**Figure 2. Management of sustained monomorphic VT.**

Colors correspond to Class of Recommendation in Table 1. See Sections 7, 8.1.3, 8.2.3, and 10 for discussion. \*Known history of verapamil sensitive or classical electrocardiographic presentation. ACLS indicates advanced cardiovascular life support; ECG, electrocardiogram; VA, ventricular arrhythmia; and VT, ventricular tachycardia.

at 24 hours.<sup>56-26</sup> For patients with recurrent, stable VT not in the setting of an AMI, intravenous procainamide has been shown to be superior to lidocaine for terminating the arrhythmia.<sup>56-11</sup> One RCT in 62 patients found procainamide superior to amiodarone for termination of stable VT.<sup>56-13</sup> Adverse events, including hypotension, were more common with amiodarone, but the difference was not statistically significant. Procainamide and its metabolite n-acetylprocainamide have potassium channel blocking properties that may prolong the QT interval. In patients who already have QT prolongation, administration of

procainamide may further prolong the QT interval and lead to torsades de pointes.<sup>56-11</sup> A single RCT of 33 patients comparing sotalol with lidocaine for treating patients with hemodynamically stable VT showed that VT was terminated in 69% of patients using sotalol and 18% using lidocaine.<sup>56-25</sup> Intravenous sotalol has been approved for use in the United States. Sotalol has potassium channel blocking properties that may prolong the QT interval. In patients who already have QT interval prolongation, administration of sotalol may further prolong the QT interval and lead to torsades de pointes.<sup>56-25</sup>

12. Epinephrine may increase coronary and cerebral perfusion pressure during CPR because of its vasoconstrictive effects. High doses of epinephrine (0.1 to 0.2 mg/kg IV, as opposed to a standard dose of 1 mg) have been studied in RCTs. In out-of-hospital cardiac arrest unresponsive to defibrillation, administration of high-dose epinephrine improved survival to hospital admission, but there was no difference compared to standard dose epinephrine in survival to hospital discharge.<sup>56-19</sup> There was also no improvement in long-term survival.<sup>56-21</sup> Of note, the administration of vasopressin is no longer recommended in the most recent advanced cardiovascular life support algorithms.<sup>56-1</sup>
13. Magnesium may suppress automaticity, suppress early and late after-depolarizations, and inhibit calcium flux into cardiomyocytes. It is effective in suppressing VA related to acquired long QT syndrome. However, 2 RCTs that investigated the use of intravenous magnesium in patients with cardiac arrest and refractory VF found no benefit.<sup>56-27,56-28</sup> In a study of out-of-hospital cardiac arrest, administration of 2 to 4 g magnesium intravenously did not improve survival to hospital admission.<sup>56-27</sup> In a similar study involving inpatient cardiac arrest, magnesium did not improve return of spontaneous circulation, survival to 24 hours, or survival to hospital discharge.<sup>56-28</sup> There are exceptions such as marked hypokalemia or medication-induced torsades de pointes in which administration of intravenous magnesium is warranted.
14. Several studies have tested the hypothesis that prophylactic administration of antiarrhythmic medications could reduce the incidence of post-MI VA and lead to better outcomes. One meta-analysis assessed studies in which beta blockers, class I antiarrhythmic agents such as lidocaine and procainamide, and amiodarone were given in the setting of AMI. The routine use of lidocaine and procainamide was associated with increased mortality, whereas beta blockers were associated with a significantly lower mortality rate.<sup>56-16</sup> Limited data with amiodarone appeared to be promising, but a subsequent RCT involving 1073 patients found that administration of high-dose amiodarone led to a higher mortality rate, although a

moderate dose of amiodarone was not superior to placebo.<sup>56-29</sup>

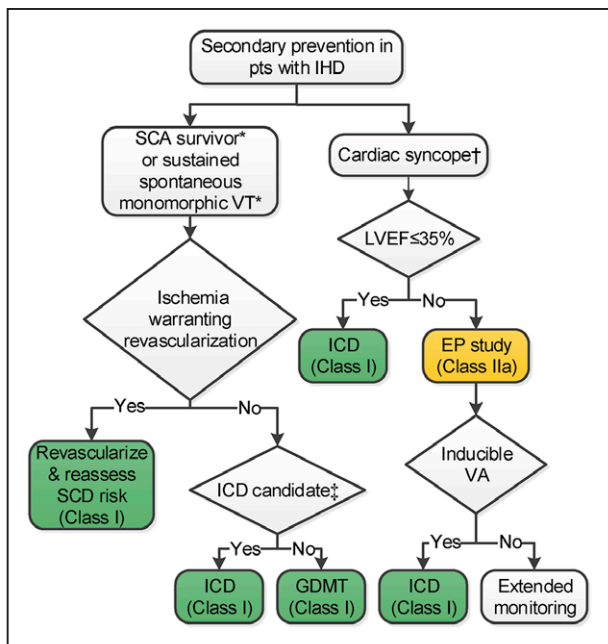
15. With a stable, wide QRS complex tachycardia, differentiation between SVT with aberrancy and VT is often possible by review of the patient's history and the 12-lead ECG during tachycardia. Patients with wide QRS complex tachycardia and known structural heart disease should be presumed to have VT until proven otherwise. Administration of a calcium channel blocker such as verapamil to a patient with VT may result in severe hypotension or syncope.<sup>56-31</sup> The exception is verapamil-sensitive VT (interfascicular reentry) that occurs in a structurally normal heart; but this is often difficult to recognize on initial presentation.<sup>56-30</sup>

## 7. ONGOING MANAGEMENT OF VA AND SCD RISK RELATED TO SPECIFIC DISEASE STATES

### 7.1. Ischemic Heart Disease

#### 7.1.1. Secondary Prevention of SCD in Patients With Ischemic Heart Disease

Recommendations for Secondary Prevention of SCD in Patients With Ischemic Heart Disease		
References that support the recommendations are summarized in Online Data Supplements 17 and 18.		
COR	LOE	Recommendations
I	B-R	1. In patients with ischemic heart disease, who either survive SCA due to VT/VF or experience hemodynamically unstable VT (LOE: B-R) <sup>57.1.1-1-57.1.1-4</sup> or stable sustained VT (LOE: B-NR) <sup>57.1.1-5</sup> not due to reversible causes, an ICD is recommended if meaningful survival greater than 1 year is expected.
	B-NR	
Value Statement: Intermediate Value (LOE: B-R)		2. A transvenous ICD provides intermediate value in the secondary prevention of SCD particularly when the patient's risk of death due to a VA is deemed high and the risk of nonarrhythmic death (either cardiac or noncardiac) is deemed low based on the patient's burden of comorbidities and functional status. <sup>57.1.1-6</sup>
I	B-NR	3. In patients with ischemic heart disease and unexplained syncope who have inducible sustained monomorphic VT on electrophysiological study, an ICD is recommended if meaningful survival of greater than 1 year is expected. <sup>57.1.1-7</sup>



**Figure 3. Secondary prevention patients with ischemic heart disease.** Colors correspond to Class of Recommendation in Table 1. See Sections 4.3.1 and 7.1.1 for discussion. \*Exclude reversible causes. †History consistent with an arrhythmic etiology for syncope. ‡ICD candidacy as determined by functional status, life expectancy, or patient preference. EP indicates electrophysiological; GDMT, guideline-directed management and therapy; ICD, implantable cardioverter-defibrillator; IHD, ischemic heart disease; LVEF, left ventricular ejection fraction; pts, patients; SCA, sudden cardiac arrest; SCD, sudden cardiac death; and VT, ventricular tachycardia.

**Recommendation-Specific Supportive Text**

1. In the AVID trial,<sup>57.1.1-1</sup> the ICD improved overall survival compared with antiarrhythmic medication therapy (primarily amiodarone) in patients who survived SCD or with hemodynamically unstable VT, with a 2-year relative risk reduction in mortality of 27% and an absolute risk reduction of 7%. CIDS (Canadian Implantable Defibrillator Study),<sup>57.1.1-2</sup> which was stopped early after the results of the AVID trial were released, showed a similar, but not statistically significant, benefit of the ICD over antiarrhythmic medication therapy. A subsequent meta-analysis using data from 3 RCTs showed a statistically significant reduction in both arrhythmic and all-cause mortality with secondary prevention ICDs.<sup>57.1.1-3</sup>

In survivors of life-threatening VA that may be due to transient or reversible factors, such as AMI, proarrhythmic medication effects, or electrolyte disturbances, an ICD is not implanted if the cause may be correctable. This is a population of patients that still requires thorough evaluation, treatment, and close follow-up and, as in the AVID registry, mortality was still high in the population that may have had a reversible cause for their arrest.<sup>57.1.1-8</sup> Small increases in troponin present a challenge in selecting patients for an ICD, as it often cannot be determined whether troponin elevation is due to ischemia from VT/VF and resuscitation, in which

case an ICD is likely warranted, or an indication that ischemia caused the arrhythmia, in which case prevention of ischemia would be the therapeutic focus.

ICDs may improve the outcomes of patients with hemodynamically tolerated sustained VT and structural heart disease<sup>57.1.1-5</sup>; however, this has not proved in any RCT. VT ablation has been used as an alternative in selected patients with well-tolerated VT and appears to reduce recurrences, but the impact on long-term mortality is unknown; there is not yet sufficient evidence to recommend this approach as an alternative to ICD implantation.<sup>57.1.1-9,57.1.1-10</sup>

- Economic outcomes of ICD implantation for secondary prevention of SCD were assessed in the AVID and CIDS trials,<sup>57.1.1-11,57.1.1-12</sup> as well as in a simulation model<sup>57.1.1-13</sup> and an observational study of Medicare beneficiaries.<sup>57.1.1-14</sup> All studies compared ICD recipients with non-ICD recipients, and all found that ICD recipients had longer overall survival and higher lifetime costs of medical care. All studies reported incremental cost-effectiveness ratios between \$64 000 and \$100 000 per year of life added by an ICD,<sup>57.1.1-11–57.1.1-14</sup> which is in the range of intermediate value by the benchmarks applied in the ACC/AHA cost/value statement.<sup>57.1.1-15</sup>
- VAs are an important cause of syncope or near syncope in patients with ischemic heart disease, particularly those with prior infarction. A study of 70 patients with unexplained syncope who underwent an electrophysiological study identified positive findings in 37 patients; 31 with VT. During 3 years of follow-up, patients with a positive electrophysiological study had higher rates of SCD and 3-year total mortality (61% versus 15%, respectively) than those with a negative electrophysiological study.<sup>57.1.1-7</sup> An ICD is warranted for patients with syncope and inducible sustained monomorphic VT even if they do not otherwise meet criteria for primary prevention (Figure 4).

**7.1.1.1. Coronary Artery Spasm**

Recommendations for Patients With Coronary Artery Spasm		
References that support the recommendations are summarized in Online Data Supplement 20.		
COR	LOE	Recommendations
I	B-NR	1. In patients with VA due to coronary artery spasm, treatment with maximally tolerated doses of a calcium channel blocker and smoking cessation are indicated to reduce recurrent ischemia and VA. <sup>57.1.1.1-1,57.1.1-2</sup>
IIa	B-NR	2. In patients resuscitated from SCA due to coronary artery spasm in whom medical therapy is ineffective or not tolerated, an ICD is reasonable if meaningful survival of greater than 1 year is expected. <sup>57.1.1.1-3–57.1.1-6</sup>
IIb	B-NR	3. In patients resuscitated from SCA due to coronary artery spasm, an ICD in addition to medical therapy may be reasonable if meaningful survival of greater than 1 year is expected. <sup>57.1.1.1-3–57.1.1-6</sup>

## Recommendation-Specific Supportive Text

1. Coronary artery spasm results from vasomotor dysfunction and can occur in the presence or absence of atherosclerotic ischemic heart disease. Vasospasm episodes can lead to VA, syncope, and SCD. Treatment includes risk factor elimination including smoking cessation, and treatment with vasodilators including dihydropyridine calcium channel blockers with or without nitrates. A more detailed summary of treatments for coronary artery spasm can be found in other guideline documents.<sup>57.1.1.1-7,57.1.1.1-8</sup>
2. Patients with coronary artery spasm who survive an SCA are a high-risk population.<sup>57.1.1.1-5</sup> Recurrent VA, even life-threatening, may be prevented if coronary artery spasm can be effectively addressed with risk factor modification, smoking cessation, and ongoing treatment with nitrates and dihydropyridine calcium channel blockers.<sup>57.1.1.1-9</sup> However, SCA or VA can recur despite medical therapy or if compliance is poor. Whether a wearable cardioverter-defibrillator may provide protection while medical therapy is being evaluated has not been assessed but is of interest.<sup>57.1.1.1-10</sup> An ICD can terminate VT/VF initiated by spasm, potentially preventing SCD.
3. Patients with coronary vasospasm who survive an SCA are a high-risk population, and some support the use of an ICD in those patients based on the reported event rates from observational studies<sup>57.1.1.1-5</sup> even before determining the patient's response to or compliance with medical therapy. Recurrent SCA can occur despite medical therapy. Regardless of the approach, risk factor modification (eg, illicit drug use), smoking cessation, and ongoing treatment with dihydropyridine calcium channel blockers with or without nitrates represent essential treatments.<sup>57.1.1.1-9</sup>

### 7.1.1.2. Post CABG VT/VF

The incidence of sustained VT or VF early after CABG is low, but these VAs are associated with high in-hospital mortality.<sup>57.1.1.2-1</sup> VF occurring very early (intraoperatively or within 24 hours postoperatively) may be due to the transient effects of reperfusion, electrolyte and acid base disturbances, and the use of inotropes. Patients who present with VF or polymorphic VT in the postoperative period more often have associated ischemia, while patients presenting with monomorphic VT usually have an old infarct and ventricular scar.<sup>57.1.1.2-2</sup> Polymorphic VT/VF occurring after CABG warrants a therapeutic approach targeting treatment of myocardial ischemia, including a possible need for assessment of graft patency, as well as identification and treatment of mechanical complications and acute electrolyte or acid base disturbances. Risk factors for occurrence of monomorphic VT early af-

ter CABG include prior MI, ventricular scar, LV dysfunction, and placement of a bypass graft across a noncollateralized occluded coronary vessel to a chronic infarct zone.<sup>57.1.1.2-3</sup> Unlike polymorphic VT and VF, sustained monomorphic VT is typically not due to acute ischemia. Many of these patients have inducible sustained VT at electrophysiological study. Management of symptomatic VA in the early period after CABG follows the recommendations for acute and ongoing management of VT detailed elsewhere in this document. In patients without sustained VT or VF but with LV dysfunction prior to undergoing CABG, implantation of an ICD did not improve survival.<sup>57.1.1.2-4</sup> For patients with LV dysfunction who are undergoing revascularization, there is a possibility that the LV function may improve, so many advocate for reassessment of the LV function 3 months after revascularization before a decision about ICD implantation is made.<sup>57.1.1.2-5</sup> For patients with a high burden of NSVT and reduced LVEF, an electrophysiological study may be helpful for risk stratification; those with inducible sustained VT may benefit from an ICD.<sup>57.1.1.2-6</sup> The wearable cardioverter-defibrillator may play a role in patients at risk of SCD in the early phase after revascularization to allow time for recovery of ventricular function.<sup>57.1.1.2-7</sup>

### 7.1.2. Primary Prevention of SCD in Patients With Ischemic Heart Disease

Recommendations for Primary Prevention of SCD in Patients With Ischemic Heart Disease		
References that support the recommendations are summarized in Online Data Supplement 21.		
COR	LOE	Recommendations
I	A	1. In patients with LVEF of 35% or less that is due to ischemic heart disease who are at least 40 days' post-MI and at least 90 days postrevascularization, and with NYHA class II or III HF despite GDMT, an ICD is recommended if meaningful survival of greater than 1 year is expected. <sup>57.1.2-1,57.1.2-2</sup>
I	A	2. In patients with LVEF of 30% or less that is due to ischemic heart disease who are at least 40 days' post-MI and at least 90 days postrevascularization, and with NYHA class I HF despite GDMT, an ICD is recommended if meaningful survival of greater than 1 year is expected. <sup>57.1.2-2,57.1.2-3</sup>
Value Statement: High Value (LOE: B-R)		3. A transvenous ICD provides high value in the primary prevention of SCD particularly when the patient's risk of death due to a VA is deemed high and the risk of nonarrhythmic death (either cardiac or noncardiac) is deemed low based on the patient's burden of comorbidities and functional status. <sup>57.1.2-4</sup>
I	B-R	4. In patients with NSVT due to prior MI, LVEF of 40% or less and inducible sustained VT or VF at electrophysiological study, an ICD is recommended if meaningful survival of greater than 1 year is expected. <sup>57.1.2-5</sup>



Recommendations for Primary Prevention of SCD in Patients With Ischemic Heart Disease (Continued)		
COR	LOE	Recommendations
IIa	B-NR	5. In nonhospitalized patients with NYHA class IV symptoms who are candidates for cardiac transplantation or an LVAD, an ICD is reasonable if meaningful survival of greater than 1 year is expected. <sup>57.1.2-6-57.1.2-9</sup>
III: No Benefit	C-EO	6. An ICD is not indicated for NYHA class IV patients with medication-refractory HF who are not also candidates for cardiac transplantation, an LVAD, or a CRT defibrillator that incorporates both pacing and defibrillation capabilities.

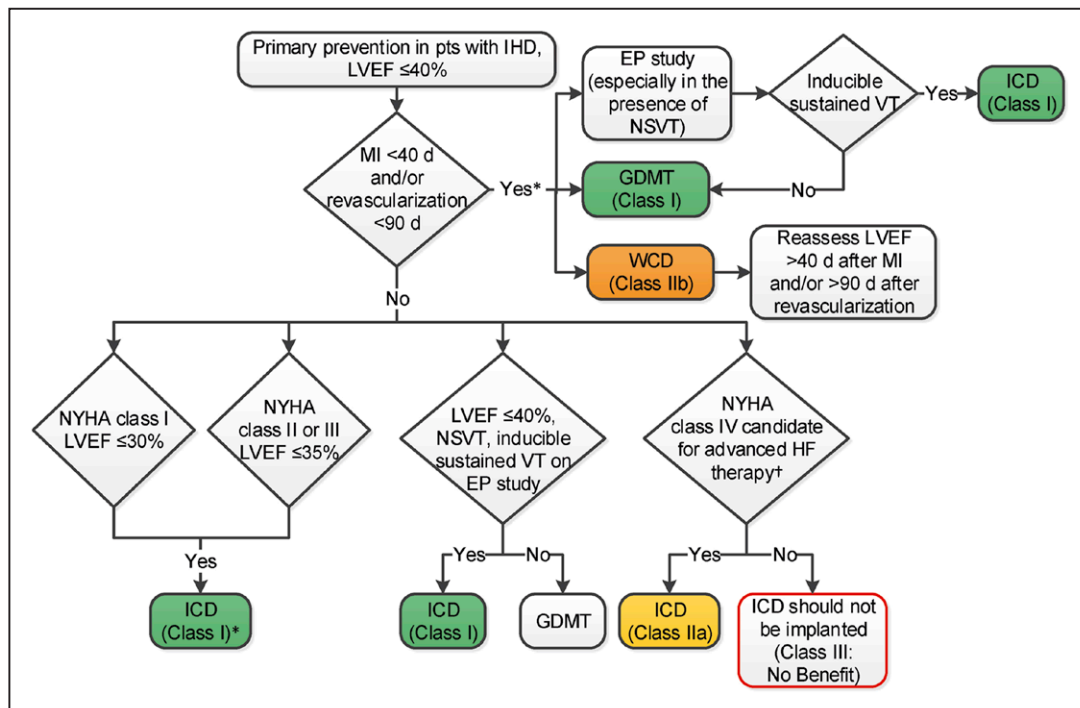
### Recommendation-Specific Supportive Text

1. The rationale for recommending that an ICD be offered to patients with NYHA class II or III HF, in addition to LVEF ≤35%, is based on the survival benefit observed in SCD-HeFT and MADIT-II (which used LVEF cutoff of below 35% and 30%, respectively). Selection for implantation of an ICD must be individualized. Patients with serious comorbidities associated with a survival of <1 year are generally not considered ICD candidates. The recommendation to wait at least 40 days after

an MI before implanting a primary prevention ICD is based on the fact that such patients were excluded from MADIT-II and SCD-HeFT and 2 other RCTs showed no survival benefit from ICDs implanted early after an acute MI.<sup>57.1.2-10,57.1.2-11</sup>

2. In the MADIT-II trial,<sup>57.1.2-2</sup> which randomized patients with LVEF ≤30% and prior MI to an ICD or not, approximately one third of the patients had NYHA class I symptoms. A subgroup analysis supported benefit of the ICD on survival in this subgroup.<sup>57.1.2-2</sup>

3. Economic outcomes of ICD implantation for primary prevention of SCD were assessed in 3 RCTs [MADIT-I,<sup>57.1.2-12</sup> MADIT-II,<sup>57.1.2-13</sup> and SCD-HeFT<sup>57.1.2-14</sup>], 1 observational study,<sup>57.1.2-15</sup> and 4 simulation models,<sup>57.1.2-16-57.1.2-19</sup> which all had generally consistent results. All studies reported increased survival and life expectancy, and higher lifetime costs of medical care with an ICD than without an ICD. The incremental cost-effectiveness ratios were generally <\$50,000 per year of life added by an ICD, which provides high value according to the benchmarks adopted for the current guideline.<sup>57.1.2-20</sup> The value provided by an ICD was consistently high when life expectancy was projected to increase by >1.4 years.<sup>57.1.2-18</sup> In



**Figure 4.** Primary prevention of SCD in patients with ischemic heart disease.

Colors correspond to Class of Recommendation in Table 1. See Section 7.1.2 for discussion. \*Scenarios exist for early ICD placement in select circumstances such as patients with a pacing indication or syncope †Advanced HF therapy includes CRT, cardiac transplant, and LVAD thought due to VT. These are detailed elsewhere in an HRS/ACC/AHA expert consensus statement.<sup>57.1.2-24</sup> CRT indicates cardiac resynchronization therapy; EP, electrophysiological; GDMT, guideline-directed management and therapy; HF, heart failure; ICD, implantable cardioverter-defibrillator; IHD, ischemic heart disease; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NSVT, nonsustained ventricular tachycardia; NYHA, New York Heart Association; pts, patients; SCD, sudden cardiac death; VT, ventricular tachycardia; and WCD, wearable cardioverter-defibrillator.

contrast, when survival was not increased by ICD implantation, as in the CABG-Patch trial,<sup>57.1.2-18</sup> the ICD did not provide value, because the higher costs were unaccompanied by a gain in life expectancy.

4. MUSTT (Multicenter Unsustained Tachycardia Trial) demonstrated that patients with prior MI, NSVT, and reduced LVEF with inducible VT at electrophysiological study have a higher overall mortality rate than similar patients without inducible sustained VT.<sup>57.1.2-21</sup> Patients who received an ICD after failing to have inducible VT suppressed by an antiarrhythmic medication had lower mortality rate than those who did not receive an ICD. Although the entry criteria into MUSTT required an LVEF of  $\leq 40\%$ , the average LVEF in enrolled patients was 30%, and ICD placement was not randomized but rather was selected by the treating physician for patients with VT that could not be suppressed with antiarrhythmic medication therapy. MUSTT allowed enrollment of patients who were  $\geq 4$  days after an acute MI or revascularization. The ICD was of no benefit in 2 other RCTs that examined the efficacy of the ICD in the acute phase of an MI.<sup>57.1.2-10,57.1.2-11</sup> In a single center observational study, an electrophysiological study was performed a median of 9 days after acute MI in 115 patients with LVEF  $< 40\%$  and ICDs recommended for those with inducible VT. Median follow-up was 12 months. Sustained VT was induced in 27% of patients, and 22% of those who received ICDs had spontaneous VT terminated by the ICD during follow-up. None of the patients without inducible VT had VT or SCD during follow-up.<sup>57.1.2-22</sup>
5. In a retrospective analysis of the UNOS (United Network for Organ Sharing) registry that extended from 1999 to 2014, data on 32 599 patients showed that during a median follow-up of 154 days, 3638 patients (11%) died while on the waitlist for cardiac transplantation (9% in the ICD group versus 15% in the non-ICD group;  $P < 0.0001$ ). The presence of an ICD at listing was associated with an adjusted 13% relative risk reduction in mortality. In the subgroup of patients with an LVAD ( $n = 9478$ ), an ICD was associated with an adjusted 19% relative risk reduction in mortality.<sup>57.1.2-9</sup> In another study of 380 patients listed for heart transplantation between 2005 and 2009 at 1 tertiary heart transplant center, 122 patients received an ICD before or within 3 months after being listed for heart transplantation. Non-ICD patients were more likely to die while on the transplant list. In a multivariable model, the ICD was not associated with improved survival; however, that analysis was limited by the small sample size.<sup>57.1.2-8</sup> Another small study ( $n = 79$ ) conducted at 1 institution suggested

that ICDs reduce the risk of SCD in patients with LVEF  $\leq 30\%$  who are awaiting heart transplantation; however, this study was limited by the small number of patients.<sup>57.1.2-6</sup> In a retrospective multicenter study of 1089 patients listed for heart transplantation, 550 patients (51%) had an ICD. In 216 patients, the ICD was for primary prevention of SCD and, in 334 patients, the ICD was for secondary prevention. The remaining 539 patients did not receive an ICD. During a median time on the waiting list of 8 months, the ICD was associated with a reduction in all-cause mortality in the primary and secondary prevention cohorts (estimated 1-year:  $88 \pm 3\%$  versus  $77 \pm 3\%$  versus  $67 \pm 3\%$ ;  $P = 0.0001$ ). This relationship between the ICD and improved survival persisted even after adjusting for potential confounders.<sup>57.1.2-7</sup>

6. There are insufficient data from RCTs regarding the value of the ICD in patients with NYHA class IV HF. Ambulatory class IV patients with HF were included in the COMPANION (Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure) trial, which showed an overall improved functional status and survival with a CRT defibrillator.<sup>57.1.2-23</sup> Unless such a patient is a candidate for CRT or advanced HF therapies such as heart transplantation or an LVAD, an ICD is not expected to meaningfully prolong survival.<sup>57.1.2-23</sup>

### 7.1.3. Treatment and Prevention of Recurrent VA in Patients With Ischemic Heart Disease

#### Recommendations for Treatment of Recurrent VA in Patients With Ischemic Heart Disease

References that support the recommendations are summarized in Online Data Supplements 22 and 23.

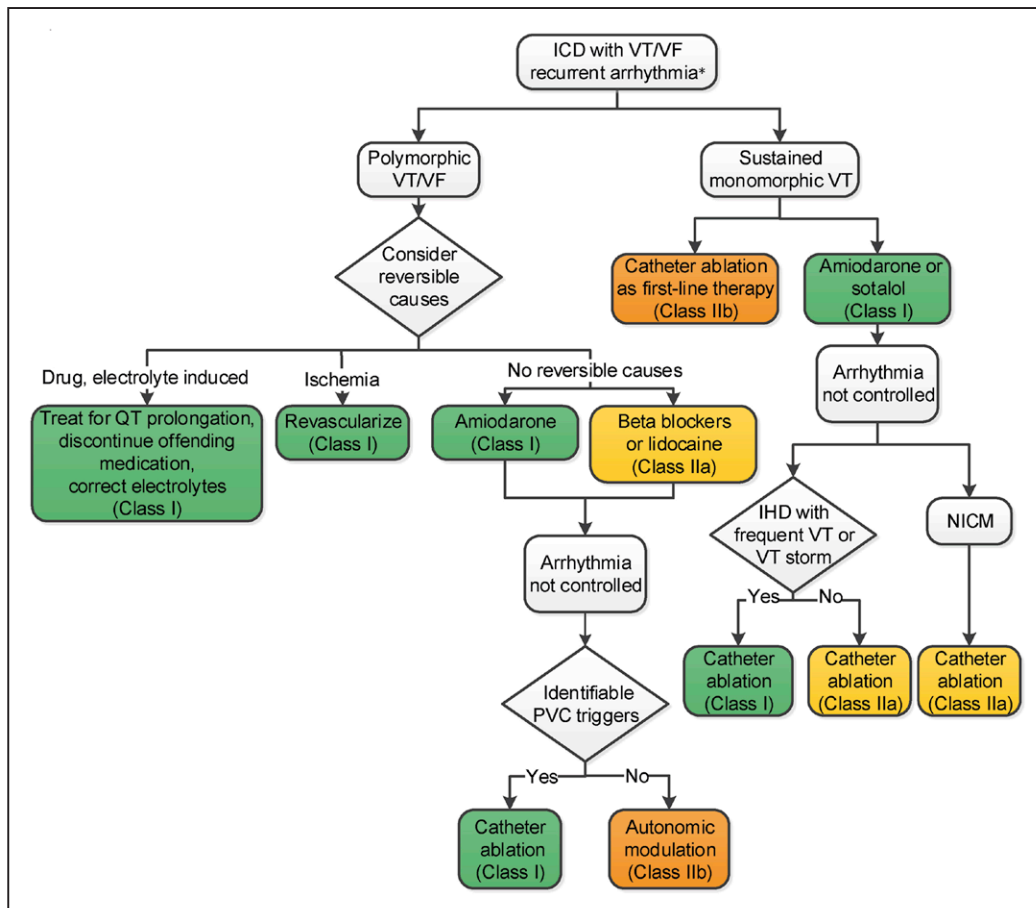
COR	LOE	Recommendations
I	B-R	1. In patients with ischemic heart disease and recurrent VA, with significant symptoms or ICD shocks despite optimal device programming and ongoing treatment with a beta blocker, amiodarone or sotalolol is useful to suppress recurrent VA. <sup>57.1.3-1-57.1.3-3</sup>
I	B-R	2. In patients with prior MI and recurrent episodes of symptomatic sustained VT, or who present with VT storm and have failed or are intolerant of amiodarone (LOE: B-R), <sup>57.1.3-4</sup> or other antiarrhythmic medications (LOE: B-NR) <sup>57.1.3-5-57.1.3-9</sup> , catheter ablation is recommended. <sup>57.1.3-10-57.1.3-12</sup>
	B-NR	
IIb	C-LD	3. In patients with ischemic heart disease and ICD shocks for sustained monomorphic VT or symptomatic sustained monomorphic VT that is recurrent, or hemodynamically tolerated, catheter ablation as first-line therapy may be considered to reduce recurrent VA. <sup>57.1.3-10,57.1.3-11</sup>
III: Harm	B-R	4. In patients with prior MI, class IC antiarrhythmic medications (eg, flecainide and propafenone) should not be used. <sup>57.1.3-13</sup>

Recommendations for Treatment of Recurrent VA in Patients With Ischemic Heart Disease (Continued)		
COR	LOE	Recommendations
III: Harm	C-LD	5. In patients with incessant VT or VF, an ICD should not be implanted until sufficient control of the VA is achieved to prevent repeated ICD shocks. <sup>57.1.3-14</sup>
III: No Benefit	C-LD	6. In patients with ischemic heart disease and sustained monomorphic VT, coronary revascularization alone is an ineffective therapy to prevent recurrent VT. <sup>57.1.3-15,57.1.3-16</sup>

### Recommendation-Specific Supportive Text

1. The most common antiarrhythmic medications used for suppression of VA include amiodarone and sotalol, while mexiletine, quinidine, and ranolazine are occasionally used.<sup>57.1.3-17,57.1.3-18</sup> Amiodarone appears to be more effective than sotalol and has a low rate of ventricular

proarrhythmia, but has an increased risk of medication-related adverse effects that lead to its discontinuation in many patients within 18 to 24 months from initiation of therapy.<sup>57.1.3-1,57.1.3-19</sup> Data supporting effectiveness of sotalol for suppression of VA are conflicting, but given its more favorable adverse effect profile than amiodarone, it may be a better first-line antiarrhythmic medication in appropriate patients.<sup>57.1.3-1-57.1.3-3</sup> However, sotalol is generally avoided in patients with a severely reduced LVEF <20% due to its negative inotropic effects and the risk of torsades de pointes. In a double-blind placebo-controlled study of 674 patients with HF and ≥10 PVCs/h and an LVEF ≤40% randomly assigned to receive amiodarone (336 patients) or placebo (338 patients), there was no significant difference in overall mortality or SCD between the 2 arms. There was a trend toward a reduction in overall



**Figure 5. Treatment of recurrent VA in patients with ischemic heart disease or NICM.** Colors correspond to Class of Recommendation in Table 1. See Sections 5.6, 6, 7.1.3, and 7.2 for discussion. \*Management should start with ensuring that the ICD is programmed appropriately and that potential precipitating causes, including heart failure exacerbation, are addressed. For information regarding optimal ICD programming, refer to the 2015 HRS/EHRA/APHS/SOLAECE expert consensus statement.<sup>57.1.3-26</sup> APHS indicates Asia Pacific Heart Rhythm Society; EHRA, European Heart Rhythm Association; HRS, Heart Rhythm Society; IHD, ischemic heart disease; ICD, implantable cardioverter-defibrillator; PVC, premature ventricular complex; NICM, nonischemic cardiomyopathy; SOLAECE, Sociedad Latinoamericana de Estimulación Cardíaca y Electrofisiología; VF, ventricular fibrillation; and VT, ventricular tachycardia.

mortality among the patients with NICM who received amiodarone ( $P=0.07$ ).<sup>S7.1.3-20</sup>

2. Patients with prior MI may present with frequent episodes of sustained monomorphic VT or recurrent VF episodes that are initiated by PVCs arising from Purkinje Fibers in the peri-infarct zone. VA storms are associated with increased mortality.<sup>S7.1.3-12</sup> The arrhythmia substrate is usually in the subendocardium. The randomized VANISH (Ventricular Tachycardia Ablation versus Escalated Antiarrhythmic Drug Therapy in Ischemic Heart Disease) trial<sup>S7.1.3-4</sup> compared escalating antiarrhythmic medication therapy versus catheter ablation for patients with prior MI and recurrent sustained monomorphic VT despite antiarrhythmic medications. The primary outcome, a composite of death, VT storm, or ICD shocks occurred in 59.1% in the ablation group and in 68.5% in the escalated-therapy group. There was no difference in mortality between the groups. Recurrent ICD shocks and VT storm and treatment-related adverse events were lower in the ablation group. In a subgroup analysis, patients having VT on amiodarone had better outcomes with ablation compared with increasing amiodarone or adding mexiletine to amiodarone. For patients receiving medications other than amiodarone, catheter ablation did not reduce the risk of ICD shocks or VT storm compared with switching to amiodarone. Although recurrent VT after catheter ablation is associated with increased mortality,<sup>S7.1.3-9</sup> whether mortality is reduced by catheter ablation has not been established. Procedural complications occur in approximately 6% of patients, most of which are related to vascular access but stroke, tamponade, and atrioventricular block can occur. Procedure mortality is <1% in experienced centers.<sup>S7.1.3-4,S7.1.3-9</sup>

Sustained monomorphic VT often occurs as occasional isolated episodes in patients with prior MI. Several nonrandomized studies have shown that catheter ablation reduces recurrent VT or ICD shocks.<sup>S7.1.3-5,S7.1.3-7,S7.1.3-8</sup> A meta-analysis of 5 VT ablation studies<sup>S7.1.3-5</sup> reported that VT recurred in 35% of patients after catheter ablation compared with 55% on antiarrhythmic medications. In a multicenter study of catheter ablation<sup>S7.1.3-7</sup> for patients with  $\geq 3$  episodes of sustained VT in the prior 6 months, 53% were free from recurrent VT at 6 months follow-up; the median number of VT episodes was reduced from 11.5 to 0. Superiority of ablation over escalating medication therapy was shown in the composite endpoint of death, VT storm, or ICD shocks by the VANISH trial.<sup>S7.1.3-4</sup>

3. Patients with prior MI who develop sustained monomorphic VT often have recurrent episodes. The VTACH (Ventricular Tachycardia Ablation in Addition to Implantable Defibrillators in Coronary Heart Disease) trial<sup>S7.1.3-11</sup> randomized patients undergoing ICD implantation for stable sustained monomorphic VT, who had not failed antiarrhythmic medication therapy, to catheter ablation versus ICD implantation alone. At 2 years, any VT had recurred in 53% of the ablation group and 71% of the control group. Ablation prolonged the time to recurrent VT from a median of 5.9 months to 18.6 months.<sup>S7.1.3-11</sup> Several non-randomized studies have shown that catheter ablation reduces the risk of recurrent VT or ICD shocks in patients with sustained VT related to prior MI.<sup>S7.1.3-5,S7.1.3-7,S7.1.3-8</sup> In a multicenter study of catheter ablation<sup>S7.1.3-7</sup> for patients with  $\geq 3$  episodes of sustained VT in the prior 6 months, 53% were free from recurrent VT at 6 months follow-up; the median number of VT episodes was reduced from 11.5 to 0. A meta-analysis of 5 VT ablation studies<sup>S7.1.3-5</sup> reported that VT recurred in 35% of patients after catheter ablation compared with 55% on antiarrhythmic medications. Another study of 63 patients with recurrent VT after MI demonstrated acute success with catheter ablation in 83% of mappable VTs and 40% of nonmappable VTs.<sup>S7.1.3-8</sup> Superiority of ablation over escalating medication therapy for patients with recurrent VT despite antiarrhythmic medications was shown by the VANISH trial.<sup>S7.1.3-4</sup> See Section 5.6.
4. CAST<sup>S7.1.3-21</sup> demonstrated higher rates of mortality or nonfatal cardiac arrest in post-MI patients treated with encainide or flecainide when used to suppress PVCs and NSVT.<sup>S7.1.3-13</sup> Propafenone is associated with increased mortality in SCA survivors compared with beta blockers, amiodarone, and the ICD.<sup>S7.1.3-22</sup>
5. Implantation of an ICD prior to achieving suppression of frequent or incessant VA places the patient at high risk of repetitive shocks, which can be psychologically detrimental and has been associated with increased mortality.<sup>S7.1.3-23,S7.1.3-24</sup>
6. Sustained monomorphic VT in the setting of prior MI is typically due to scar-related reentry and is not due to acute ischemia. Although it may be appropriate to recommend revascularization when another indication for revascularization exists, revascularization alone is unlikely to reduce the recurrence of monomorphic VT and specific therapies such as antiarrhythmic medications or ablation may be needed to prevent recurrence.<sup>S7.1.3-16</sup> On the contrary, revascularization might be beneficial in patients with

ischemic heart disease and VF, polymorphic VT, or exercise-induced arrhythmias associated with ischemia.<sup>57.1.3-25</sup>

## 7.2. Nonischemic Cardiomyopathy

Recommendations for Patients With NICM References that support the recommendations are summarized in Online Data Supplement 24.		
COR	LOE	Recommendations
I	B-NR	1. In patients with suspected NICM from myocardial infiltrative processes, cardiac MRI with late gadolinium enhancement is useful for diagnosis. <sup>57.2.1-57.2.3</sup>
Ila	B-NR	2. In patients with suspected NICM, cardiac MRI with late gadolinium enhancement can be useful for assessing risk of SCA/SCD. <sup>57.2.1-57.2.3</sup>
Ila	C-EO	3. In patients with NICM who develop conduction disease or LV dysfunction at less than 40 years of age, or who have a family history of NICM or SCD in a first-degree relative (<50 years of age), genetic counseling and genetic testing are reasonable to detect a heritable disease that may clarify prognosis and facilitate cascade screening of relatives. <sup>57.2.4,57.2.5</sup>

### Recommendation-Specific Supportive Text

1. Cardiac MRI allows for evaluation of structural heart disease and assessment of LV and RV function including quantification of LVEF, LV mass and volume, and valvular structure. Cardiac MRI can help in the evaluation for myocardial infiltrative processes and evidence of scar, indicated by delayed hyperenhancement, associated with VA.<sup>57.2.1-57.2.4,57.2.6</sup>
2. The presence of delayed hyperenhancement has been associated with worse outcomes, including SCD.<sup>57.2.1-57.2.3</sup>
3. It is important to consider genetic etiologies for NICM. Goals of genetic testing for NICM are to identify at-risk relatives who host a disease-causing mutation and to help clarify prognosis. *Lamin A/C* and *NKX 2.5* mutations<sup>57.2.7-57.2.12</sup> are associated with a particularly high risk of early conduction disease, arrhythmias, and SCD, and their identification often prompts consideration of early use of an ICD. It is unknown, however, whether early pharmacological treatment of mutation-positive, asymptomatic subjects can prevent or delay manifestation of the disease or whether genetic testing ultimately improves survival.

### 7.2.1. Secondary Prevention of SCD in Patients With NICM

Recommendations for Secondary Prevention of SCD in Patients With NICM References that support the recommendations are summarized in Online Data Supplements 25 and 26.		
COR	LOE	Recommendations
I	B-R	1. In patients with NICM who either survive SCA due to VT/VF or experience hemodynamically unstable VT (LOE: B-R) <sup>57.2.1-1,57.2.1-4</sup> or stable sustained VT (LOE: B-NR) <sup>57.2.1-5</sup> not due to reversible causes, an ICD is recommended if meaningful survival greater than 1 year is expected.
	B-NR	
Ila	B-NR	2. In patients with NICM who experience syncope presumed to be due to VA and who do not meet indications for a primary prevention ICD, an ICD or an electrophysiological study for risk stratification for SCD can be beneficial if meaningful survival greater than 1 year is expected. <sup>57.2.1-6-57.2.1-11</sup>
Ilib	B-R	3. In patients with NICM who survive a cardiac arrest, have sustained VT, or have symptomatic VA who are ineligible for an ICD (due to a limited life-expectancy and/or functional status or lack of access to an ICD), amiodarone may be considered for prevention of SCD. <sup>57.2.1-12,57.2.1-13</sup>

### Recommendation-Specific Supportive Text

1. Three prospective RCTs compared the ICD with pharmacological therapy in patients resuscitated from SCA due to VT/VF or hemodynamically significant VT.<sup>57.2.1-1,57.2.1-2,57.2.1-4</sup> The antiarrhythmic medications most commonly used were amiodarone, a beta blocker, or both, although in the CASH (Cardiac Arrest Study Hamburg) trial,<sup>57.2.1-4</sup> there was also a propafenone arm that was terminated early due to increased mortality. The 3 trials enrolled 1963 patients, but only 292 (14.8%) had NICM. A meta-analysis in which data from AVID and CIDS were pooled found a nonsignificant 31% reduction in all-cause mortality relative to medical therapy in patients with NICM.<sup>57.2.1-3</sup> Although this analysis was underpowered, the observed mortality reduction was consistent with the observed benefit in the entire study population. In the AVID trial,<sup>57.2.1-1</sup> patients who were ineligible for the RCT were included in a registry, and sustained VT without serious symptoms or hemodynamic compromise was associated with a mortality rate similar to that of patients with unstable VT who were assigned to medical therapy. Therefore, stable VT is likely a marker for a substrate capable of producing subsequent lethal arrhythmias.<sup>57.2.1-5</sup>

2. Small observational studies demonstrated high mortality and frequent appropriate ICD shocks in patients with syncope and NICM.<sup>57.2.1-7–57.2.1-9</sup> The assumption that malignant VAs are the likely cause of syncope and that the ICD would be protective has recently been challenged. In a subgroup analysis of SCD-HeFT that included 472 patients, the ICD did not reduce either recurrent syncope or the increased risk of mortality associated with syncope.<sup>57.2.1-10</sup> A subgroup analysis of the MADIT-RIT (Multicenter Automatic Defibrillator Implantation Trial-Reduce Inappropriate Therapy) trial found syncope to be arrhythmic only in 39% of patients.<sup>57.2.1-11</sup> These studies suggest that syncope in some HF patients may be an indicator of an end-stage cardiomyopathy associated with a poor prognosis.<sup>57.2.1-11</sup> In a substudy of DEFINITE, inducible sustained VT/VF was found in a minority of patients, but it was associated with appropriate ICD therapy.<sup>57.2.1-14</sup> Another study of electrophysiological testing in NICM found inducible VT/VF in 27.8% of patients, which was associated with future ICD events.<sup>57.2.1-15</sup> In a study of patients with NICM, cardiac mortality correlated with LVEF but not with inducibility on electrophysiological study.<sup>57.2.1-16</sup> Based on these data, many experts are uncomfortable withholding an ICD from patients with NICM who experience syncope potentially due to a VA even if the electrophysiological study shows no inducible sustained VT.
3. Access to ICDs may be limited by financial, medical, or personal considerations. In addition, not all patients at high risk of SCD meet ICD indications, such as those with class IV HF without CRT possibility or with a life expectancy <1 year. A meta-analysis of RCTs, which examined the use of amiodarone for the prevention of SCD, included 15 studies with 8522 patients assigned to amiodarone or placebo/control.<sup>57.2.1-12</sup> Amiodarone reduced the risk of SCD by 29%; however, it did not reduce all-cause mortality and was associated with an increased risk of pulmonary and thyroid toxicity. In a subgroup analysis, the benefit of amiodarone appeared similar in patients with ischemic cardiomyopathy and those with NICM.<sup>57.2.1-12</sup> In a separate meta-analysis,<sup>57.2.1-13</sup> the evidence was insufficient to support amiodarone's efficacy for reduction of SCD and all-cause mortality in survivors of cardiac arrest or those with syncope due to VA. A subgroup analysis of the VALIANT (Valsartan in Acute Myocardial Infarction) trial found that amiodarone was associated with increased mortality in patients with NYHA class III HF.<sup>57.2.1-17</sup> These data call for a careful and nuanced approach to using amiodarone

for the secondary prevention of SCD in patients with NICM.

### 7.2.2. Primary Prevention of SCD in Patients With NICM

Recommendations for Primary Prevention of SCD in Patients With NICM		
References that support the recommendations are summarized in Online Data Supplements 27 and 28.		
COR	LOE	Recommendations
I	A	1. In patients with NICM, HF with NYHA class II–III symptoms and an LVEF of 35% or less, despite GDMT, an ICD is recommended if meaningful survival of greater than 1 year is expected. <sup>57.2.2-1–57.2.2-6</sup>
IIa	B-NR	2. In patients with NICM due to a <i>Lamin A/C</i> mutation who have 2 or more risk factors (NSVT, LVEF <45%, nonmissense mutation, and male sex), an ICD can be beneficial if meaningful survival of greater than 1 year is expected. <sup>57.2.2-7–57.2.2-10</sup>
IIb	B-R	3. In patients with NICM, HF with NYHA class I symptoms and an LVEF of 35% or less, despite GDMT, an ICD may be considered if meaningful survival of greater than 1 year is expected. <sup>57.2.2-5</sup>
III: No Benefit	C-EO	4. In patients with medication-refractory NYHA class IV HF who are not also candidates for cardiac transplantation, an LVAD, or a CRT defibrillator that incorporates both pacing and defibrillation capabilities, an ICD should not be implanted.

### Recommendation-Specific Supportive Text

1. For all patients with NICM, it is imperative that patients be on GDMT for HF for at least 3 months before a primary prevention ICD is offered. Four prospective RCTs<sup>57.2.2-1,57.2.2-2,57.2.2-5,57.2.2-6</sup> initially evaluated ICDs for primary prevention of SCD in patients with NICM. Two<sup>57.2.2-2,57.2.2-6</sup> were small studies that were terminated early due to a low event rate. In DEFINITE,<sup>57.2.2-5</sup> an ICD reduced the risk of SCD, with a trend toward reduced all-cause mortality. SCD-HeFT included 792 NICM patients.<sup>57.2.2-1</sup> Total mortality at 5 years was 27% in the placebo group and 21% in the ICD group ( $P=0.06$ ). A pooled analysis of these studies demonstrated a significant 31% reduction in all-cause mortality for ICD relative to medical therapy.<sup>57.2.2-4</sup> The DANISH (Danish Study to Assess the Efficacy of ICDs in Patients with Non-ischemic Systolic Heart Failure on Mortality) trial<sup>57.2.2-11</sup> raised questions about the role of primary prevention ICDs in patients with NICM. This trial randomized 1116 patients with NICM LVEF <35% and class II, III, or IV (if CRT was planned) HF to an ICD or no ICD. CRT (either ICD or pacemaker) was present in 58% of patients in the ICD and medical

therapy arms. Therefore, the results of DANISH should not be generalized to patients with NICM who are ineligible for CRT. During a median follow-up of 5.6 years, ICD reduced SCD from 8.4% to 4.3%, but there was no difference in all-cause mortality.<sup>57.2.2-11</sup> Several meta-analyses have been published.<sup>57.2.2-12,57.2.2-13</sup> One provided data on ICDs with and without CRT and showed survival benefit from the ICD.<sup>57.2.2-13</sup> The second used patient level data from 2 trials and adopted a more robust approach to reducing heterogeneity by excluding patients with CRT and those randomized to antiarrhythmic medications; a 25% relative risk reduction in mortality with an ICD was shown.<sup>57.2.2-12</sup>

2. Laminopathies are diseases caused by mutations mainly in the *Lamin A/C* gene that produce various inherited diseases including subtypes of muscular dystrophy and progeria. Isolated cardiac involvement is also observed and is an important cause of familial cardiomyopathy.<sup>57.2.2-9</sup> The disease is highly penetrant such that all affected individuals have evidence of disease by 60 years of age. Cardiac manifestations may include atrial fibrillation, conduction disturbances, VA, and NICM. A number of observational studies reported a high risk of SCD when cardiac involvement is present.<sup>57.2.2-7-57.2.2-10</sup> One study reported SCD as the most frequent mode of death (46%) in both the isolated cardiac and the neuromuscular phenotypes of *Lamin* diseases.<sup>57.2.2-9</sup> In a cohort of 269 *LMNA* mutation positive individuals,<sup>57.2.2-10</sup> NSVT during ambulatory electrocardiographic monitoring, LVEF <45% at first evaluation, male sex, and nonmissense mutations were independent risk factors for VA. Malignant VA were observed only in persons with  $\geq 2$  of these risk factors.<sup>57.2.2-10</sup> No studies have tested the effect of the ICD on long-term survival.
3. Patients with NICM and class I HF symptoms were not included in SCD-HeFT or DANISH.<sup>57.2.2-1,57.2.2-11</sup> Although such patients were included in the DEFINITE trial, only 99 (21.6%) of 458 patients in the DEFINITE trial had class I HF.<sup>57.2.2-5</sup> Therefore, it is uncertain whether a primary prevention ICD in such patients improves survival.
4. There are insufficient data from RCTs regarding the value of the ICD in patients with NYHA class IV. Ambulatory class IV HF patients were included in the COMPANION trial that, overall, showed improved functional status and survival with a CRT defibrillator.<sup>57.2.2-3</sup> Unless such a patient is a candidate for CRT or advanced HF therapies such as heart transplantation or an LVAD, an ICD is not expected to meaningfully prolong survival.<sup>57.2.2-3</sup>

### 7.2.3. Treatment of Recurrent VA in Patients With NICM

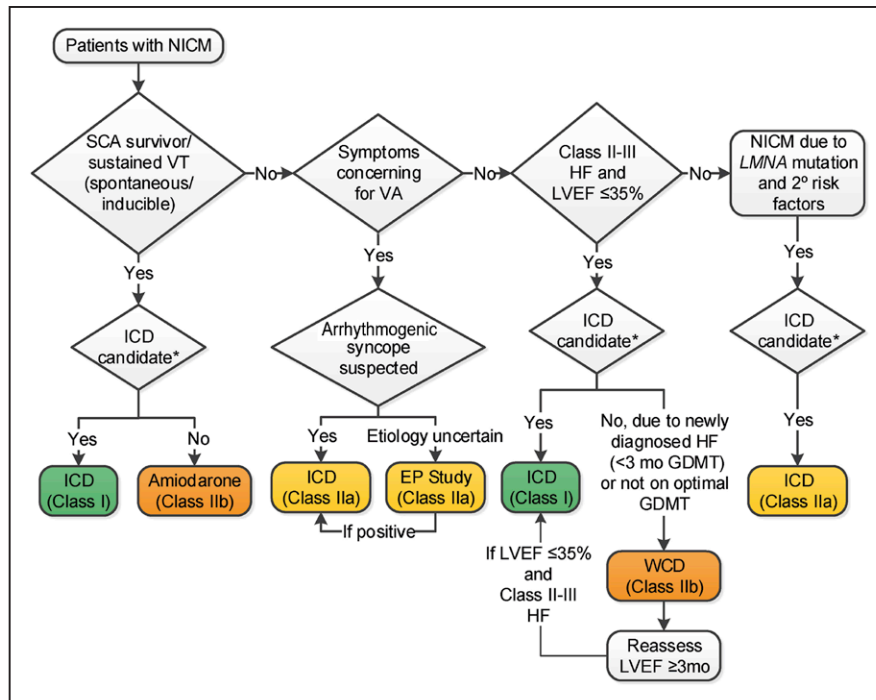
#### Recommendations for Treatment of Recurrent VA in Patients With NICM

References that support the recommendations are summarized in Online Data Supplement 29.

COR	LOE	Recommendations
Ia	B-R	1. In patients with NICM and an ICD who experience spontaneous VA or recurrent appropriate shocks despite optimal device programming and treatment with a beta blocker, amiodarone or sotalol can be beneficial. <sup>57.2.3-1</sup>
Ia	B-NR	2. In patients with NICM and recurrent sustained monomorphic VT who fail or are intolerant of antiarrhythmic medications, catheter ablation can be useful for reducing recurrent VT and ICD shocks. <sup>57.2.3-2,57.2.3-3</sup>

### Recommendation-Specific Supportive Text

1. ICDs reduce mortality from VA, yet ICD shocks are painful and associated with significant morbidity and poor QoL. Although ICDs are highly programmable and provide antitachycardia pacing therapy that can terminate most VT episodes without the need for a shock, prevention of shocks, both appropriate and inappropriate, remains an important concern. In the OPTIC (Optimal Pharmacological Therapy in Cardioverter Defibrillator Patients) study, 412 patients with documented VT and VF who received an ICD within 21 days of the documented arrhythmia<sup>57.2.3-1</sup> were randomized to amiodarone plus beta blocker, sotalol alone, or beta blocker alone. Over 1 year, shocks occurred in 38.5% assigned to beta blocker alone, 24.3% assigned to sotalol, and 10.3% assigned to amiodarone plus beta blocker. The rates of study medication discontinuation at 1 year were 18.2% for amiodarone, 23.5% for sotalol, and 5.3% for beta blocker alone. Adverse pulmonary and thyroid events and symptomatic bradycardia were more common among patients randomized to amiodarone. Thus, amiodarone plus beta blocker were more effective than sotalol in preventing ICD shocks but at the expense of increased risk of medication-related adverse effects.<sup>57.2.3-1</sup> Sotalol should not be used in patients with an LVEF <20% due to its negative inotropic effects.
2. Sustained monomorphic VT due to NICM is most often due to scar-related reentry. Cardiac MRI often indicates scar location, which tends to be basal along the mitral annulus or in the septum.<sup>57.2.3-4,57.2.3-5</sup> The VT substrate can be



**Figure 6. Secondary and primary prevention of SCD in patients with NICM.**

Colors correspond to Class of Recommendation in Table 1. See Section 7.2 for discussion. \*ICD candidacy as determined by functional status, life expectancy or patient preference. 2° indicates secondary; EP, electrophysiological; GDMT, guideline-directed management and therapy; HF, heart failure; ICD, implantable cardioverter-defibrillator; LVEF, left ventricular ejection fraction; NICM, nonischemic cardiomyopathy; SCA, sudden cardiac arrest; SCD, sudden cardiac death; VA, ventricular arrhythmia; and WCD, wearable cardioverter-defibrillator.

subendocardial, subepicardial, or intramyocardial, and all locations may be affected and require endocardial and epicardial ablation. In the HELP-VT (Heart Center of Leipzig VT) study,<sup>57.2.3-2</sup> successful ablation of all VT morphologies was achieved in 66.7% of patients with NICM, compared with the 77.4% success rate in ischemic cardiomyopathy. An epicardial approach to ablation was required in 30.2% of NICM patients, compared with only 1.2% with ischemic cardiomyopathy. Epicardial ablation was an independent predictor of successful ablation. Acute and long-term success of ablation is lower for NICM, compared with post-MI patients. The long-term survival-free of VT recurrence after catheter ablation appears to be better for patients with ischemic than NICM (57% versus 40.5% at 1 year).<sup>57.2.3-2</sup> Risks are similar to those observed for post-MI VT ablation, with additional risks of epicardial access and ablation when required. Although any NICM can produce scar-related VT, cardiac sarcoidosis (see Section 7.6) and *Lamin* mutations are particularly associated with sustained monomorphic VT.<sup>57.2.3-6</sup>

### 7.3. Arrhythmic Right Ventricular Cardiomyopathy

Recommendations for Arrhythmic Right Ventricular Cardiomyopathy		
References that support the recommendations are summarized in Online Data Supplement 30.		
COR	LOE	Recommendations
I	B-NR	1. In selected first-degree relatives of patients with arrhythmic right ventricular cardiomyopathy, clinical screening for the disease is recommended along with genetic counseling and genetic testing, if the proband has a disease causing mutation. <sup>57.3-1-57.3-4</sup>
I	B-NR	2. In patients with suspected arrhythmic right ventricular cardiomyopathy and VA or electrocardiographic abnormalities, cardiac MRI is useful for establishing a diagnosis and for risk stratification. <sup>57.3-5-57.3-8</sup>
I	B-NR	3. In patients with arrhythmic right ventricular cardiomyopathy and an additional marker of increased risk of SCD (resuscitated SCA, sustained VT, significant ventricular dysfunction with RVEF or LVEF ≤35%), an ICD is recommended if meaningful survival greater than 1 year is expected. <sup>57.3-9-57.3-13</sup>
I	B-NR	4. In patients with arrhythmic right ventricular cardiomyopathy and VA, a beta blocker is recommended. <sup>57.3-11,57.3-14,57.3-15</sup>

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Recommendations for Arrhythmogenic Right Ventricular Cardiomyopathy (Continued)		
COR	LOE	Recommendations
I	B-NR	5. In patients with a clinical diagnosis of arrhythmogenic right ventricular cardiomyopathy, avoiding intensive exercise is recommended. <sup>57.3-11,57.3-12,57.3-16-57.3-21</sup>
IIa	B-NR	6. In patients with clinically diagnosed or suspected arrhythmogenic right ventricular cardiomyopathy, genetic counseling and genetic testing can be useful for diagnosis and for gene-specific targeted family screening. <sup>57.3-1,57.3-4,57.3-22-57.3-26</sup>
IIa	B-NR	7. In patients with arrhythmogenic right ventricular cardiomyopathy and syncope presumed due to VA, an ICD can be useful if meaningful survival greater than 1 year is expected. <sup>57.3-10,57.3-11,57.3-13</sup>
IIa	B-NR	8. In patients with clinical evidence of arrhythmogenic right ventricular cardiomyopathy but not VA, a beta blocker can be useful. <sup>57.3-14,57.3-15</sup>
IIa	B-NR	9. In patients with arrhythmogenic right ventricular cardiomyopathy and recurrent symptomatic sustained VT in whom a beta blocker is ineffective or not tolerated, catheter ablation with availability of a combined endocardial/epicardial approach can be beneficial. <sup>57.3-27-57.3-33</sup>
IIa	B-NR	10. In patients with suspected arrhythmogenic right ventricular cardiomyopathy, a signal averaged ECG can be useful for diagnosis and risk stratification. <sup>57.3-14,57.3-34,57.3-35</sup>
IIb	B-NR	11. In asymptomatic patients with clinical evidence of arrhythmogenic right ventricular cardiomyopathy, an electrophysiological study may be considered for risk stratification. <sup>57.3-9,57.3-36</sup>

## Synopsis

Arrhythmogenic right ventricular cardiomyopathy is an inherited cardiomyopathy that predominantly affects the right ventricle but can affect the left ventricle causing areas of myocardial replacement with fibrosis and adipose tissue that frequently causes VA and SCD.

## Recommendation-Specific Supportive Text

1. Selected first-degree relatives refers to relatives who are willing to undergo further testing and who could benefit from further screening and testing (and not the terminally ill patients or those who do not want to be screened and tested). Arrhythmogenic right ventricular cardiomyopathy is often due to a mutation involving a desmosomal protein, and it usually has autosomal dominant inheritance with variable penetrance. SCD can be the initial manifestation of

arrhythmogenic right ventricular cardiomyopathy. Clinical screening with ECG, cardiac imaging, and ambulatory rhythm monitoring and/or exercise testing may identify family members at risk for arrhythmogenic right ventricular cardiomyopathy. Arrhythmogenic right ventricular cardiomyopathy is detected clinically in approximately 35% to 40% of first-degree relatives,<sup>57.3-3,57.3-4</sup> most commonly in siblings or symptomatic first-degree relatives.<sup>57.3-4</sup> When a proband is identified with a disease-causing mutation, targeted genotype screening can identify mutation positive relatives,<sup>57.3-1</sup> with approximately 35% of mutation positive individuals ultimately developing progressive disease expression.<sup>57.3-1,57.3-4</sup> In studies of arrhythmogenic right ventricular cardiomyopathy mutation-positive individuals who do not initially manifest the disease, 8% to 16% have a major arrhythmic event over the next 7 to 39 years.<sup>57.3-1,57.3-4,57.3-26</sup> Early identification of affected or potentially affected family members can allow lifestyle modifications in sports participation and serial monitoring for development of electrocardiographic abnormalities, symptoms, ventricular dysfunction, or arrhythmia. As genetic testing for arrhythmogenic right ventricular cardiomyopathy has subtle complexities, the decision to proceed with family screening is facilitated by informed genetic counseling to discuss the cost of testing, the potential lack of a single gene as the determinant for disease expression, psychological implications of uncertain disease progression, and implications for lifestyle modification, screening, and potential treatment.

2. Cardiac MRI provides high-quality assessment of ventricular function, size, regional wall motion abnormalities, and extent of scar and fibrosis (late gadolinium enhancement) that are seen in 30% to 95% of patients with the clinical diagnosis of arrhythmogenic right ventricular cardiomyopathy.<sup>57.3-5,57.3-6,57.3-37,57.3-38</sup> Cardiac MRI detects biventricular involvement in 34% to 56% of patients, with isolated LV involvement noted in 4% to 9% of patients.<sup>57.3-37-57.3-40</sup> Cardiac MRI should include assessment of late gadolinium enhancement with quantification of fibrosis. Application of the 2010 Task Force Criteria to cardiac MRI criteria for diagnosis of arrhythmogenic right ventricular cardiomyopathy has improved the specificity of this test.<sup>57.3-5,57.3-8</sup> Electrocardiographic and Holter findings precede detectable cardiac MRI abnormalities in arrhythmogenic right ventricular cardiomyopathy mutation-positive individuals, with only 4% of patients with normal electrocardiographic and Holter results having cardiac MRI abnormalities,

suggesting that evaluation of cardiac structure and function using cardiac MRI may be unnecessary in mutation-positive individuals who do not have electrical abnormalities.<sup>57.3-7</sup> The presence of both electrocardiographic abnormalities and abnormal cardiac MRI findings may identify patients at an increased risk for developing sustained VA.<sup>57.3-7,57.3-38</sup> Areas of scar identified on cardiac MRI have correlated with the location of VT substrate identified by endocardial and epicardial mapping.<sup>57.3-38</sup> During early stages of disease, a baseline cardiac MRI may provide useful information along with electrocardiographic and rhythm abnormalities to monitor disease progression over time. Experience and expertise in interpretation of cardiac MRI are important.<sup>57.3-5,57.3-8</sup>

3. Arrhythmogenic right ventricular cardiomyopathy is characterized by progressive ventricular myocyte loss with replacement by fatty or fibrous tissue, and is associated with progressive ventricular dysfunction that may involve both ventricles. VA, syncope, and SCD may occur at a relatively young age, particularly in the second and third decades of life and often occurring during physical activity.<sup>57.3-1,57.3-16,57.3-22,57.3-41</sup> Sustained VT is an important predictor of SCA and SCD or appropriate ICD shocks in patients with arrhythmogenic right ventricular cardiomyopathy.<sup>57.3-10,57.3-13</sup> In patients receiving an ICD for primary prevention, appropriate ICD shocks are reported in 24% to 48% of patients.<sup>57.3-9,57.3-10,57.3-12,57.3-13</sup> As sustained VT in arrhythmogenic right ventricular cardiomyopathy patients is monomorphic in 55% to 90% of episodes based on ICD interrogation or electrophysiological studies,<sup>57.3-12,57.3-36</sup> antitachycardia pacing algorithms are used to terminate VT.
4. Frequent PVCs, >760 per 24 hours during ambulatory rhythm monitoring, correlate with arrhythmic risk.<sup>57.3-9,57.3-23</sup> The presence of NSVT or sustained VT is an important predictor of adverse cardiac events.<sup>57.3-9,57.3-12,57.3-13,57.3-42,57.3-43</sup> The increased arrhythmia risk conferred by intense exercise is consistent with beta-adrenergic modulation of disease expression.<sup>57.3-17,57.3-20,57.3-21</sup> An observational registry reported that treatment with atenolol or amiodarone was associated with less clinically relevant VA, while sotalol was associated with no effect or increased arrhythmia.<sup>57.3-15</sup> Ambulatory monitoring to assess VA burden and adequacy of beta-blocker therapy is usually used.<sup>57.3-9,57.3-14,57.3-23,57.3-42</sup>
5. Patients with arrhythmogenic right ventricular cardiomyopathy have a significantly increased risk of SCD during exertion.<sup>57.3-16,57.3-17,57.3-20,57.3-21</sup> Vigorous exercise in patients with arrhythmogenic

- right ventricular cardiomyopathy has been shown to impair myocardial function by echocardiography and cardiac MRI.<sup>57.3-19</sup> Participation in high intensity/duration or endurance physical activity accelerates the penetrance/disease progression and arrhythmic risk for arrhythmogenic right ventricular cardiomyopathy patients and mutation positive individuals, as well as mutation positive family members.<sup>57.3-17,57.3-19-57.3-21</sup> Patients with arrhythmogenic right ventricular cardiomyopathy who participate in competitive sports are at increased risk for VT or SCD, compared with those who participate in recreational sports or are inactive.<sup>57.3-17-57.3-19,57.3-21</sup> Exercise influences disease progression in a linear manner; family members who limited activity to less than the AHA recommended minimum for activity guidelines (<650 metabolic equivalent hours per year [MET-Hr/year]) were less likely to develop VA or disease progression.<sup>57.3-21</sup> In a study of arrhythmogenic right ventricular cardiomyopathy probands and exercise, athletes (defined as subjects with ≥4h vigorous exercise/week) were found to have reduced biventricular function compared with nonathletes in arrhythmogenic right ventricular cardiomyopathy patients and in mutation-positive family members.<sup>57.3-19</sup> Many advise limiting exercise intensity and duration to <650 MET-Hr/year, or 12.5 MET-Hr/week.<sup>57.3-21</sup>
6. The proband with arrhythmogenic right ventricular cardiomyopathy is usually diagnosed by the presence of clinical symptoms along with the presence of arrhythmogenic right ventricular cardiomyopathy Task Force criteria including: abnormalities on ECG, structural and functional changes of either ventricle, arrhythmias, and arrhythmogenic right ventricular cardiomyopathy in first-degree relatives.<sup>57.3-6</sup> A pathogenic genetic mutation was added to the major Task Force criteria in 2010.<sup>57.3-44</sup> The yield of genetic testing in probands with suspected arrhythmogenic right ventricular cardiomyopathy is generally 30% to 54%, and is up to 58% among patients with a strong family history of SCD in multiple members.<sup>57.3-3,57.3-25,57.3-45</sup> A negative genetic test for arrhythmogenic right ventricular cardiomyopathy does not exclude the disease, and a positive genetic test currently does not guide therapy.<sup>57.3-22</sup> For the proband with a clinical diagnosis of arrhythmogenic right ventricular cardiomyopathy, identification of pathogenic mutations provides limited prognostic information relative to the risk of VT/VF<sup>57.3-22,57.3-26</sup> or development of HF.<sup>57.3-22</sup> In a large multicenter study, the presence of positive mutations among probands was not associated with a difference in mortality or cardiac

transplantation.<sup>57.3-1</sup> However, the identification of a pathogenic mutation facilitates targeted genetic screening for that mutation in first-degree relatives, that may identify approximately 60% to 70% as gene positive,<sup>57.3-1</sup> highest among siblings, and those with symptoms.<sup>57.3-4</sup> Screening for the specific mutation can identify some gene positive family members prior to disease expression, while relieving others from the need for lifestyle changes and long-term monitoring.<sup>57.3-2,57.3-3</sup>

7. Syncope is reported in 16% to 39% of arrhythmogenic right ventricular cardiomyopathy patients at the time of diagnosis,<sup>57.3-13,57.3-14,57.3-16,57.3-41,57.3-43</sup> is frequently exercise-related, and has been associated with high arrhythmic risk in some studies.<sup>57.3-10,57.3-41</sup> Among patients with arrhythmogenic right ventricular cardiomyopathy and implanted ICDs, syncope was an important predictor of appropriate shocks in 1 study,<sup>57.3-10</sup> but not in other studies.<sup>57.3-9,57.3-12,57.3-13,57.3-43</sup> Studies have not provided information about ventricular function or abnormalities on ECG in patients with syncope, limiting its assessment as an independent risk factor. Syncope may be a harbinger of progression of underlying disease and should be integrated into the decision-making process for ICD implantation with the patient.
8. Asymptomatic patients with arrhythmogenic right ventricular cardiomyopathy and no VA or ventricular dysfunction are generally observed without antiarrhythmic therapy other than beta-blocker therapy, with ongoing periodic reassessment for the development of arrhythmias or ventricular dysfunction.<sup>57.3-46,57.3-47</sup> Atenolol was shown to reduce VA in 1 study.<sup>57.3-15</sup> Ambulatory monitoring and/or exercise testing can be performed to assess adequacy of beta-blocking dosing.
9. Interrogation of ICDs shows that >90% of spontaneous sustained VTs in arrhythmogenic right ventricular cardiomyopathy are monomorphic,<sup>57.3-12</sup> while sustained monomorphic VT is inducible at electrophysiological study in 55% of patients.<sup>57.3-36</sup> VT is usually related to scar-related reentry, and the subepicardium usually has more extensive scar than the endocardium.<sup>57.3-27</sup> In experienced centers, use of epicardial mapping and ablation is associated with better outcomes.<sup>57.3-27,57.3-28,57.3-30,57.3-31,57.3-33</sup> Important complications including pericardial tamponade, MI, and death occur in 2.3% to 3.3% of ablation cases,<sup>57.3-27-57.3-29</sup> emphasizing the need for performance in centers with specialized expertise in epicardial procedures. Ablation reduces the frequency of recurrent VT, although 27% to 55% of patients<sup>57.3-27,57.3-28</sup> have at least 1 recurrence; ablation of VT in arrhythmogenic right ventricular

cardiomyopathy patients does not eliminate the need for an ICD in appropriate candidates. The potential risk of VT recurrence due to disease progression should be reviewed with patients when considering ablation. There are no randomized comparisons of antiarrhythmic therapy to suppress recurrent VT. Beta blockers, sotalol and amiodarone have been used.<sup>57.3-15</sup> In an observational series, sotalol suppressed inducible VT in 58% of patients with <10% of patients experiencing arrhythmia recurrence during follow-up.<sup>57.3-48</sup> Effectiveness of the different medications appears to be variable, and so more studies are needed.

10. In arrhythmogenic right ventricular cardiomyopathy, areas of fibrofatty scar in the RV free wall create areas of delayed ventricular activation causing fractionated deflections following the QRS, known as epsilon waves on the surface ECG (a major criterion) and late potentials in the signal averaged ECG (minor criterion) in the 2010 Task Force Criteria for diagnosis of arrhythmogenic right ventricular cardiomyopathy.<sup>57.3-6</sup> When the standard ECG QRS duration is  $\leq 110$  ms, criteria for abnormal signal-averaged ECG include any 1 of the following: filtered QRS duration  $\geq 114$  ms, duration of the terminal QRS  $< 40$   $\mu$ V exceeding 37 ms, or a root mean square voltage in the terminal 40 ms of  $\leq 20$   $\mu$ V.<sup>57.3-6</sup> Abnormal findings on signal averaged ECG correlated with disease severity on cardiac MRI,<sup>57.3-35</sup> and increased adverse events in males.<sup>57.3-34</sup> In an assessment of the diagnostic use of testing for arrhythmogenic right ventricular cardiomyopathy, signal averaged ECG was of greater value than cardiac MRI or biopsy.<sup>57.3-14</sup>
11. The value of an electrophysiological study is uncertain in asymptomatic arrhythmogenic right ventricular cardiomyopathy patients with preserved ventricular function in predicting subsequent risk for SCD. Studies of programmed ventricular stimulation in patients with definite or probable arrhythmogenic right ventricular cardiomyopathy include most symptomatic patients, making recommendations on asymptomatic patients difficult. Electrophysiological studies induce sustained VT in approximately 60% of patients<sup>57.3-10,57.3-36</sup>; many of whom have had prior spontaneous episodes of sustained VT. In patients with primary prevention ICDs, inducible sustained VT did not predict subsequent appropriate ICD shocks.<sup>57.3-13</sup> In 1 study including symptomatic patients, patients without inducible VT were less likely to receive appropriate ICD shocks.<sup>57.3-9</sup> In asymptomatic patients without evidence of VA on ambulatory monitoring, a negative electrophysiological study may have limited value in decision-making for an ICD.

### 7.4. Hypertrophic Cardiomyopathy

Recommendations for HCM		
References that support the recommendations are summarized in Online Data Supplement 31.		
COR	LOE	Recommendations
I	B-NR	1. In patients with HCM, SCD risk stratification should be performed at the time of initial evaluation and periodically thereafter. <sup>57.4-1-57.4-8</sup>
I	B-NR	2. In patients with HCM who have survived an SCA due to VT or VF, or have spontaneous sustained VT causing syncope or hemodynamic compromise, an ICD is recommended if meaningful survival greater than 1 year is expected. <sup>57.4-1,57.4-6,57.4-9,57.4-10</sup>
I	B-NR	3. In first-degree relatives of patients with HCM, an ECG and echocardiogram should be performed. <sup>57.4-11-57.4-17</sup>
I	B-NR	4. In first-degree relatives of patients with HCM due to a known causative mutation, genetic counseling and mutation-specific genetic testing are recommended. <sup>57.4-13-57.4-15,57.4-18,57.4-19</sup>
IIa	B-NR	5. In patients with clinically suspected or diagnosed HCM, genetic counseling and genetic testing are reasonable. <sup>57.4-13-57.4-15,57.4-18-57.4-22</sup>
IIa	B-NR	6. In patients with HCM and 1 or more of the following risk factors, an ICD is reasonable if meaningful survival of greater than 1 year is expected: a. Maximum LV wall thickness $\geq 30$ mm (LOE: B-NR). <sup>57.4-2,57.4-3,57.4-23,57.4-24</sup> b. SCD in 1 or more first-degree relatives presumably caused by HCM (LOE: C-LD). <sup>57.4-25,57.4-26</sup> c. 1 or more episodes of unexplained syncope within the preceding 6 months (LOE: C-LD). <sup>57.4-8,57.4-26</sup>
	C-LD	
	C-LD	
IIa	B-NR	7. In patients with HCM who have spontaneous NSVT (LOE: C-LD). <sup>57.4-2,57.4-26,57.4-27</sup> or an abnormal blood pressure response with exercise (LOE: B-NR). <sup>57.4-5,57.4-28,57.4-29</sup> , who also have additional SCD risk modifiers or high-risk features, an ICD is reasonable if meaningful survival greater than 1 year is expected.
	C-LD	
IIb	B-NR	8. In patients with HCM who have NSVT (LOE: B-NR). <sup>57.4-2,57.4-26,57.4-27</sup> or an abnormal blood pressure response with exercise (LOE: B-NR). <sup>57.4-5,57.4-28,57.4-29</sup> but do not have any other SCD risk modifiers, an ICD may be considered, but its benefit is uncertain.
	B-NR	
IIb	C-LD	9. In patients with HCM and a history of sustained VT or VF, amiodarone may be considered when an ICD is not feasible or not preferred by the patient. <sup>57.4-30,57.4-31</sup>
III: No Benefit	B-NR	10. In patients with HCM, an invasive electrophysiological study with programmed ventricular stimulation should not be performed for risk stratification. <sup>57.4-32,57.4-33</sup>
III: No Benefit	B-NR	11. In patients with an identified HCM genotype in the absence of SCD risk factors, an ICD should not be implanted. <sup>57.4-7,57.4-34,57.4-35</sup>

**Table 8. Major Clinical Features Associated With Increased Risk of SCD in Patients With HCM**

Established risk factors*
Survival from a cardiac arrest due to VT or VF <sup>57.4-1,57.4-5,57.4-6</sup>
Spontaneous sustained VT causing syncope or hemodynamic compromise <sup>57.4-1,57.4-5,57.4-6</sup>
Family history of SCD associated with HCM <sup>57.4-25,57.4-26</sup>
LV wall thickness $\geq 30$ mm <sup>57.4-2,57.4-3,57.4-23,57.4-24</sup>
Unexplained syncope within 6 mo <sup>57.4-8,57.4-26</sup>
NSVT $\geq 3$ beats <sup>57.4-2,57.4-26,57.4-27</sup>
Abnormal blood pressure response during exercise† <sup>57.4-5,57.4-28,57.4-29</sup>
Potential risk modifiers‡
<30 y <sup>57.4-5,57.4-26</sup>
Delayed hyperenhancement on cardiac MRI <sup>57.4-37-57.4-39,57.4-54</sup>
LVOT obstruction <sup>57.4-2,57.4-4</sup>
Syncope >5 y ago <sup>57.4-8,57.4-26</sup>
High-risk subsets§
LV aneurysm <sup>57.4-40,57.4-55,57.4-56</sup>
LVEF <50% <sup>57.4-52</sup>

\*There is general agreement in the literature that these factors independently convey an increased risk for SCD in patients with HCM.

†Decrease in blood pressure of 20 mm Hg or failure to increase systolic blood pressure  $>20$  mm Hg during exertion.

‡There is a lack of agreement in the literature that these modifiers independently convey an increased risk of SCD in patients with HCM; however, a risk modifier when combined with a risk factor often identifies a patient with HCM at increased risk for SCD beyond the risk conveyed by the risk factor alone.

§A small subset of patients with an LVEF <50% (end-stage disease) or an LV aneurysm warrant consideration for ICD implantation.<sup>57.4-52</sup>

HCM indicates hypertrophic cardiomyopathy; ICD, implantable cardioverter-defibrillator; LV, left ventricular; LVEF, left ventricular ejection fraction; LVOT, left ventricular outflow tract; NSVT, nonsustained ventricular tachycardia; SCD, sudden cardiac death; VT, ventricular tachycardia; and VF, ventricular fibrillation.

Refer to the ACCF/AHA HCM guideline for the definition of HCM.<sup>57.4-36</sup>

### Recommendation-Specific Supportive Text

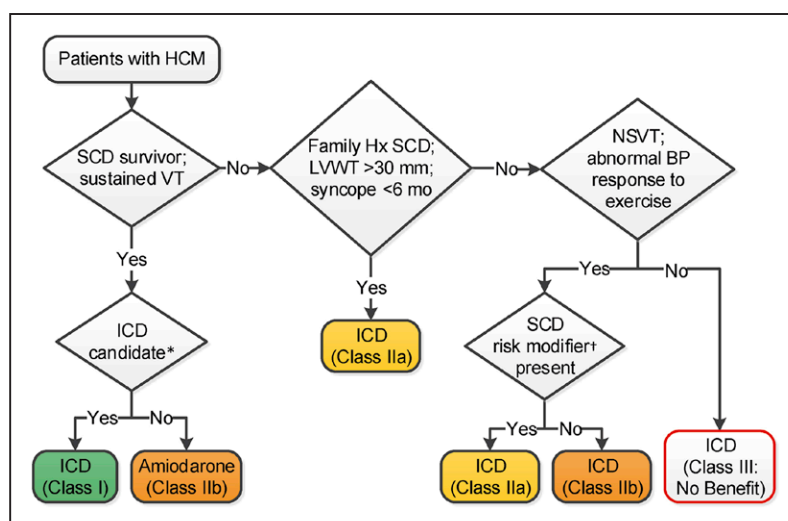
1. Patients with HCM have approximately a 1% risk of SCD per year.<sup>57.4-1,57.4-6</sup> Selection of patients who are appropriate candidates for implantation of an ICD can be a difficult clinical decision because of the individuality of each patient and family, variable definitions of risk factors and risk modifiers, sparse clinical data, the relative infrequency of both HCM and SCD in most clinical practices, and the potential complications of living with an ICD. Table 8 lists risk factors and risk modifiers associated with SCD in patients with HCM. ICD risk stratification should be performed every 1 to 3 years in patients with HCM. There is increasing evidence supporting the association of late gadolinium enhancement on cardiac MRI with the risk of sudden death and it is included as a risk modifier.<sup>57.4-37-57.4-39</sup> LV aneurysm may be

associated with a risk of sustained monomorphic VT.<sup>S7.4-40</sup> Age is also an important consideration, as sudden death risk is greater in those <30 years of age, and low in patients whose initial presentation is after the age of 60 years.<sup>S7.4-5,S7.4-26, S7.4-41</sup>

- HCM is the most common cause of SCD in individuals <40 years of age.<sup>S7.4-26</sup> Individuals who have survived an episode of SCD, VF, or sustained VT resulting in syncope or hemodynamic compromise warrant ICD implantation.<sup>S7.4-1,S7.4-6,S7.4-9,S7.4-10</sup> Although there are no RCTs assessing the use of the ICD in patients with HCM who have survived SCD, 1 study reported that 54% of patients with an ICD placed for secondary prevention received appropriate ICD therapy during an average follow-up of 4.6 years.<sup>S7.4-10</sup> Select patients with HCM may be candidates for implantation of the subcutaneous implantable cardioverter-defibrillator<sup>S7.4-42</sup>; however, more data on this group are needed especially given their higher risk of T wave oversensing that may increase the risk of inappropriate ICD shocks.
- Clinical and/or genetic screening of first- and second-degree family members of patients with HCM is important to identify those with unrecognized disease. Genetic counseling should precede genetic testing of family members to enhance their understanding of the usefulness and cost of testing.<sup>S7.4-18,S7.4-20,S7.4-43</sup> On the basis of family history, clinical screening, and pedigree analyses, the pattern of inheritance is ascertained to identify and manage

relatives at risk.<sup>S7.4-13,S7.4-14,S7.4-18,S7.4-19,S7.4-43-S7.4-45</sup> Because familial HCM is a dominant disorder, the risk that an affected patient will transmit disease to each offspring is 50%. When a pathogenic mutation is identified in an index patient, the genetic status of each family member can be readily ascertained. Relatives with overt HCM will have the same pathogenic HCM mutation as the index patient. Pathogenic mutations may also be identified in other relatives with unknown clinical status. These mutation-positive individuals should be evaluated by physical examination, electrocardiography,<sup>S7.4-11,S7.4-17</sup> and echocardiography<sup>S7.4-12,S7.4-16,S7.4-17</sup> and, if HCM is identified, these individuals should undergo risk stratification. Gene-positive subjects without evidence of HCM may be at risk for future development of HCM and benefit from ongoing clinical evaluation.<sup>S7.4-15,S7.4-46,S7.4-47</sup> If the proband's implicated mutation is the bona fide disease-causing mutation, then mutation-negative family members and their descendants are not at an increased risk for developing HCM and do not need further evaluation. However, such mutation-negative family members must have an echocardiogram to ensure genotype and phenotype concordance.

- In a study of 1053 unrelated patients with clinically manifest HCM, 359 patients (34%) were genotype positive for an HCM-associated mutation in  $\geq 1$  HCM-associated genes.<sup>S7.4-22</sup> Whether the results of genetic testing in the proband improve outcomes is uncertain, but identification



**Figure 7. Prevention of SCD in patients with HCM.**

Colors correspond to Class of Recommendation in Table 1. See Section 7.4 for discussion. \*ICD candidacy as determined by functional status, life expectancy, or patient preference. †Risk modifiers: Age <30 y, late gadolinium enhancement on cardiac MRI, LVOT obstruction, LV aneurysm, syncope >5 y. BP indicates blood pressure; HCM, hypertrophic cardiomyopathy; Hx, history; ICD, implantable cardioverter-defibrillator; LVOT, left ventricular outflow tract; LVWT, left ventricular wall thickness; MRI, magnetic resonance imaging; NSVT, nonsustained ventricular tachycardia; SCD, sudden cardiac death; and VT, ventricular tachycardia.

of a mutation can help inform screening of relatives.

5. Genetic counseling is important in patients with HCM, and genetic screening of relatives is also important unless there are no living first- or second-degree relatives. Most HCM is caused by an autosomal dominant mutation in genes that encode sarcomere proteins or sarcomere-associated proteins. Presence of a pathogenic sarcomere protein gene mutation in patients with HCM identifies risk of LV dysfunction and adverse outcome irrespective of the myofilament involved.<sup>S7.4-13-S7.4-15,S7.4-18,S7.4-19,S7.4-22</sup> A single mutation in 1 of the 2 alleles (or copies) of a gene is sufficient to cause HCM; however, 5% of patients with HCM have  $\geq 2$  mutations in the same gene or different genes, which can be a marker for worse outcomes.<sup>S7.4-13,S7.4-34,S7.4-48</sup> When genetic testing reveals a mutation in the index patient, ascertainment of genetic status in first- and second-degree relatives can be predictive of risk for developing HCM.<sup>S7.4-14,S7.4-49</sup> Relatives with overt HCM will have the same pathogenic HCM mutation as the index patient.
6. Several studies have described an independent relationship between hypertrophy and SCD when the magnitude of hypertrophy is  $\geq 30$  mm.<sup>S7.4-2,S7.4-3,S7.4-23,S7.4-24</sup> Risk does not abruptly increase for patients with a  $\geq 30$  mm wall thickness, but it rather increases in a linear manner<sup>S7.4-24</sup> and appears to carry more prognostic significance in younger patients. A young adult with hypertrophy that approaches 30 mm may have similar or greater SCD risk than an older patient with maximum wall thickness  $\geq 30$  mm.<sup>S7.4-23,S7.4-50</sup>

Patients with HCM are at an increased risk for SCD if they have a first-degree relative who experienced SCD presumably caused by HCM. Family history appears to be an independent predictor of SCD although the supportive studies are small and observational.<sup>S7.4-25,S7.4-26</sup> Syncope can be neurally mediated or medication-related as well as due to VA and requires a careful evaluation before considering it a risk factor for SCD.<sup>S7.4-8,S7.4-26</sup> In an analysis, syncope that was unexplained or thought not to be neurally mediated was associated with SCD risk only when it occurred within the past 6 months but not if the most episode occurred  $>5$  years previously.<sup>S7.4-8</sup>
7. Although sustained VT is clearly associated with SCD, the data for NSVT are less robust. Most studies do not support NSVT as an independent risk factor for SCD in patients with HCM,<sup>S7.4-2,S7.4-26,S7.4-27</sup> but the risk increases if risk modifiers are present, especially in patients  $<30$  years of age.<sup>S7.4-27</sup> Up to one third of patients with

HCM have an abnormal blood pressure response during exercise testing (defined variably as either a 20 mm Hg decrease in blood pressure or a failure to increase systolic blood pressure by at least 20 mm Hg during effort).<sup>S7.4-28,S7.4-29</sup> This finding has been postulated to be a risk factor for SCD; however, it is unclear how this relates to the increase in dynamic LV outflow tract obstruction that occurs with exertion, a hemodynamic condition that is readily modifiable with medication or mechanical procedures. The significance of an abnormal blood pressure response with exercise predicting SCD risk increases in the presence of risk modifiers (Table 8).

8. Most studies have found that NSVT alone has a low positive predictive value for SCD<sup>S7.4-2,S7.4-26,S7.4-27</sup>; therefore, use of an ICD is more appropriate if risk modifiers are also present. An abnormal blood pressure response to exercise has also been associated with the risk of sudden death,<sup>S7.4-5,S7.4-28,S7.4-29</sup> but it is unclear how this relates to the increase in dynamic LV outflow tract obstruction that occurs with effort, which is often treatable. The significance of an abnormal blood pressure response with exercise for predicting SCD risk increases when risk modifiers are present (Table 8).
9. The ICD is recommended for the prevention of SCD in patients with HCM who have survived sustained VT or VF as antiarrhythmic medications have limited effectiveness.<sup>S7.4-31</sup> Amiodarone has been associated with improved survival in observational studies and is an option for patients for whom an ICD is not feasible due to limited expectation for survival or patient preference.<sup>S7.4-30,S7.4-31</sup>
10. Approximately one third of consecutive patients with HCM undergoing an electrophysiological study have polymorphic VT or VF induced by programmed ventricular stimulation, but the results of programmed stimulation do not predict SCD risk. Programmed ventricular stimulation in patients with HCM has low predictive value and a nontrivial risk of complications.<sup>S7.4-32,S7.4-33,S7.4-51</sup> Electrophysiological studies can help to clarify the diagnosis of wide complex tachycardia or guide therapy for supraventricular tachycardia or bundle branch reentry.
11. SCD may cluster in certain families with HCM, and the possibility that specific sarcomere mutations may confer SCD risk has been hypothesized. However, subsequent studies of selected patients with HCM<sup>S7.4-34,S7.4-35</sup> were unable to establish a clinically useful relation between genotype and SCD risk. In some cases, the rate of adverse events (and prevalence of associated SCD risk factors) was lower in patients with mutations initially felt to be malignant than it was in those with mutations believed to be

benign.<sup>57.4-34,57.4-35</sup> Data from series of unselected consecutive outpatients suggest that most mutations are novel and limited to particular families.<sup>57.4-34,57.4-35</sup> Therefore, routine mutation screening would appear to be of little prognostic value in HCM.<sup>57.4-52</sup> The short-term risk of sudden death in patients who are genotype positive but have no other manifestations of the disease appears to be low.<sup>57.4-53</sup> Therefore, an ICD is not indicated in these individuals.

## 7.5. Myocarditis

Recommendations for Myocarditis		
References that support the recommendations are summarized in Online Data Supplement 32.		
COR	LOE	Recommendations
I	C-LD	1. In patients with life-threatening VT or VF associated with confirmed or clinically suspected myocarditis, referral to centers with mechanical hemodynamic support and advanced arrhythmia management is recommended. <sup>57.5-1</sup>
IIb	C-LD	2. In patients with giant cell myocarditis with VF or hemodynamically unstable VT treated according to GDMT, an ICD and/or an antiarrhythmic medication may be considered if meaningful survival of greater than 1 year is expected. <sup>57.5-2-57.5-4</sup>

## Recommendation-Specific Supportive Text

1. Myocarditis is an inflammatory process often related to infection.<sup>57.5-1,57.5-5-57.5-9</sup> When patients are treated in centers with the availability of mechanical hemodynamic support procedures, cardiac catheterization, endomyocardial biopsy, advanced cardiac imaging procedures, and arrhythmia management including ICD implantation, outcomes appear improved.<sup>57.5-1</sup> The acute course of myocarditis varies ranging from an asymptomatic finding of transient ST-T changes noted on ECG to cardiogenic shock and recurrent VA.<sup>57.5-10-57.5-12</sup> Acute management is largely supportive and can rapidly advance to requiring mechanical support.<sup>57.5-13,57.5-14</sup> Cardiac arrhythmias range from conduction abnormalities to life-threatening VT and VF.<sup>57.5-15-57.5-17</sup> Arrhythmias may require antiarrhythmic medications and/or device therapy.<sup>57.5-18</sup> Giant cell myocarditis is fairly uncommon, but it is of particular importance because it typically affects young individuals and is usually fatal if untreated.<sup>57.5-2-57.5-4,57.5-19</sup> VT may require antiarrhythmic medications such as amiodarone and/or an ICD that in some instances can be used as a bridge to more advanced HF therapies

such as LVAD or transplant. Myocarditis and SCD have been reported with HIV infection.<sup>57.5-20,57.5-21</sup> Systemic lupus erythematosus can cause myocarditis but only rarely VT or VF.<sup>57.5-8,57.5-22</sup> In patients with Chagas disease, acute myocarditis is rare but more than one third of affected patients develop late myocardial damage with progressive HF. Conduction defects with progression to complete heart block and VT or VF are common. Amiodarone appears to be effective in treating VA.<sup>57.5-23</sup> An ICD is frequently used in the late phase of myocarditis,<sup>57.5-24</sup> and radiofrequency catheter ablation has been successfully used to control recurrent VA in some patients.<sup>57.5-25</sup>

2. Giant cell myocarditis is fairly uncommon, but it is of particular importance as it typically affects young individuals and is usually fatal if untreated. The diagnosis is confirmed by endomyocardial biopsy. Patients may develop heart block, requiring a temporary or a permanent pacemakers. An ICD and antiarrhythmic medications, such as amiodarone are often used in the acute phase to treat VT or VF and reduce the risk of SCD.<sup>57.5-2-57.5-4,57.5-19,57.5-26-57.5-28</sup>

## 7.6. Cardiac Sarcoidosis

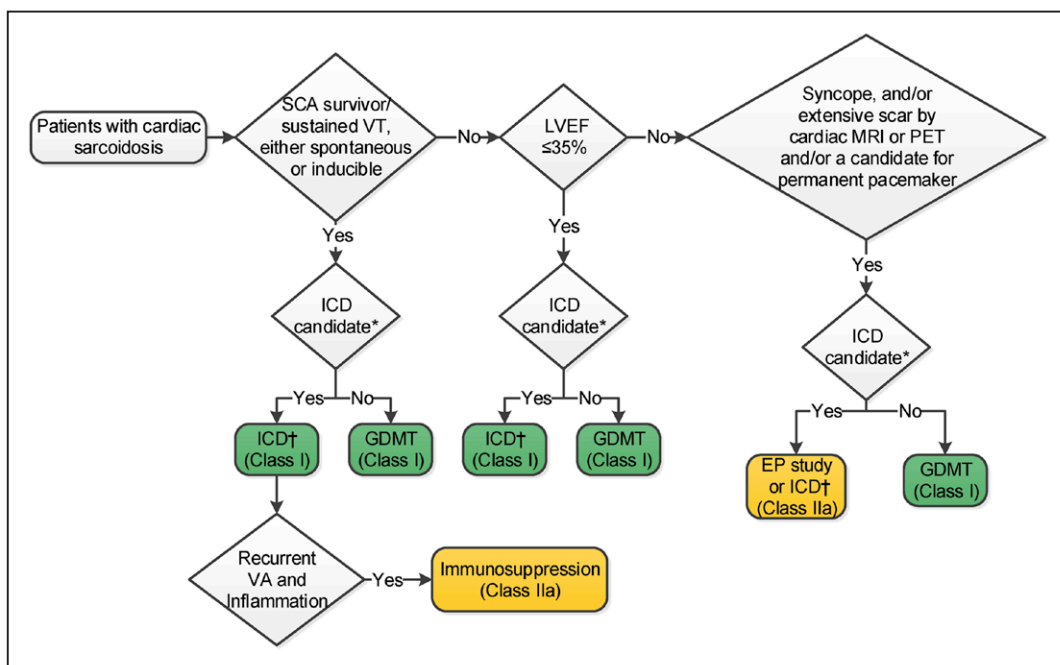
Recommendations for Cardiac Sarcoidosis		
References that support the recommendations are summarized in Online Data Supplement 33.		
COR	LOE	Recommendations
I	B-NR	1. In patients with cardiac sarcoidosis who have sustained VT or are survivors of SCA or have an LVEF of 35% or less, an ICD is recommended, if meaningful survival of greater than 1 year is expected. <sup>57.6-1-57.6-5</sup>
IIa	B-NR	2. In patients with cardiac sarcoidosis and LVEF greater than 35% who have syncope and/or evidence of myocardial scar by cardiac MRI or positron emission tomographic (PET) scan, and/or have an indication for permanent pacing, implantation of an ICD is reasonable, provided that meaningful survival of greater than 1 year is expected. <sup>57.6-6-57.6-10</sup>
IIa	C-LD	3. In patients with cardiac sarcoidosis and LVEF greater than 35%, it is reasonable to perform an electrophysiological study and to implant an ICD, if sustained VA is inducible, provided that meaningful survival of greater than 1 year is expected. <sup>57.6-11,57.6-12</sup>
IIa	C-LD	4. In patients with cardiac sarcoidosis who have an indication for permanent pacing, implantation of an ICD can be beneficial. <sup>57.6-13</sup>
IIa	C-LD	5. In patients with cardiac sarcoidosis with frequent symptomatic VA and evidence of myocardial inflammation, immunosuppression in combination with antiarrhythmic medication therapy can be useful to reduce VA burden. <sup>57.6-14-57.6-16</sup>

### Recommendation-Specific Supportive Text

1. Sarcoidosis is a systemic granulomatous disease of unknown cause. Pulmonary involvement is most frequent but any organ can be affected. Cardiac involvement, diagnosed by cardiac MRI or positron emission tomography (PET), has been reported in up to 55% of patients with extra-cardiac disease, while isolated cardiac sarcoidosis was seen in most patients diagnosed with cardiac sarcoidosis in 1 report.<sup>57,6-17</sup> Cardiac manifestations include conduction abnormalities, VA, and depressed ventricular function with or without HF, and these contribute greatly to a higher mortality in cardiac sarcoidosis compared with sarcoidosis without cardiac involvement.<sup>57,6-2</sup> In a 25-year study of 110 patients with cardiac sarcoidosis in Finland with HF at presentation, marked LV dysfunction at diagnosis (LVEF <35%), and isolated cardiac sarcoidosis predicted an adverse outcome.<sup>57,6-1</sup> VA can also occur in patients with relatively normal LV function, some of whom have RV involvement that can mimic arrhythmogenic right ventricular cardiomyopathy. Several reports of patients with cardiac sarcoidosis and ICDs implanted for either primary or secondary prevention of SCD show a high frequency of appropriate ICD therapies,<sup>57,6-3-57,6-5</sup> supporting

use of ICDs for primary and secondary prevention of SCD according to the indications applied for other cardiomyopathies. The frequency of conduction abnormalities often warrants a device that provides bradycardia pacing as well.

2. Patients with cardiac sarcoidosis can experience VA and SCD, even if the LVEF is normal, and approaches to identification of patients at risk of SCD despite preserved LV function are not well defined. A number of studies have evaluated the role of cardiac MRI for predicting VA and SCD. A meta-analysis,<sup>57,6-6</sup> which included 760 patients in 10 studies, found that late gadolinium enhancement was associated with increased all-cause mortality and more VA compared with those without late gadolinium enhancement. Applicability is limited by the lack of precise quantification of late gadolinium enhancement burden that may allow for more nuanced risk stratification. Some studies suggested that a threshold effect exists, with extensive LV and RV involvement being a particularly high-risk feature.<sup>57,6-7,57,6-8</sup> However, late gadolinium enhancement can be present even if the LVEF is >50% and was associated with a risk of death or VT of 4.9% per year compared to 0.24% per year when late gadolinium enhancement was absent in 1 observational study.<sup>57,6-7</sup> PET for assessing inflammation and scar is also being increasingly used, but data are limited. In 1 report, the



**Figure 8.** prevention of SCD in patients with cardiac sarcoidosis.

Colors correspond to Class of Recommendation in Table 1. See Section 7.6 for discussion. \*ICD candidacy as determined by functional status, life expectancy, or patient preference. †For recurrent sustained monomorphic VT, refer to Figure 2. CEP indicates electrophysiological; GDMT, guideline-directed management and therapy; ICD, implantable cardioverter-defibrillator; LVEF, left ventricular ejection fraction; MRI, magnetic resonance imaging; PET, positron emission tomography; SCA, sudden cardiac arrest; SCD, sudden cardiac death; VA, ventricular arrhythmia; and VT, ventricular tachycardia.



presence of inflammation and RV involvement on PET scanning was associated with increased risk of death or e.g. of relatives.<sup>57.6-10</sup> Electrophysiological studies in a series of 76 patients with evidence of cardiac sarcoid found that 11% had inducible VT. During a median follow-up of 5 years, 75% of patients with inducible VT had spontaneous VT or death compared with 1.5% of those who did not have inducible VT.<sup>57.6-18</sup>

3. Electrophysiological study has been proposed as a potential tool for risk stratification of VA and SCD in patients who had demonstrable evidence of cardiac sarcoidosis based on imaging studies or biopsy, but do not have documented arrhythmias or arrhythmic symptoms nor meet standard primary prevention criteria for ICD implantation.

One study evaluated 76 patients with documented cardiac sarcoidosis by PET or cardiac MRI who underwent electrophysiological study.<sup>57.6-12</sup> Eight (11%) were inducible for sustained VAs and received an ICD, while the rest did not receive an ICD because they were not inducible. LVEF was lower in patients with inducible VA (36.4 + 4.2% versus 55.8 + 1.5%). Over a median follow-up of 5 years, 6 of 8 patients in the group with inducible VA had VA or died, compared with 1 death in the negative group.<sup>57.6-12</sup> An important caveat is that it remains unclear if electrophysiological study is more predictive than LVEF alone, because inducibility appears to reversely correlate with LVEF. Furthermore, in this study the average LVEF of the inducible patients declined further during the followup period.<sup>57.6-12</sup>

4. In addition to VA and LV dysfunction, conduction abnormalities, including heart block, can also be a common manifestation of cardiac sarcoidosis. Patients with documented VA and LV dysfunction are at increased risk of cardiac events including cardiac death. One study compared outcomes in 22 patients with high-degree atrioventricular block as the initial manifestation of cardiac sarcoidosis, to 31 patients who initially presented with VT and/or HF. After a median follow up of 34 months, the patients who presented with heart block had fewer HF hospitalization, yet fatal cardiac events, including sustained VAs, were similar to those with VT and/or HF, suggesting that the risk of fatal cardiac events is high regardless of the initial clinical presentation.<sup>57.6-13</sup> In the same study, administration of steroids led to some clinical improvement, with some patients recovering conduction, yet steroid effectiveness was not universal and did not seem to be protective against adverse cardiac events.<sup>57.6-13</sup>
5. Several studies have attempted to evaluate the role of immunosuppression for reducing VA in patients with cardiac sarcoidosis, but results

have been inconsistent.<sup>57.6-14-57.6-16</sup> Furthermore, a worsening of VA has been reported with immunosuppressive therapy (usually glucocorticoids) in a number of patients, including electrical storm developing in some within 12 months of initiating therapy.<sup>57.6-15</sup> One study reported a decrease of arrhythmia burden with steroid therapy but only when given in the early stages of the disease; those with advanced LV dysfunction did not experience benefit.<sup>57.6-16</sup> A systematic combined treatment approach was successful in 63% of patient in a series in which medical therapy included both steroids and antiarrhythmic medications, followed by radiofrequency catheter ablation if needed.<sup>57.6-14</sup> Immunosuppressive therapy may serve a dual purpose beyond arrhythmia effects as it may help stabilize disease progression and prevent further deterioration of LV function, although this has yet to be demonstrated in RCTs. Steroids do not appear to reverse advanced ventricular dysfunction once present, which supports the importance of early diagnosis and intervention.<sup>57.6-1</sup> PET scanning for assessing inflammation and scar is being increasingly used in sarcoidosis as well, but data supporting its use for guiding therapy of arrhythmias are limited.

### 7.6.1. Other Infiltrative Cardiomyopathies

Infiltrative cardiomyopathies are a heterogeneous group of uncommon systemic diseases with associated cardiac involvement. In some infiltrative cardiomyopathies, such as Fabry's disease, VAs are uncommon. Some, such as hemochromatosis, are highly treatable especially when diagnosed early. In all cases, treatment of the underlying condition must accompany management of cardiac arrhythmias. Most studies of infiltrative cardiomyopathies and arrhythmias are small and observational<sup>57.6.1-1</sup> but, in general, unless contraindications are present, VAs should be treated as in any other cardiomyopathy. See Section 7.6 for sarcoidosis. Until recently, cardiac amyloidosis was associated with a very poor prognosis with patients ultimately succumbing to progressive HF.<sup>57.6.1-2</sup> This perception is changing with advances in medical therapy for light-chain amyloidosis, which have led to improved outcomes.<sup>57.6.1-3</sup> Yet, decisions must be individualized because data remain too limited to allow formal recommendations as published reports on ICD effectiveness in amyloidosis are small, observational and with limited follow up.<sup>57.6.1-4</sup> Whether there is greater benefit to ICD placement in light chain amyloidosis versus transthyretin-related amyloidosis remains uncertain, because most studies included mainly patients with amyloid light-chain amyloidosis for which the rate of VA may be greater and prog-

nosis is generally worse. Whether ICDs are effective for primary prevention of SCD is uncertain, but many deaths in patients with cardiac amyloidosis do not appear to be preventable by an ICD.<sup>57.6.1-2</sup>

## 7.7. Heart Failure

### 7.7.1. HF With Reduced Ejection Fraction

Recommendation for HFrEF		
References that support the recommendation are summarized in Online Data Supplement 35.		
COR	LOE	Recommendation
Ia	B-NR	1. In patients with HFrEF who are awaiting heart transplant and who otherwise would not qualify for an ICD (eg, NYHA class IV and/or use of inotropes) with a plan to discharge home, an ICD is reasonable. <sup>57.7.1-1-57.7.1-5</sup>

### Synopsis

Patients with HFrEF are at an increased risk for VA and SCD. The risk is increased irrespective of HFrEF etiology.<sup>57.7.1-6</sup> SCD makes up a greater proportion of deaths in patients with milder HF symptoms and lesser proportion in those with moderate/severe HF symptoms.<sup>57.7.1-7</sup> The reported incidence of SCD varies depending on the definition used and the population studied. Although many deaths, classified as sudden, are indeed due to lethal VA, others may be due to bradyarrhythmias, pulseless electrical activity, and sudden hemodynamic deterioration.<sup>57.7.1-7-57.7.1-9</sup>

Medical therapy with neurohormonal agents decreases the risk of SCD by reducing both the incidence of VA and disease progression.<sup>57.7.1-7,57.7.1-10-57.7.1-12</sup> Despite GDMT for HFrEF, some patients remain at risk for SCD, and an ICD may be helpful. See Sections 7.1 and 7.2 for the indications on ICDs in patients with reduced LVEF. CRT, in appropriate patients, has also been shown to reduce the incidence of SCD.<sup>57.7.1-13</sup>

The pathophysiology of SCD in HF is complex, resulting from interactions between both functional and structural changes that occur in patients with HFrEF that result in increased susceptibility to SCD.<sup>57.7.1-14</sup> Although many of the risk factors are shared among HFrEF patients, the reason that SCD strikes a particular individual is usually unknown; however, some individuals may have a genetic susceptibility.<sup>57.7.1-15</sup> Varying degrees of myocardial fibrosis, neurohormonal activation, and increased wall stress alter the electrophysiological properties with changes in cell coupling, ionic currents (electrical remodeling), and calcium handling that likely contribute to the development of lethal VA.<sup>57.7.1-16</sup> Contributing factors extrinsic to the heart include electrolyte abnormalities related to volume shifts and diuretic use, sympathetic activation, hemodynamic stress, and hypoxia.

### Recommendation-Specific Supportive Text

1. Many patients with advanced HF listed for heart transplant would not otherwise qualify for ICD given the severity of illness including NYHA class IV status and/or use of inotropic infusion. Although no randomized data on ICD use in this population exist, data from observational and large registry studies of patients awaiting heart transplant suggest improved survival in patients with an ICD.<sup>57.7.1-1,57.7.1-4,57.7.1-5</sup> One alternative to ICD in this population is the wearable cardioverter-defibrillator.<sup>57.7.1-2,57.7.1-3</sup> The recommendation in this section is relevant to those patients without an ICD where there is a plan to discharge the patient to home to await cardiac transplant and not, for example, to those patients who remain hospitalized with no intention to discharge home until transplant occurs. For those patients with an LVAD, the decision to place an ICD is generally independent of whether they are awaiting heart transplant but rather the indication in those patients is generally based on the need to treat VA.<sup>57.7.1-17</sup>

### 7.7.2. HF With Preserved Ejection Fraction

Nearly half of the patients with HF have a preserved LVEF.<sup>57.7.2-1</sup> These patients tend to be older and have more comorbidities than patients with HFrEF. However, although the rate of SCD is lower in patients with HF with preserved ejection fraction (HFpEF) than in patients with HFrEF,<sup>57.7.2-2</sup> nearly a quarter of all deaths among patients with HFpEF are sudden.<sup>57.7.2-3-57.7.2-5</sup> The challenge in preventing SCD in patients with HFpEF is identifying which patients are at a high enough risk to benefit from preventive therapies. Studies exploring noninvasive risk factors for SCD in patients with HFpEF do not identify consistent factors with the exception of ischemic heart disease.<sup>57.7.2-2,57.7.2-6</sup> Consequently, there is no accepted noninvasive test to identify high-risk patients with HFpEF. Invasive risk stratification with an electrophysiological study shows promise in this population.<sup>57.7.2-7,57.7.2-8</sup> This topic is currently being studied in the PRESERVE-EF (Risk Stratification in Patients With Preserved Ejection Fraction) trial (NCT02124018).

Whether to include a recommendation related to an electrophysiological study in patients with HFpEF and ischemic heart disease was carefully considered by the writing committee. However, evidence was deemed insufficient to support a formal recommendation. Still, the pros and cons of an electrophysiological study can reasonably be considered in select patients with HFpEF and ischemic heart disease who are experiencing symptoms suggestive of a VA.

### 7.7.3. Left Ventricular Assist Device

Recommendation for Patients With an LVAD		
References that support the recommendation are summarized in Online Data Supplement 36.		
COR	LOE	Recommendation
Ia	C-LD	1. In patients with an LVAD and sustained VA, an ICD can be beneficial. <sup>57.7.3-1</sup>

#### Recommendation-Specific Supportive Text

1. Patients with an LVAD have a high risk of VA, particularly those with a history of arrhythmias.<sup>57.7.3-2-57.7.3-4</sup> The increased risk of VA may be due to myocardial irritation from insertion of the LVAD inflow cannula, LV compression due to a suctioning effect from the LVAD, inotropic support frequently needed by some patients, and repolarization changes that can occur after LVAD placement. Although VT/VF is tolerated by some patients with an LVAD, others experience a decrease in flow as the RV is unsupported; syncope and hypoperfusion can result. Having an ICD can allow for prompt termination of VA before significant hemodynamic consequences occur. Data on ICDs in patients with an LVAD are from observational series. A systematic review of 6 observational studies observed that within 7 months, 26% of patients with an LVAD had died.<sup>57.7.3-1</sup> The death rate was lower among patients who previously had an ICD (16% versus 32%), suggesting a 39% relative-risk reduction in all-cause mortality in an adjusted analysis.<sup>57.7.3-1</sup> Patients with a history of pre-LVAD VA have nearly a  $\geq 10$ -fold risk of post-LVAD VA.<sup>57.7.3-2-57.7.3-4</sup> In many of the initial studies demonstrating ICD benefit, older pulsatile LVAD devices were in use.<sup>57.7.3-2,57.7.3-5</sup> Studies of ICD use with the newer, continuous flow LVADs have inconsistently shown benefit.<sup>57.7.3-1,57.7.3-4,57.7.3-6,57.7.3-7</sup> Of note, approximately 2 of 10 patients with an LVAD develop an LVAD related infection in the first year.<sup>57.7.3-8,57.7.3-9</sup>

### 7.7.4. ICD Use After Heart Transplantation

Recommendation for ICD Use After Heart Transplantation		
References that support the recommendation are summarized in Online Data Supplement 37.		
COR	LOE	Recommendation
IIB	B-NR	1. In patients with a heart transplant and severe allograft vasculopathy with LV dysfunction, an ICD may be reasonable if meaningful survival of greater than 1 year is expected. <sup>57.7.4-1-57.7.4-3</sup>

#### Recommendation-Specific Supportive Text

1. Development of disease in the transplanted heart places some patients at an increased risk

of SCD that has ranged from 10% to 35% in observational studies.<sup>57.7.4-4,57.7.4-5</sup> Both rejection and a decreased LVEF are predictors of SCD. The mechanisms underlying SCD in patients with a heart transplant include damage to the conduction system itself and VA due to coronary vasculopathy or during episodes of acute rejection. Several small case series observing appropriate ICD termination of VA suggest that an ICD can be beneficial in selected patients, particularly those with severe allograft vasculopathy, unexplained syncope, a history of SCA, and severe LV dysfunction.<sup>57.7.4-1-57.7.4-3</sup> Additionally, a patient with severe allograft vasculopathy who is being considered for retransplant may be appropriate for an ICD as a bridging device. Secondary prevention indications for an ICD in patients with a heart transplant are identical to those in other patients.

### 7.8. Neuromuscular Disorders

Recommendations for Neuromuscular Disorders		
References that support the recommendations are summarized in Online Data Supplement 38.		
COR	LOE	Recommendations
I	B-NR	1. In patients with neuromuscular disorders, primary and secondary prevention ICDs are recommended for the same indications as for patients with NICM if meaningful survival of greater than 1 year is expected. <sup>57.8-1,57.8-2</sup>
Ia	B-NR	2. In patients with Emery-Dreifuss and limb-girdle type IB muscular dystrophies with progressive cardiac involvement, an ICD is reasonable if meaningful survival of greater than 1 year is expected. <sup>57.8-3-57.8-8</sup>
Ia	B-NR	3. In patients with muscular dystrophy, follow-up for development of cardiac involvement is reasonable, even if the patient is asymptomatic at presentation. <sup>57.8-9-57.8-12</sup>
IIB	B-NR	4. In patients with myotonic dystrophy type 1 with an indication for a permanent pacemaker, an ICD may be considered to minimize the risk of SCA from VT if meaningful survival of greater than 1 year is expected. <sup>57.8-9,57.8-13,57.8-14</sup>

#### Synopsis

The muscular dystrophies are a group of inherited diseases affecting skeletal and cardiac muscle. Some present primarily as a NICM (eg, Duchenne, Becker, and limb-girdle types 2C, 2F, and 2I), while others present primarily as conduction system degeneration with a variable association with cardiomyopathy (eg, myotonic dystrophy types 1 and 2, Emery-Dreifuss, limb-girdle type 1B; summarized in Table 9).<sup>57.8-15</sup> Because SCD can occur either due to VA or due to bradyarrhythmias from rapid and unpredictable progression of conduction system disease, the clinician is faced with the challenge of identifying those patients who would benefit from prophylactic pacemak-

er or ICD implantation. There should be a high level of concern for those patients with muscular dystrophy who present with arrhythmia symptoms.<sup>57,8-15</sup> The current guideline focuses on VA and indications for implantation of an ICD. The indications for permanent pacemaker are discussed in another ACC/AHA/HRS guideline.<sup>57,8-16</sup>

### Recommendation-Specific Supportive Text

1. In general, the indications for an ICD in patients with muscular dystrophy should follow standard ICD recommendations for patients with NICM (see Section 7.2.1 on Secondary Prevention and Section 7.2.2 on Primary Prevention of SCD with NICM). A high index of suspicion for bundle-branch reentrant tachycardia is warranted in patients with myotonic dystrophy who exhibit wide QRS complex tachycardia or tachycardia-related symptoms.<sup>57,8-2</sup>
2. In patients with Emery-Dreifuss and limb-girdle type 1B muscular dystrophies associated with *Lamin A/C* mutations, SCD accounts for about one third of all deaths.<sup>57,8-4</sup> Observational studies show a significant rate of appropriate ICD therapy in patients with cardiac conduction disorders who are gene positive for *Lamin A/C* mutation even if LV function is preserved.<sup>57,8-3,57,8-5,57,8-17</sup> In an observational study in which 38% had isolated skeletal muscular involvement but included patients with conduction defects and other risk factors (including PR interval >240 ms, left bundle-branch block,

NSVT, or bradycardia requiring a permanent pacemaker) life-threatening VAs were relatively common; with 52% of patients receiving appropriate ICD therapy including approximately 40% of those patients with an LVEF  $\geq$ 45%.<sup>57,8-3</sup> A study of patients who had *Lamin A/C* mutation, in which approximately 21% had a skeletal muscular dystrophy phenotype, SCD and appropriate ICD therapy were associated with NSVT, LVEF <45%, male sex, and *Lamin A/C* nonmissense mutations.<sup>57,8-4</sup> These observational studies support the use of an ICD when a pacing indication is present and likely also when evidence of progressive cardiac involvement such as cardiac conduction defects, NSVT or reduced LVEF is present.<sup>57,8-8</sup>

There is a paucity of data regarding the rare form of x-linked recessive Emery-Dreifuss muscular dystrophy (related to the *Emerin* gene mutation), but arrhythmias may be less frequent than for the *Lamin A/C* mutations.<sup>57,8-15</sup>

3. Cardiac involvement can occur in a number of neuromuscular dystrophies (Table 9). To determine cardiac involvement, a 12-lead ECG and echocardiogram are important for the initial clinical assessment, independent of symptom status. In general, the more extensive the cardiac involvement, including evidence of distal conduction disease, ventricular dysfunction, and atrial arrhythmias, the more likely a VA will occur. The initial evaluation for myotonic dystrophy patients includes ambulatory monitoring. In asymptomatic patients, some experts advocate for annual follow-up during the concealed phase of the disease with an annual

**Table 9. Neuromuscular Disorders Associated With Heart Disease**

Muscular Dystrophy	Inheritance	Gene/Protein Affected	Primary Cardiac Pathology	Frequency of Cardiac Involvement	Causes of Death	Associated With Sudden Death?
Duchenne	X-linked recessive	Dystrophin	NICM	>90%	Respiratory, HF	Yes, uncertain etiology
Becker	X-linked recessive	Dystrophin	NICM	60%–75%	HF, respiratory	Yes, uncertain etiology
Limb-girdle type 1B	Autosomal dominant	<i>Lamin A/C</i>	Conduction system disease and NICM	>90%	Sudden, HF	Yes
Limb-girdle type 2C-2F	Autosomal recessive	Sarcoglycan	NICM	<25%	Respiratory, HF	Uncertain
Limb-girdle type 2I	Autosomal recessive	Fukutin-related protein	NICM	20%–80%	Respiratory, HF	Uncertain
Myotonic type 1	Autosomal dominant	CTG repeat expansion	Conduction system disease and NICM	60%–80%	Respiratory, sudden, HF	30% of deaths, uncertain bradycardia versus tachycardia
Myotonic type 2	Autosomal dominant	CCTG repeat expansion	Conduction system disease	10%–25%	Normal causes	Reported
Emery-Dreifuss	X-linked and autosomal dominant or recessive	<i>Emerin</i> , <i>Lamin A/C</i>	Conduction system disease and NICM	>90%	Sudden, HF	Yes
Facioscapulohumeral	Autosomal dominant	D4Z4 repeat contraction	Possibly conduction disease	5%–15%	Normal causes, respiratory rarely	Not reported

HF indicates heart failure; and NICM, nonischemic cardiomyopathy. Adapted with permission from Groh, et al.<sup>57,8-15</sup>

12-lead ECG to screen for development of conduction abnormalities. However, the optimal frequency of electrocardiographic screening is unknown.<sup>57,8-18</sup> Once cardiac involvement is present, either on the basis of conduction delay, atrial arrhythmias, or ventricular dysfunction, a low threshold for investigating symptoms or electrocardiographic findings by the clinician to determine the need for pacemaker implantation, invasive electrophysiological studies, or ICD implantation is optimal.

- Up to one third of deaths in myotonic dystrophy patients are sudden.<sup>57,8-9</sup> Although commonly attributed to conduction block and asystole, SCD due to VT/VF has been recognized in patients with functioning permanent pacemakers, and spontaneous VA have been documented in some.<sup>57,8-13,57,8-19</sup> The risk of SCD in patients with pacemakers suggests that an ICD may be preferred to a pacemaker. However, these patients are also at high risk of respiratory failure as a competing cause of death. Therefore, in patients with severe skeletal muscle involvement, a pacemaker or ICD may not improve outcomes.<sup>57,8-15</sup> A shared decision-making approach to selecting ICD or pacing therapy is warranted. Compared with myotonic type 1 patients, myotonic dystrophy type 2 patients are not well studied but may also benefit from the same approach.

## 7.9. Cardiac Channelopathies

Recommendations for Cardiac Channelopathies		
References that support the recommendations are summarized in Online Data Supplement 39.		
COR	LOE	Recommendations
I	B-NR	1. In first-degree relatives of patients who have a causative mutation for long QT syndrome, catecholaminergic polymorphic ventricular tachycardia, short QT syndrome, or Brugada syndrome, genetic counseling and mutation-specific genetic testing are recommended. <sup>57,9-1-57,9-6</sup>
I	B-NR	2. In patients with a cardiac channelopathy and SCA, an ICD is recommended if meaningful survival of greater than 1 year is expected. <sup>57,9-7-57,9-13</sup>

### Synopsis

Implantation of an ICD in asymptomatic low-risk patients with a cardiac channelopathy for a positive family history of SCD as the sole indication is unsupported by published data.<sup>57,9-13-57,9-18</sup>

### Recommendation-Specific Supportive Text

- Clinical screening of first-degree relatives of patients with inherited arrhythmia syndromes

is crucial to identifying affected family members. Due to the increased risk of adverse cardiac events in genotype positive patients with long QT syndrome, catecholaminergic polymorphic ventricular tachycardia, and Brugada syndrome, targeted screening for the identified family-specific mutation can identify individuals who are at risk for these adverse outcomes.<sup>57,9-2-57,9-5</sup> Screening ECGs may be insufficient for diagnosis, because the resting ECG in patients with catecholaminergic polymorphic ventricular tachycardia is normal, and as many as 25% of genotype-positive patients with long QT syndrome have QTc intervals  $\leq 440$  ms.<sup>57,9-2</sup> Due to the increased risk of adverse cardiac events in young patients with long QT syndrome and catecholaminergic polymorphic ventricular tachycardia,<sup>57,9-2,57,9-19-57,9-22</sup> screening infants and young children is particularly important to guide therapy and institute preventive measures, including the avoidance of possible provocative medications ([www.crediblemeds.org](http://www.crediblemeds.org)).<sup>57,9-23</sup> However, because up to 15% of mutations previously associated with catecholaminergic polymorphic ventricular tachycardia do not appear to cause disease,<sup>57,9-24</sup> caution is advised to avoid unnecessary treatment or sports restriction in phenotype-negative catecholaminergic polymorphic ventricular tachycardia mutation positive individuals. Notably, some patients may prefer not to undergo genetic testing, so genetic counseling should focus on this issue.

- Patients with cardiac channelopathies (ie, long QT syndrome, catecholaminergic polymorphic ventricular tachycardia, Brugada syndrome, early repolarization syndrome, and short QT syndrome) and prior SCA have a significantly increased risk of subsequent SCA or SCD.<sup>57,9-7-57,9-13,57,9-25-57,9-28</sup> Implantation of an ICD reduces the risk of death in high-risk patients.<sup>57,9-9,57,9-29-57,9-31</sup> Appropriate ICD therapy for VF/fast VT is reported in 8% to 33% of channelopathy patients, while inappropriate shocks and device complications are reported in 8% to 35%.<sup>57,9-10,57,9-29,57,9-30,57,9-32-57,9-36</sup> To minimize inappropriate shocks, concurrent beta blockers in long QT syndrome and catecholaminergic polymorphic ventricular tachycardia patients, optimal device programming, and appropriate lead selection are necessary. Ventricular pacing without ICD implantation was associated with a significant risk of recurrent SCA or SCD in long QT syndrome patients.<sup>57,9-37-57,9-39</sup> In selected patients with LQT1 in whom the SCA occurred in the absence of beta-blocker treatment, beta-blocker therapy is offered as an alternative to ICD

implantation in patients who refuse to receive an ICD.<sup>S7.9-40</sup>

**7.9.1. Specific Cardiac Channelopathy Syndromes**  
**7.9.1.1. Congenital Long QT Syndrome**

Recommendations for Long QT Syndrome		
References that support the recommendations are summarized in Online Data Supplement 40.		
COR	LOE	Recommendations
I	B-NR	1. In patients with long QT syndrome with a resting QTc greater than 470 ms, a beta blocker is recommended. <sup>S7.9.1.1-57.9.1.1-5</sup>
I	B-NR	2. In high-risk patients with symptomatic long QT syndrome in whom a beta blocker is ineffective or not tolerated, intensification of therapy with additional medications (guided by consideration of the particular long QT syndrome type), left cardiac sympathetic denervation, and/or an ICD is recommended. <sup>S7.9.1.1-2,57.9.1.1-6-57.9.1.1-12</sup>
I	B-NR	3. In patients with long QT syndrome and recurrent appropriate ICD shocks despite maximum tolerated doses of a beta blocker, intensification of medical therapy with additional medications (guided by consideration of the particular long QT syndrome type) or left cardiac sympathetic denervation, is recommended. <sup>S7.9.1.1-6,57.9.1.1-7,57.9.1.1-10,57.9.1.1-13-57.9.1.1-16</sup>
I	B-NR	4. In patients with clinically diagnosed long QT syndrome, genetic counseling and genetic testing are recommended. <sup>S7.9.1.1-17-57.9.1.1-21</sup>
IIa	B-NR	5. In patients with suspected long QT syndrome, ambulatory electrocardiographic monitoring, recording the ECG lying and immediately on standing, and/or exercise treadmill testing can be useful for establishing a diagnosis and monitoring the response to therapy. <sup>S7.9.1.1-22-57.9.1.1-29</sup>
IIa	B-NR	6. In asymptomatic patients with long QT syndrome and a resting QTc less than 470 ms, chronic therapy with a beta blocker is reasonable. <sup>S7.9.1.1-3,57.9.1.1-30,57.9.1.1-31</sup>
IIb	B-NR	7. In asymptomatic patients with long QT syndrome and a resting QTc greater than 500 ms while receiving a beta blocker, intensification of therapy with medications (guided by consideration of the particular long QT syndrome type), left cardiac sympathetic denervation or an ICD may be considered. <sup>S7.9.1.1-2,57.9.1.1-8,57.9.1.1-11,57.9.1.1-30</sup>
III: Harm	B-NR	8. In patients with long QT syndrome, QT-prolonging medications are potentially harmful. <sup>S7.9.1.1-5,57.9.1.1-12,57.9.1.1-32-57.9.1.1-34</sup>

long QT syndrome type 3<sup>S7.9.1.1-3,57.9.1.1-35,57.9.1.1-36</sup> but, in selected patients, beta blockers can be protective against SCA.<sup>S7.9.1.1-36,57.9.1.1-37</sup> Several observational studies have reported effectiveness for risk reduction in long QT syndrome with propranolol, atenolol, and nadolol with appropriate dosing,<sup>S7.9.1.1-26,57.9.1.1-28,57.9.1.1-38-57.9.1.1-40</sup> while metoprolol appears less effective.<sup>S7.9.1.1-41</sup> RCTs to assess comparative efficacy of specific beta blockers are unavailable, although many centers favor the use of nadolol. For long QT syndrome type 1, 1 study reported atenolol reduced risk of VA while nadolol was not associated with risk reduction.<sup>S7.9.1.1-2</sup> For long QT syndrome type 2, nadolol was reported to show superior efficacy.<sup>S7.9.1.1-1,57.9.1.1-2</sup> Patients receiving a beta blocker should undergo ongoing monitoring to assess changes in QTc over time, and adequacy of beta blockade with exertion.<sup>S7.9.1.1-26,57.9.1.1-28</sup>

2. High-risk patients with long QT syndrome include those with QTc >500 ms, genotypes long QT syndrome type 2 and long QT syndrome type 3, females with genotype long QT syndrome type 2, <40 years of age, onset of symptoms at <10 years of age, and patients with prior cardiac arrest or recurrent syncope.<sup>S7.9.1.1-3,57.9.1.1-8,57.9.1.1-11,57.9.1.1-30,57.9.1.1-38</sup> Women with long QT syndrome type 2 are at a higher risk of postpartum cardiac arrest/SCD<sup>S7.9.1.1-42,57.9.1.1-43</sup> and should receive pre-pregnancy counseling. Patients with long QT syndrome and recurrent syncope while receiving a beta blocker have an increased risk of SCA or appropriate ICD shocks<sup>S7.9.1.1-9</sup> and escalation of therapy is warranted to prevent SCD. Earlier studies reported benefit of antibradycardia pacing,

**Table 10. Commonly Used QT-Prolonging Medications**<sup>S7.9.1.1-59,57.9.1.1-62</sup>

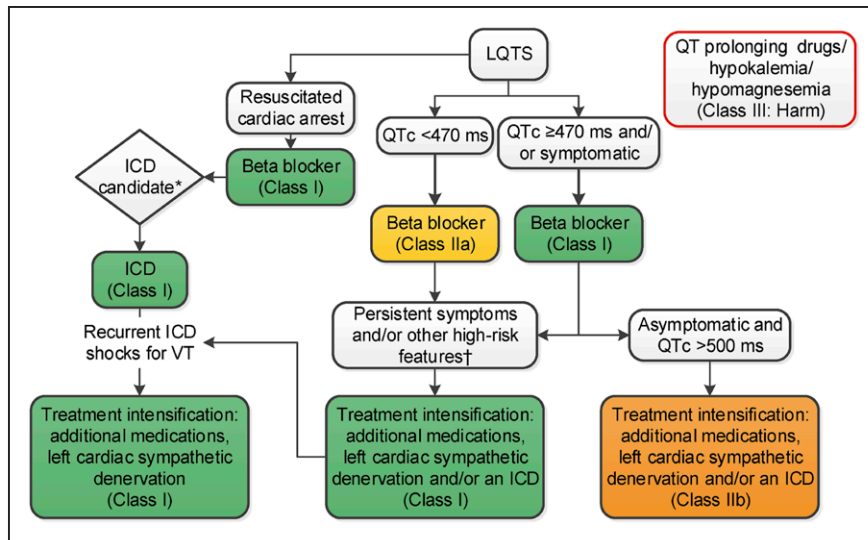
Examples of QT Prolonging Medications*			
Antiarrhythmic Medications	Psychotropic Medications	Antibiotics	Others
Disopyramide	Haloperidol	Erythromycin	Methadone
Procainamide (N-acetylprocainamide)	Phenothiazines	Pentamidine	Probucol
Quinidine	Citalopram	Azithromycin	Droperidol
Dofetilide	Tricyclic	Chloroquine	Ondansetron
Dronedarone	antidepressants	Ciprofloxacin	
Ibutilide		Fluconazole	
Sotalol		Levofloxacin	
Amiodarone†		Moxifloxacin Clarithromycin Itraconazole Ketoconazole	

\*A more complete list is maintained at: [www.crediblemeds.org](http://www.crediblemeds.org).<sup>S7.9.1.1-59</sup>  
 †Amiodarone rarely causes torsades de pointes.

**Recommendation-Specific Supportive Text**

- Beta blockers reduce adverse cardiac events for long QT syndrome type 1 (Figure 10) (>95%), long QT syndrome type 2 (Figure 11) (>75%), and females with long QT syndrome type 3 (Figure 12) by >60%.<sup>S7.9.1.1-1-57.9.1.1-5</sup> There are limited data regarding efficacy of beta blockers in males with

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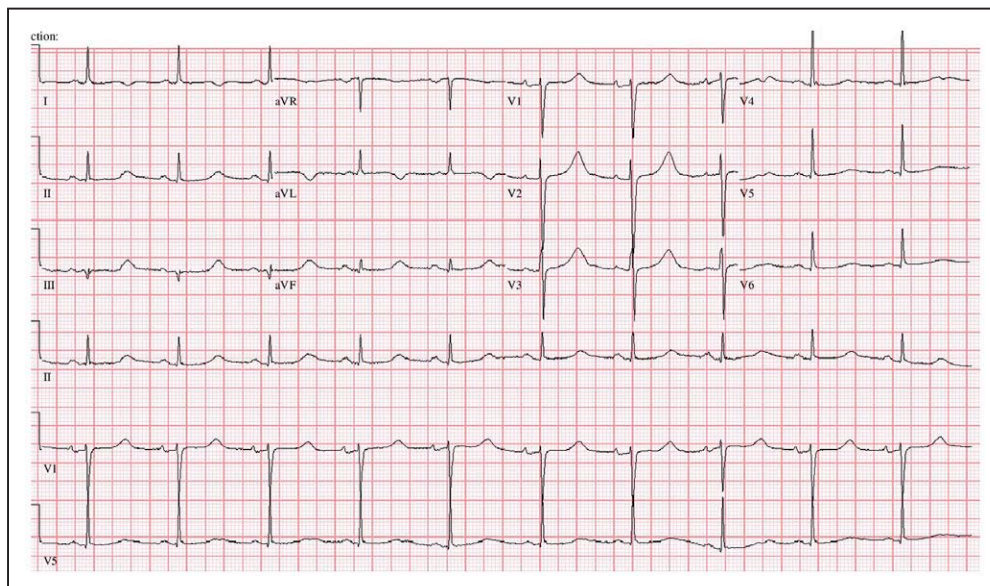


**Figure 9.** Prevention of SCD in patients with long QT syndrome.

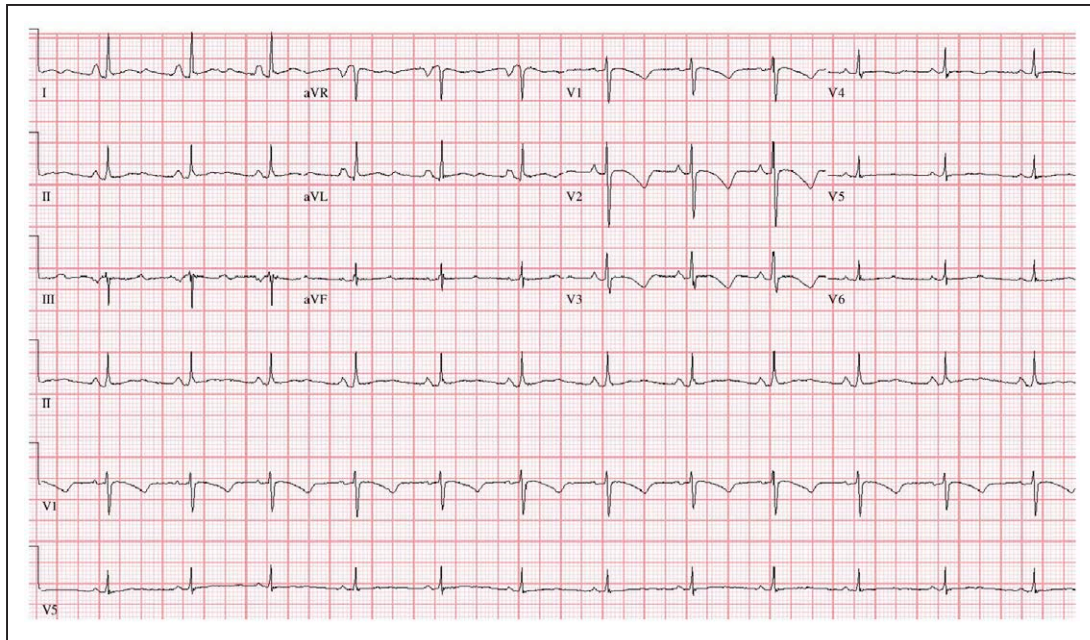
Colors correspond to Class of Recommendation in Table 1. See Section 7.9.1.1 for discussion. \*ICD candidacy as determined by functional status, life expectancy, or patient preference. †High-risk patients with LQTS include those with QTc >500 ms, genotypes LQT2 and LQT3, females with genotype LQT2, <40 years of age, onset of symptoms at <10 years of age, and patients with recurrent syncope. ICD indicates implantable cardioverter-defibrillator; LQTS, long QT syndrome; VT, ventricular tachycardia.

with recurrent syncope or cardiac arrest reported in 7% to 24% of patients.<sup>S7.9.1.1-44–S7.9.1.1-47</sup> In high-risk patients, observational studies support effectiveness of the ICD in preventing SCD, with consideration of left cardiac sympathetic denervation to reduce the frequency of ICD shocks.<sup>S7.9.1.1-16,S7.9.1.1-48,S7.9.1.1-49</sup> Left cardiac sympathetic denervation can reduce VA burden, but up to 27% of high-risk patients experience at least 1 recurrence.<sup>S7.9.1.1-16,S7.9.1.1-48,S7.9.1.1-50</sup> Left cardiac sympathetic denervation may be more effective in patients with long QT syndrome type 1 and

long QT syndrome type 3.<sup>S7.9.1.1-16</sup> Complications related to left cardiac sympathetic denervation occur in 8% to 20% of patients.<sup>S7.9.1.1-48,S7.9.1.1-51</sup> Syncope in patients with long QT syndrome may occur due to vasovagal syncope, noncompliance with medications, or proarrhythmia from concurrent medications.<sup>S7.9.1.1-5</sup> Clinical evaluation that incorporates consideration of genotype, QTc interval, medication compliance, and shared decision-making regarding the need to change or escalate therapy is important. Use of additional medications is guided by long QT syndrome type. In long



**Figure 10.** Long QT syndrome type 1.

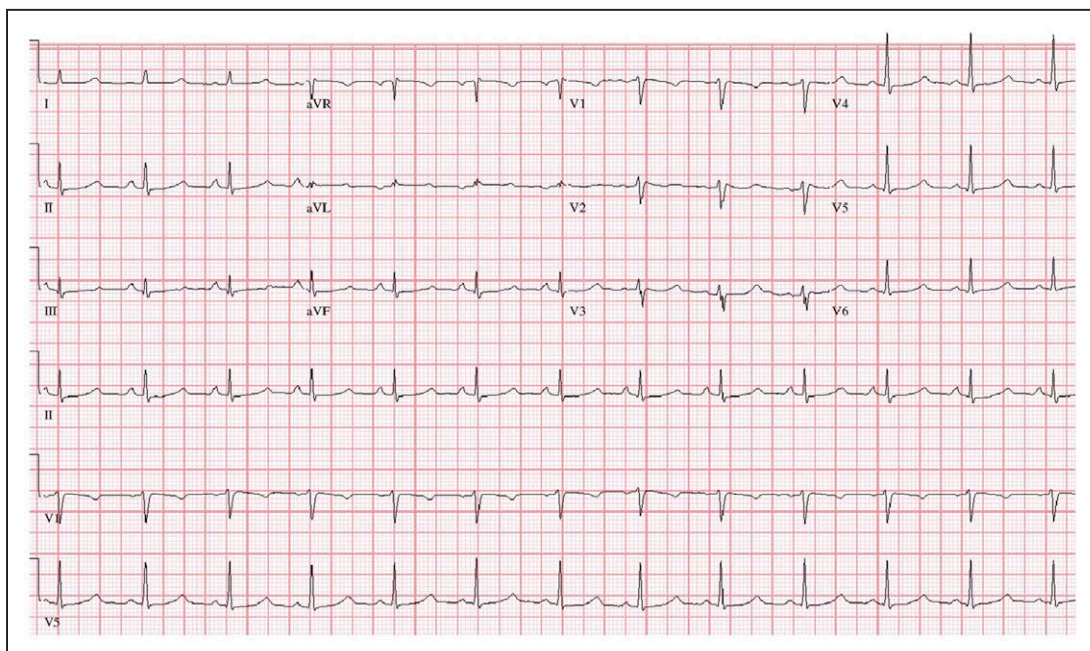


**Figure 11.** Long QT syndrome type 2.

QT syndrome type 3 ranolazine, mexiletine, and flecainide shorten the QTc and have been used to reduce recurrent arrhythmias.<sup>S7.9.1.1-6,S7.9.1.1-7,S7.9.1.1-10</sup>

3. Mexiletine is an additional medication that can be used in patients with long QT syndrome and recurrent ICD shocks. Left cardiac sympathetic denervation is associated with a reduction the number of appropriate ICD shocks and VA burden.<sup>S7.9.1.1-13–S7.9.1.1-16</sup> Reduction of the QTc to <500 ms after left cardiac sympathetic denervation has been correlated with

reduced risk of recurrent ICD shocks and frequency of symptoms<sup>S7.9.1.1-16,S7.9.1.1-52</sup>; however, SCD or SCA is reported in 3% to 10% of patients.<sup>S7.9.1.1-15,S7.9.1.1-16,S7.9.1.1-48,S7.9.1.1-50</sup> Although arrhythmia burden is often reduced, up to 27% of high-risk patients experience at least 1 recurrence.<sup>S7.9.1.1-13,S7.9.1.1-14,S7.9.1.1-48</sup> Patient outcomes are improved if the left cardiac sympathetic denervation is performed in centers with surgical expertise in this procedure. Use of additional medications is guided by long QT



**Figure 12.** Long QT syndrome type 3.



- syndrome type. In long QT syndrome type 3, ranolazine, mexiletine, and flecainide shorten the QTc and have been used to reduce recurrent arrhythmias.<sup>S7.9.1.1-6,S7.9.1.1-7,S7.9.1.1-10</sup>
- Genetic testing for disease-causing mutations in long QT syndrome offers important diagnostic, prognostic, and therapeutic information in addition to the clinical evaluation, and a positive test can facilitate establishing risk for family members. The yield of genetic testing in long QT syndrome phenotype-positive patients is 50% to 86%, with the higher range present in patients with marked QT prolongation or positive family history of SCD.<sup>S7.9.1.1-17,S7.9.1.1-21,S7.9.1.1-53</sup> A negative genetic test does not exclude the diagnosis of long QT syndrome, which relies on the clinical evaluation. In asymptomatic patients with otherwise unexplained prolonged QTc  $\geq 480$  ms on serial ECGs, genetic testing may help confirm the diagnosis and supplement prognostic information in addition to clinical symptoms and QTc duration.<sup>S7.9.1.1-5,S7.9.1.1-18–S7.9.1.1-20,S7.9.1.1-30,S7.9.1.1-35,S7.9.1.1-54–S7.9.1.1-56</sup>
  - In a prospective, observational study of patients with suspected long QT syndrome, patients with a history of syncope or cardiac arrest and either an affected first-degree relative or a borderline or prolonged QTc interval underwent exercise treadmill testing and bicycle exercise, with ECGs recorded before, during, and after exercise, as well as in different positions.<sup>S7.9.1.1-27</sup> long QT syndrome was confirmed by genetic testing in all affected individuals. Among patients with borderline-to-normal resting QTc intervals, prolongation of the 4-minute recovery QTc  $\geq 445$  ms had high sensitivity for correctly identifying patients with long QT syndrome.<sup>S7.9.1.1-27</sup> A study in younger patients demonstrated QTc prolongation  $>460$  ms at 7 minutes of recovery predicted long QT syndrome type 1 or long QT syndrome type 2 patients versus controls.<sup>S7.9.1.1-23</sup> In a study using burst bicycle exercise, patients with latent long QT syndrome had a significantly greater increase in QTc with exercise than either controls or those with QTc prolongation at baseline.<sup>S7.9.1.1-24</sup> These findings can be useful in establishing whether long QT syndrome is present. Monitoring adequacy of beta-blocker therapy using exercise testing can be beneficial, particularly in school-aged patients.<sup>S7.9.1.1-26,S7.9.1.1-28</sup> Beta-blocker therapy may be associated with a decrease in supine and peak exercise QTc, with the exception of long QT syndrome type 1 patients with C-loop mutations.<sup>S7.9.1.1-25</sup>
  - Approximately 10% to 36% of genotype-positive patients with long QT syndrome have QTc intervals  $\leq 440$  ms, most commonly patients with long QT syndrome type 1.<sup>S7.9.1.1-31,S7.9.1.1-35</sup> Patients with long QT syndrome and normal QTc have a lower risk of VA and SCD compared to those with prolonged QTc,<sup>S7.9.1.1-35</sup> but still have an increased risk of SCA or SCD compared with genotype-negative, age- and sex-matched general patients.<sup>S7.9.1.1-31</sup> Beta blockers reduce the risk of adverse cardiac events substantially.<sup>S7.9.1.1-1–S7.9.1.1-5,S7.9.1.1-30,S7.9.1.1-36,S7.9.1.1-38,S7.9.1.1-41,S7.9.1.1-57</sup> During the periods of highest risk in the first 3 decades of life,<sup>S7.9.1.1-11,S7.9.1.1-18</sup> treatment with a beta blocker may reduce risk of SCA.<sup>S7.9.1.1-26,S7.9.1.1-28,S7.9.1.1-36,S7.9.1.1-38</sup> Changes in QTc occur over time, particularly during puberty and during and after pregnancy, indicating the need for assessment of QTc on ECG annually or with medication changes, and assessing medication efficacy with exercise testing as feasible. Asymptomatic adult (male) long QT syndrome patients with normal QTc intervals may choose to decline beta-blocker therapy.<sup>S7.9.1.1-11,S7.9.1.1-34</sup>
  - The risk of adverse cardiac events from VA is influenced by the patient's resting QTc interval, age, sex, and long QT syndrome genotype/mutation. For asymptomatic males with long QT syndrome, the risk of cardiac events is highest in childhood,<sup>S7.9.1.1-2,S7.9.1.1-8,S7.9.1.1-11,S7.9.1.1-30</sup> during a time when medication compliance is challenging. Young women with LQT2 and QTc  $>500$  ms are at increased risk of SCA.<sup>S7.9.1.1-2,S7.9.1.1-11,S7.9.1.1-18–S7.9.1.1-20,S7.9.1.1-30,S7.9.1.1-35</sup> especially in the 9 months postpartum, and may be candidates for primary prevention ICD placement or use of a wearable cardioverter-defibrillator.<sup>S7.9.1.1-30</sup>
  - The risk of adverse events increases in patients with long QT syndrome with prolongation of the QTc  $>500$  ms.<sup>S7.9.1.1-2,S7.9.1.1-12,S7.9.1.1-26,S7.9.1.1-35,S7.9.1.1-41,S7.9.1.1-58</sup> QT-prolonging medications ([www.crediblemeds.org](http://www.crediblemeds.org))<sup>S7.9.1.1-59</sup> should not be used in patients with long QT syndrome unless there is no suitable alternative; careful monitoring of the QTc during therapy is recommended, with consideration for discontinuing therapy with marked QTc prolongation. Concurrent use of stimulant or nonstimulant attention deficit/hyperactivity medications was associated with an increased risk of syncope/cardiac arrest in long QT syndrome, particularly males, in 1 study,<sup>S7.9.1.1-34</sup> but it did not appear to be associated with increased risk in another retrospective study.<sup>S7.9.1.1-60</sup> Episodes of torsades de pointes can be precipitated by exposure to a QT prolonging medication, or hypokalemia induced by diuretics or gastrointestinal illness. Attention to maintaining normal potassium and magnesium balance when medications or situations

that promote depletion are encountered is an important component of management. Rare case reports exist of fever prolonging the QT interval in patients with long QT syndrome type 2; fever should be reduced with antipyretics<sup>57.9.1.1-61</sup> (Table 10).

### 7.9.1.2. Catecholaminergic Polymorphic Ventricular Tachycardia

Recommendations for Catecholaminergic Polymorphic Ventricular Tachycardia		
References that support the recommendations are summarized in Online Data Supplement 41.		
COR	LOE	Recommendations
I	B-NR	1. In patients with catecholaminergic polymorphic ventricular tachycardia, a beta blocker is recommended. <sup>57.9.1.2-1,57.9.1.2-2</sup>
I	B-NR	2. In patients with catecholaminergic polymorphic ventricular tachycardia and recurrent sustained VT or syncope, while receiving adequate or maximally tolerated beta blocker, treatment intensification with either combination medication therapy (eg, beta blocker, flecainide), left cardiac sympathetic denervation, and/or an ICD is recommended. <sup>57.9.1.2-2-57.9.1.2-6</sup>
IIa	B-NR	3. In patients with catecholaminergic polymorphic ventricular tachycardia and with clinical VT or exertional syncope, genetic counseling and genetic testing are reasonable. <sup>57.9.1.2-7</sup>

### Recommendation-Specific Supportive Text

1. Catecholaminergic polymorphic ventricular tachycardia is characterized by exertion-related polymorphic or bidirectional VT (Figure 13), associated with syncope and SCA. SCA/SCD is reported in 3% to 13% of patients.<sup>57.9.1.2-1,57.9.1.2-2,57.9.1.2-8</sup> Treatment with beta blockers is associated with a reduction in adverse cardiac events.<sup>57.9.1.2-1,57.9.1.2-2</sup> Some experts prefer the use of nadolol over other types of beta blockers; direct comparison data among beta blockers are unavailable. Use of a maximally tolerated dose of a beta blocker is important. Small observational studies suggest possible benefit of nondihydropyridine calcium channel blockers in the treatment of catecholaminergic polymorphic ventricular tachycardia.<sup>57.9.1.2-9,57.9.1.2-10</sup>
2. Flecainide in combination with a beta blocker can suppress ventricular ectopy by as much as 76% in patients with catecholaminergic polymorphic ventricular tachycardia during exercise testing or clinical follow-up.<sup>57.9.1.2-2,57.9.1.2-6,57.9.1.2-11</sup> For refractory VA, verapamil or propafenone may also be effective.<sup>57.9.1.2-9,57.9.1.2-10,57.9.1.2-12</sup> ICD

implantation in patients with catecholaminergic polymorphic ventricular tachycardia should be reserved for patients with prior SCA, or patients with refractory VAs on combination medical therapy. Inappropriate shocks are reported in 20% to 30% of catecholaminergic polymorphic ventricular tachycardia patients with ICDs.<sup>57.9.1.2-2,57.9.1.2-13-57.9.1.2-16</sup> ICD programming in patients with catecholaminergic polymorphic ventricular tachycardia should be optimized to deliver therapy for VF and to minimize inappropriate shocks and the risk of potentially fatal electrical storms.<sup>57.9.1.2-13,57.9.1.2-15</sup> Left cardiac sympathetic denervation for catecholaminergic polymorphic ventricular tachycardia may reduce the frequency of recurrent ICD shocks by 32% to 75%<sup>57.9.1.2-3-57.9.1.2-5,57.9.1.2-17,57.9.1.2-18</sup> although recurrent syncope, SCA, or SCD is reported in 9% to 32% of patients, with other minor complications in 20% to 70% of patients. It is best if the left cardiac sympathetic denervation is performed in centers with expertise in this procedure. Intensification of medical therapy or left cardiac sympathetic denervation is important in treating patients who present with recurrent appropriate ICD shocks.<sup>57.9.1.2-19</sup>

3. Genetic testing may be useful to confirm the diagnosis of catecholaminergic polymorphic ventricular tachycardia, which is suggested by the development of bidirectional VT with exertion or stress. Recognition of catecholaminergic polymorphic ventricular tachycardia as the cause for exertional symptoms should prompt aggressive therapy to prevent the significant risk of SCD. Therapy for catecholaminergic polymorphic ventricular tachycardia is not guided by genotype status, but screening of first-degree relatives may be facilitated with genetic testing.<sup>57.9.1.2-20</sup> Ryanodine receptor mutations have been reported in 47% of probands, which were de novo mutations in >70%.<sup>57.9.1.2-7</sup> Ryanodine genotype status has not correlated with disease severity or response to medications.<sup>57.9.1.2-7</sup> In very young patients presenting with idiopathic VF, mutations in calmodulin have been identified and are associated with high lethality.<sup>57.9.1.2-21-57.9.1.2-24</sup> Studies of proposed pathogenic mutations in catecholaminergic polymorphic ventricular tachycardia genes report up to 15% of variants were present in exome databases of the general population, raising questions as to the monogenic cause of catecholaminergic polymorphic ventricular tachycardia.<sup>57.9.1.2-20,57.9.1.2-25</sup>



Figure 13. Exercise-induced polymorphic VT in catecholaminergic polymorphic ventricular tachycardia.

7.9.1.3. Brugada Syndrome

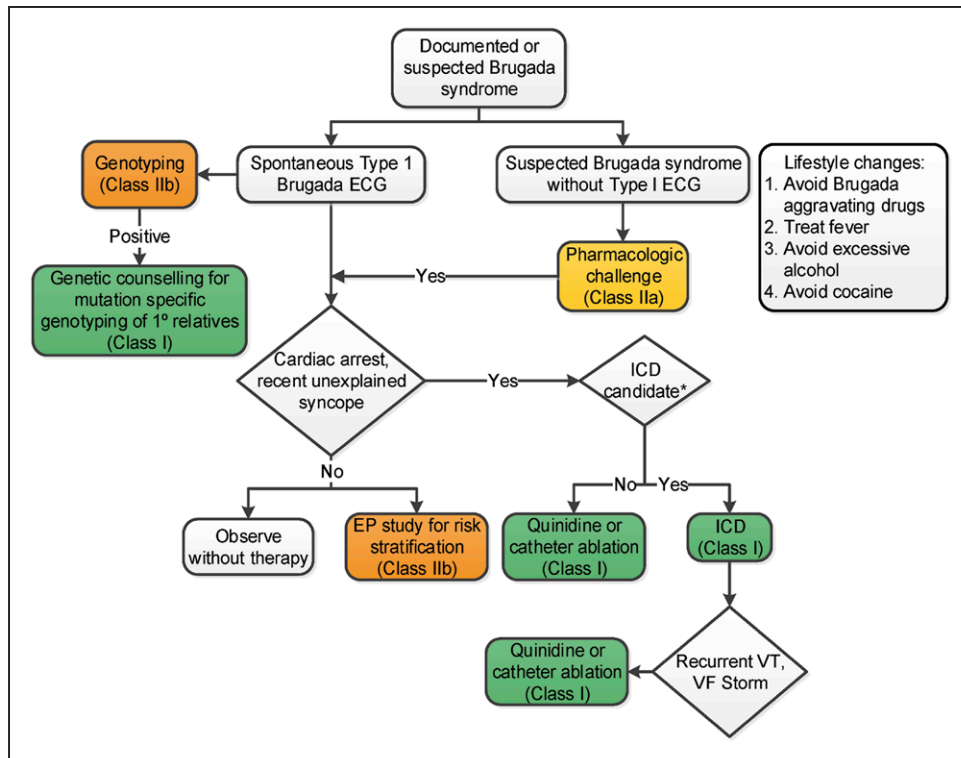
Recommendations for Brugada Syndrome		
References that support the recommendations are summarized in Online Data Supplement 42 and Systematic Review Report.		
COR	LOE	Recommendations
I	B-NR	1. In asymptomatic patients with only inducible type 1 Brugada electrocardiographic pattern, observation without therapy is recommended. <sup>57.9.1.3-1-57.9.1.3-5</sup>
I	B-NR	2. In patients with Brugada syndrome with spontaneous type 1 Brugada electrocardiographic pattern and cardiac arrest, sustained VA or a recent history of syncope presumed due to VA, an ICD is recommended if meaningful survival of greater than 1 year is expected. <sup>57.9.1.3-4,57.9.1.3-6</sup>
I	B-NR	3. In patients with Brugada syndrome experiencing recurrent ICD shocks for polymorphic VT, intensification of therapy with quinidine or catheter ablation is recommended. <sup>57.9.1.3-7-57.9.1.3-11</sup>
I	B-NR	4. In patients with spontaneous type 1 Brugada electrocardiographic pattern and symptomatic VA who either are not candidates for or decline an ICD, quinidine or catheter ablation is recommended. <sup>57.9.1.3-7,57.9.1.3-9-57.9.1.3-11</sup>
IIa	B-NR	5. In patients with suspected Brugada syndrome in the absence of a spontaneous type 1 Brugada electrocardiographic pattern, a pharmacological challenge using a sodium channel blocker can be useful for diagnosis. <sup>57.9.1.3-12-57.9.1.3-14</sup>

Recommendations for Brugada Syndrome (Continued)		
COR	LOE	Recommendations
IIb	B-NR <sup>SR</sup>	6. In patients with asymptomatic Brugada syndrome and a spontaneous type 1 Brugada electrocardiographic pattern, an electrophysiological study with programmed ventricular stimulation using single and double extrastimuli may be considered for further risk stratification. <sup>57.9.1.3-1,57.9.1.3-6,57.9.1.3-13,57.9.1.3-15-57.9.1.3-17</sup>
IIb	C-EO	7. In patients with suspected or established Brugada syndrome, genetic counseling and genetic testing may be useful to facilitate cascade screening of relatives. <sup>57.9.1.3-18-57.9.1.3-20</sup>

SR indicated systematic review.

Synopsis

Refer to the “Systematic Review for the 2017 ACC/AHA/HRS Guideline for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death” for the complete systematic evidence review for additional data and analyses.<sup>57.9.1.3-15</sup> The results from the question “For asymptomatic patients with Brugada syndrome, what is the association between an abnormal EP study and SCD and other arrhythmia endpoints? (Part 1)” and the writing committee’s review of the totality of the literature were used to frame decision-making. Recommendations that are based on a body of evidence that includes the system-



**Figure 14. Prevention of SCD in patients with Brugada syndrome.**

Colors correspond to Class of Recommendation in Table 1. See Section 7.9.1.3 for discussion. \*ICD candidacy as determined by functional status, life expectancy or patient preference. 1° indicates primary; ECG, electrocardiogram; EP, electrophysiological; ICD implantable cardioverter-defibrillator; SCD, sudden cardiac death; VT, ventricular tachycardia; and VF, ventricular fibrillation.

atic review conducted by the ERC are denoted by the superscript SR (eg, LOE: B-R<sup>SR</sup>).

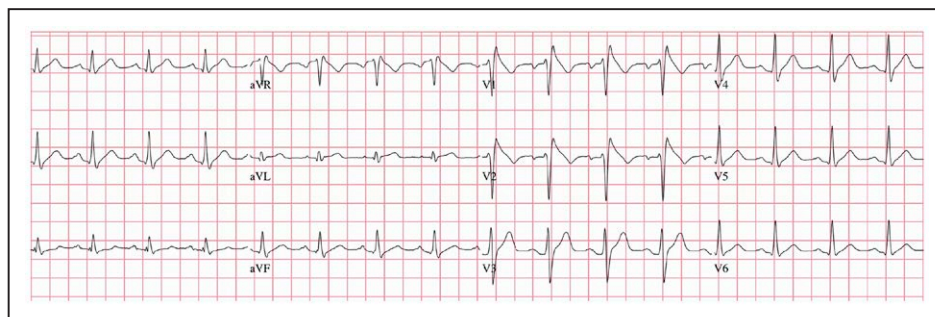
Factors identified as potential triggers of VF and SCA in Brugada syndrome include some psychotropic medications, and anesthetic agents, cocaine, excessive alcohol intake, and fever ([www.brugadadrugs.org](http://www.brugadadrugs.org)).<sup>S7.9.1.3-21,S7.9.1.3-22</sup> These agents should be avoided, and fever warrants early and aggressive measures to reduce temperature.<sup>S7.9.1.3-23</sup>

**Recommendation-Specific Supportive Text**

1. The risk of major adverse cardiac events in asymptomatic patients without spontaneous

type 1 electrocardiographic changes of Brugada syndrome (Figure 15), or with only medication-induced electrocardiographic changes, is low.<sup>S7.9.1.3-1–S7.9.1.3-5</sup> A positive family history of Brugada syndrome or SCA is not a significant predictor of adverse events in Brugada syndrome.<sup>S7.9.1.3-1,S7.9.1.3-2,S7.9.1.3-4,S7.9.1.3-5</sup> Implantation of an ICD in an asymptomatic patient without a spontaneous type 1 Brugada electrocardiographic has not been shown to confer any benefit.

2. Brugada syndrome is characterized by coved ST elevation in leads V1 or V2 positioned in the second, third, or fourth intercostal space either spontaneously or induced by administration of a sodium channel–blocking drug in the absence



**Figure 15. Brugada syndrome.**

- of other causes of ST elevation<sup>57.9.1.3-24</sup> and negative T waves in the right precordial leads, and is associated with syncope or SCA due to VF, predominantly in young males, although it has been reported in all age groups. The type 1 Brugada ECG with coved ST elevation in right precordial leads may be present spontaneously, during fever or vagotonic states, or after medication challenge with sodium channel blockers. QRS complex fractionation is seen in a minority of patients. Patients with spontaneous coved type ST elevation and a history of syncope or prior SCA are at the highest risk for potentially lethal VA. ICD implantation has been shown to reduce mortality in symptomatic patients with Brugada syndrome.<sup>57.9.1.3-25,57.9.1.3-26</sup>
3. Ablation of abnormal areas of epicardial late activation in the RV can suppress recurrent VA as shown in a small number of patients.<sup>57.9.1.3-8,57.9.1.3-9,57.9.1.3-11,57.9.1.3-27</sup> In these reports, the spontaneous type 1 Brugada pattern on ECG may be eliminated in >75% of patients, and recurrences of VT/VF are markedly reduced.<sup>57.9.1.3-9–57.9.1.3-11</sup> Experience and follow-up after ablation are limited, and an ICD for patients who have had syncope or SCA is recommended. A series of patients with Brugada syndrome treated with quinidine had no deaths during a mean follow-up of over 9 years, although adverse effects of quinidine were reported in 38% of patients, these authors felt that quinidine could be used as an alternative to the ICD in selected patients.<sup>57.9.1.3-7</sup>
  4. Observational studies show that quinidine can suppress VF storm in patients with Brugada syndrome, and a low risk of arrhythmia was observed in a long-term observational study.<sup>7.9.1.3-7</sup> No patient treated with quinidine experienced SCD. Adverse effects of quinidine occur in up to 37% of patients. Catheter ablation targeting the epicardial right ventricular areas of abnormality has also been shown to reduce recurrent VF episodes and normalize the ECG.<sup>7.9.1.3-9–7.9.1.3-11</sup>
  5. Administration of procainamide, flecainide, or ajmaline may be useful to provoke type 1 ST elevation in patients suspected to have Brugada syndrome as a cause of symptoms but who do not have a type 1 electrocardiographic pattern at baseline. Medication challenge should be terminated with the development of VA, marked QRS widening, or type 1 Brugada electrocardiographic pattern.<sup>57.9.1.3-14,57.9.1.3-28</sup> The use of high electrocardiographic electrode positioning in the second and third interspaces for electrocardiographic recording improves detection of a type 1 Brugada ECG.<sup>57.9.1.3-29</sup> Asymptomatic patients with a family history of Brugada syndrome may be offered sodium channel blocker challenge for diagnostic evaluation, although a positive test does not require chronic therapy due to a low risk in this setting.<sup>57.9.1.3-12</sup> In asymptomatic patients with type 1 Brugada electrocardiographic findings, medication challenge does not offer additional diagnostic value.
  6. Polymorphic VT/VF induced by programmed stimulation has been associated with an increased risk of VA in some patients with spontaneous type 1 Brugada ECG.<sup>57.9.1.3-13</sup> The specificity of programmed stimulation for assessing risk decreases with the inclusion of triple extrastimuli.<sup>57.9.1.3-6,57.9.1.3-13</sup> The value of programmed stimulation in asymptomatic patients with spontaneous type 1 Brugada ECGs has been the subject of multiple studies.<sup>57.9.1.3-1,57.9.1.3-2,57.9.1.3-4,57.9.1.3-5</sup> A report found that the prognostic value has decreased over time, possibly as patients with less severe phenotypes have been recognized and studied.<sup>57.9.1.3-1</sup> Some experts use the results of programmed ventricular stimulation for informing shared decision-making in consideration of the ICD. In symptomatic patients with Brugada syndrome, programmed ventricular stimulation for risk stratification does not add anything to the evaluation of the patients as an ICD is warranted.<sup>57.9.1.3-2,57.9.1.3-4,57.9.1.3-6</sup>
  7. The yield of genetic testing in phenotype positive patients is approximately 20% to 30% in Brugada syndrome.<sup>57.9.1.3-4,57.9.1.3-16,57.9.1.3-18,57.9.1.3-19,57.9.1.3-30,57.9.1.3-31</sup> *SCN5A* variants account for most of this subset of genotype positive Brugada syndrome. However, 2% to 10% of otherwise healthy individuals host a rare variant of *SCN5A*.<sup>57.9.1.3-20,57.9.1.3-31</sup> A negative genetic test does not exclude the diagnosis of Brugada syndrome, which is usually based on electrocardiographic and clinical characteristics. Risk stratification is based on symptoms and clinical findings<sup>57.9.1.3-32</sup>; genotype status is not correlated with the risk of adverse events.<sup>57.9.1.3-5,57.9.1.3-18,57.9.1.3-19,57.9.1.3-33</sup> Identification of a pathogenetic mutation may help facilitate recognition of carrier status in family members, allowing for lifestyle modification and potential treatment.
  8. Factors identified as potential triggers of VF and SCA in Brugada syndrome include some psychotropic medications, and anesthetic agents, cocaine, excessive alcohol intake, and fever ([www.brugadadrugs.org](http://www.brugadadrugs.org)).<sup>57.9.1.3-21,57.9.1.3-22</sup> These agents should be avoided and fever warrants early and aggressive measures to reduce temperature.<sup>57.9.1.3-23</sup>

#### 7.9.1.4. Early Repolarization “J-wave” Syndrome

Recommendations for Early Repolarization Syndrome		
References that support the recommendations are summarized in Online Data Supplement 43.		
COR	LOE	Recommendations
I	B-NR	1. In asymptomatic patients with an early repolarization pattern on ECG, observation without treatment is recommended. <sup>S7.9.1.4-1,S7.9.1.4-2</sup>
I	B-NR	2. In patients with early repolarization pattern on ECG and cardiac arrest or sustained VA, an ICD is recommended if meaningful survival greater than 1 year is expected. <sup>S7.9.1.4-3,S7.9.1.4-4</sup>
III: No Benefit	B-NR	3. In patients with early repolarization pattern on ECG, genetic testing is not recommended. <sup>S7.9.1.4-5</sup>

#### Recommendation-Specific Supportive Text

1. The prevalence of an early repolarization pattern on ECG with J point elevation in the inferior or lateral leads of at least 0.1 mV has been reported to be as high as 5.8% in adults<sup>S7.9.1.4-1</sup> and is more common in males. The early repolarization pattern was lost during 10-year follow-up in >60% of young males.<sup>S7.9.1.4-2</sup> Patients are determined to have an early repolarization syndrome when, in addition to having early repolarization pattern on an ECG, they either have symptoms such as syncope or present with an arrhythmia. When patients present with an early repolarization pattern on an ECG, it is important to rule out reversible causes such as ischemia. Patients with early repolarization are more susceptible to the development of VF during acute cardiac ischemia and/or in the presence of QRS abnormalities due to LV hypertrophy or bundle-branch block.<sup>S7.9.1.4-6–S7.9.1.4-8</sup>
2. Patients with cardiac arrest or VF in the setting of an electrocardiographic pattern of early repolarization are at increased risk for subsequent recurrent episodes of VF, occurring in at least 40% of patients.<sup>S7.9.1.4-3,S7.9.1.4-4,S7.9.1.4-9</sup> Antiarrhythmic medications, with the exception of quinidine/hydroquinidine, have limited efficacy in preventing recurrent VA.<sup>S7.9.1.4-3,S7.9.1.4-4</sup>
3. To date, genetic testing has not reliably identified mutations predisposing to early repolarization.<sup>S7.9.1.4-5</sup>

#### 7.9.1.5. Short QT Syndrome

Recommendations for Short QT Syndrome		
References that support the recommendations are summarized in Online Data Supplement 44.		
COR	LOE	Recommendations
I	B-NR	1. In asymptomatic patients with a short QTc interval, observation without treatment is recommended. <sup>S7.9.1.5-1,S7.9.1.5-2</sup>

Recommendations for Short QT Syndrome (Continued)		
COR	LOE	Recommendations
I	B-NR	2. In patients with short QT syndrome who have a cardiac arrest or sustained VA, an ICD is recommended if meaningful survival greater than 1 year is expected. <sup>S7.9.1.5-3–S7.9.1.5-5</sup>
IIa	C-LD	3. In patients with short QT syndrome and recurrent sustained VA, treatment with quinidine can be useful. <sup>S7.9.1.5-3,S7.9.1.5-5,S7.9.1.5-6</sup>
IIa	C-LD	4. In patients with short QT syndrome and VT/VF storm, isoproterenol infusion can be effective. <sup>S7.9.1.5-7</sup>
IIb	C-EO	5. In patients with short QT syndrome, genetic testing may be considered to facilitate screening of first-degree relatives. <sup>S7.9.1.5-4</sup>

#### Recommendation-Specific Supportive Text

1. The prevalence of short QTc  $\leq 340$  ms is estimated to be 5 in 10000 in persons <21 years of age and is more common in males.<sup>S7.9.1.5-1,S7.9.1.5-4,S7.9.1.5-8,S7.9.1.5-9</sup> An incidental finding of a short QTc  $\leq 320$  ms in an asymptomatic patient warrants monitoring and follow-up without prophylactic medication treatment.<sup>S7.9.1.5-1,S7.9.1.5-2</sup>
2. Patients with cardiac arrest in the setting of short QT syndrome are known to be at increased risk for recurrent cardiac arrest.<sup>S7.9.1.5-3–S7.9.1.5-5</sup> Approximately 18% of the small number of reported patients with short QT and implanted ICDs have experienced appropriate ICD therapies during short-term follow-up.<sup>S7.9.1.5-3,S7.9.1.5-5,S7.9.1.5-6</sup> Therapy with quinidine may reduce the number of ICD shocks.<sup>S7.9.1.5-3,S7.9.1.5-5,S7.9.1.5-6</sup>
3. Markedly shortened QTc values  $\leq 300$  ms are associated with increased risk of SCD, especially during sleep or rest, in young persons, in whom the median QTc was 285 ms.<sup>S7.9.1.5-5,S7.9.1.5-9</sup> A clinical score including QTc duration, clinical history of documented polymorphic VT or VF, unexplained syncope, family history of autopsy-negative SCD or sudden infant death syndrome, and positive genotype results has been proposed to identify patients at increased risk for SCD.<sup>S7.9.1.5-4,S7.9.1.5-10</sup> Treatment with quinidine results in lengthening of the QTc and, in selected patients, may be an alternative to ICD implantation.<sup>S7.9.1.5-3,S7.9.1.5-5,S7.9.1.5-6</sup>
4. In the setting of electrical storm with refractory VF and short QT syndrome, infusion of isoproterenol can be effective in restoring/maintaining sinus rhythm.<sup>S7.9.1.5-7</sup>
5. Pathogenic mutations in potassium channels have been identified in approximately 10% to

20% of patients with short QT syndrome including in *KCNH2* (SQT1), *KCNQ1* (SQT2), and *KCNJ2* (SQT3).<sup>S7,9,1,5-4</sup> Due to the rarity of the disease, genotype/phenotype correlations are unavailable, limiting the use of knowledge of genotype status.

## 8. VA IN THE STRUCTURALLY NORMAL HEART

Recommendations for VA in the Structurally Normal Heart		
References that support the recommendations are summarized in Online Data Supplement 45.		
COR	LOE	Recommendations
I	B-R	1. In patients with symptomatic PVCs in an otherwise normal heart, treatment with a beta blocker or nondihydropyridine calcium channel blocker is useful to reduce recurrent arrhythmias and improve symptoms. <sup>S8-1,S8-2</sup>
IIa	B-R	2. In patients with symptomatic VA in an otherwise normal heart, treatment with an antiarrhythmic medication is reasonable to reduce recurrent symptomatic arrhythmias and improve symptoms if beta blockers and nondihydropyridine calcium channel blockers are ineffective or not tolerated. <sup>S8-3,S8-4</sup>

### Synopsis

Most idiopathic VA are due to a focal mechanism of triggered activity or abnormal automaticity, some, notably interfascicular reentrant LV tachycardias, are due to reentry. The clinical manifestations of idiopathic VA are highly variable and range from benign, asymptomatic PVCs to sustained VT or even VF. On initial discovery, an evaluation for structural heart disease is warranted with physical examination, an ECG, and imaging, usually with echocardiography. In the absence of any abnormality or a family history of SCD, further assessment and treatment are guided by symptoms. If the patient is asymptomatic and does not have evidence of a cardiac channelopathy, reassurance as to the benign nature is sufficient. If the arrhythmia is suspected of being sufficiently frequent to cause ventricular dysfunction over time, periodic follow-up with reassessment of ventricular function is warranted (see Section 10.8). For mild symptoms, avoidance of aggravating factors such as excessive consumption of caffeine or sympathomimetic agents, may be sufficient. Therapy with a beta blocker or nondihydropyridine calcium channel blocker reduces symptoms for some patients. Class I antiarrhythmic medications can be effective, but those are generally avoided due to concerns for adverse effects. For patients who require arrhythmia suppression for whom antiarrhythmic medications are ineffective, not tolerated, or undesired, catheter ablation can be a highly effective treatment (see Section 9). The ablation strategy is to identify the site of

origin manifested by the earliest site of electrical activation or, when this is not feasible, by pace-mapping. The most common site of origin for idiopathic VA is from the right ventricular outflow tract (RVOT) or the ostium of the LV, which is comprised of the oval opening of the LV to which the aorta is attached anteriorly and the left atrium is attached posteriorly. The likely origin can be reasonably predicted from the QRS morphology of the VA, which provides a good indication of the type of approach required and the likelihood of success and risks. Ablation failure is often related to the absence of the VA for mapping at the time of the procedure, or origin of the VA in an inaccessible region of the heart. These foci occasionally produce sustained monomorphic VT.<sup>S8-5-S8-7</sup>

### Recommendation-Specific Supportive Text

1. In a randomized, double-blinded, placebo-controlled study of 52 patients with symptomatic VA and a mean PVC count of  $21407 \pm 1740$  beats per 24 hours, atenolol significantly decreased symptom frequency ( $P=0.03$ ) and PVC count ( $P=0.001$ ), whereas placebo had no effect on PVC count ( $P=0.78$ ) or average heart rate ( $P=0.44$ ).<sup>S8-8</sup> A prospective randomized comparison of antiarrhythmic medications versus catheter ablation, metoprolol or propafenone had modest efficacy to suppress RVOT VA although with a far higher rate of recurrence than catheter ablation.<sup>S8-9</sup>
2. In an RCT of 233 patients with  $\geq 30$  PVCs per hour, d-sotalol was shown to reduce frequent PVCs, but only racemic dl-sotalol is presently available.<sup>S8-10</sup> In a prospective randomized comparison of antiarrhythmic medications versus catheter ablation, therapy with metoprolol or propafenone was shown to have modest efficacy when used to suppress RVOT PVCs although with a far higher rate of recurrence than catheter ablation.<sup>S8-9</sup> Nondihydropyridine calcium channel blockers reduce arrhythmias.<sup>S8-1,S8-2,S8-11,S8-12</sup>

### 8.1. Outflow Tract and Atrioventricular Annular VA

Recommendations for Outflow Tract VA		
References that support the recommendations are summarized in Online Data Supplement 46.		
COR	LOE	Recommendations
I	B-NR	1. In patients with symptomatic outflow tract VA in an otherwise normal heart for whom antiarrhythmic medications are ineffective, not tolerated, or not the patient's preference, catheter ablation is useful. <sup>S8,1-1-S8,1-3</sup>
I	B-NR	2. In patients with symptomatic outflow tract VT in an otherwise normal heart, a beta blocker or a calcium channel blocker is useful. <sup>S8,1-1-S8,1-3</sup>

## Recommendation-Specific Supportive Text

- In 1 RCT, catheter ablation was superior to antiarrhythmic medications at suppressing frequent PVCs arising from the RVOT.<sup>58.1-4</sup> Observational studies have shown that radiofrequency catheter ablation is effective in the treatment of idiopathic VA arising from the RVOT and LV outflow tract.<sup>58.1-2,58.1-5-58.1-16</sup> The site of ablation may be below or above the pulmonic valve in the RVOT.<sup>58.1-9,58.1-13</sup> Although most RVOT VA can be ablated within the RV, 10% may require ablation within the pulmonic sinus cusps.<sup>58.1-9</sup> Serious complications are infrequent. For LV outflow tract VA, the site of ablation may be within the aortic cusp sinuses,<sup>58.1-11,58.1-14,58.1-16</sup> below the aortic valve,<sup>58.1-2,58.1-6</sup> at the aorto-mitral continuity<sup>58.1-1-58.1-3</sup> or on the epicardial surface of the LV summit.<sup>58.1-3,58.1-17,58.1-18</sup> The mitral and tricuspid annulae are less common sites of idiopathic VA, but these VA can also be effectively treated with catheter ablation.<sup>58.1-1,58.1-19,58.1-20</sup> Approximately 10% of idiopathic VA may arise from the summit of the LV. Some can be ablated from the great cardiac vein or the epicardial surface, but others arise from an inaccessible region in close proximity to the left coronary artery precluding effective ablation.<sup>58.1-14</sup> Intramural sites of origin are infrequent but may require ablation on both the endocardial and epicardial surfaces of the LV ostium.<sup>58.1-3</sup> Complications from ablation of outflow tract VA are infrequent, but bleeding complications related to arterial and venous access, pericardial tamponade, and damage to the coronary arteries can occur.
- In a prospective randomized comparison of antiarrhythmic medications versus catheter ablation, metoprolol or propafenone was shown to have modest effectiveness when used to suppress RVOT PVCs, though with a far higher rate of recurrence than catheter ablation.<sup>58.1-4</sup> Non-dihydropyridine calcium channel blockers suppress arrhythmia in some patients.<sup>58.1-4</sup>

## 8.2. Papillary Muscle VA

Recommendation for Papillary Muscle VA (PVCs and VT)		
References that support the recommendation are summarized in Online Data Supplement 47.		
COR	LOE	Recommendation
I	B-NR	1. In patients with symptomatic VA arising from the papillary muscles for whom antiarrhythmic medications are ineffective, not tolerated, or not the patient's preference, catheter ablation is useful. <sup>58.2-1-58.2-5</sup>

## Recommendation-Specific Supportive Text

- The papillary muscles of the LV or RV can be the site of origin of VA in the presence or absence of structural heart disease.<sup>58.2-1-58.2-5</sup> Idiopathic left and right ventricular papillary muscle VA are most commonly PVCs and NSVT, and are usually exercise-related and may be induced by intravenous epinephrine or isoproterenol administration.<sup>58.2-3</sup> These arrhythmias have a focal, nonreentrant mechanism. Any of the 3 RV papillary muscles may be the site of origin and catheter ablation is usually effective.<sup>58.2-2</sup> In 1 study, successful ablation was achieved in all 8 patients with a reduction in PVC burden from 17±20% to 0.6±0.8%.<sup>58.2-2</sup> In the left ventricle, the site of origin may be either the posteromedial or the anterolateral papillary muscles.<sup>58.2-1,58.2-4,58.2-5</sup> Multiple VA QRS morphologies were observed in 47% of patients, and ablation on both sides of the papillary muscle is required in some patients.<sup>58.2-4</sup> Achieving adequate catheter stability can be challenging. Acute ablation success is high, but recurrences are more frequent than for idiopathic outflow tract VA. Serious complications, including valve injury, appear to be infrequent. The risks of catheter ablation include bleeding related to arterial and venous access and a low risk of pericardial tamponade.

## 8.3. Interfascicular Reentrant VT (Belhassen Tachycardia)

Recommendations for Interfascicular Reentrant VT (Belhassen Tachycardia)		
References that support the recommendations are summarized in Online Data Supplement 48.		
COR	LOE	Recommendations
I	B-NR	1. In patients with verapamil-sensitive, idiopathic LVT related to interfascicular reentry for whom antiarrhythmic medications are ineffective, not tolerated, or not the patient's preference, catheter ablation is useful. <sup>58.3-1-58.3-3</sup>
I	B-NR	2. In patients with sustained hemodynamically tolerated verapamil-sensitive, idiopathic LVT related to interfascicular reentry, intravenous verapamil is recommended for VT termination. <sup>58.3-3-58.3-6</sup>
Ia	C-LD	3. In patients with recurrent verapamil-sensitive idiopathic LVT, chronic therapy with oral verapamil can be useful. <sup>58.3-7-58.3-10</sup>

## Recommendation-Specific Supportive Text

- Idiopathic LVT is due to reentry involving a portion of the LV Purkinje system, usually the left posterior fascicle as the retrograde limb of the circuit and an incompletely defined segment of LV tissue as the anterograde limb, a portion of which is verapamil



sensitive.<sup>58.3-1-58.3-3</sup> These VTs are typically sustained with a QRS that has a right bundle-branch block configuration with a superior axis. Less frequently an inferior axis VT or a relatively narrow QRS VT occurs as a result of alternate reentry paths, also involving a part of the Purkinje system. Beta blockers or verapamil typically terminate these arrhythmias, but they fail to prevent recurrences in some patients.<sup>58.3-1-58.3-3</sup> The target of catheter ablation for the most common form is usually the distal insertion of the anterograde limb of the Purkinje system along the inferior portion of the LV septum near its junction with the left posterior fascicle. Catheter ablation is acutely successful in >90% of patients with a risk of recurrence of approximately 10%. This VT may resemble fascicular VA that are due to a focal mechanism in the left anterior or left posterior fascicles of the LV His-Purkinje system. These fascicular arrhythmias usually have a focal mechanism with the target of catheter ablation being the site of earliest electrical activation recorded with a presystolic fascicular potential. Catheter ablation is highly effective for intrafascicular and fascicular VA. Serious complications are infrequent and include bleeding at the site of arterial or venous access and a small risk of bundle branch block or atrioventricular block.

2. Idiopathic LVT is based on reentrant mechanism involving tissue with slow conduction properties along the LV septum as the anterograde limb and the normal left posterior fascicle of the His-Purkinje system as the retrograde limb. The slow conduction zone is verapamil-sensitive.<sup>58.3-3-58.3-6</sup> These arrhythmias typically have a right bundle-branch block morphology with superior axis, though reversal of the circuit may produce a relatively narrow QRS during VT. Verapamil typically terminates these arrhythmias in the anterograde slow conduction zone.<sup>58.3-3-58.3-6</sup>
3. Although no RCTs have been published, the chronic use of oral verapamil for verapamil-sensitive idiopathic LVT has been reported to control this tachycardia in many patients, including both adults and children.<sup>58.3-5,58.3-8-58.3-10</sup>

Recommendations for Idiopathic Polymorphic VT/VF (Continued)		
COR	LOE	Recommendations
I	B-NR	2. In patients resuscitated from SCA due to idiopathic polymorphic VT or VF, an ICD is recommended if meaningful survival greater than 1 year is expected. <sup>58.4-9-58.4-13</sup>
I	B-NR	3. For patients with recurrent episodes of idiopathic VF initiated by PVCs with a consistent QRS morphology, catheter ablation is useful. <sup>58.4-11,58.4-14</sup>

### Recommendation-Specific Supportive Text

1. When combined with clinical evaluation, genetic testing can provide a diagnosis in up to 13% to 60% of younger (<40 years of age) survivors of SCA,<sup>58.4-3</sup> with the most common genotypes identified associated with long QT syndrome, catecholaminergic polymorphic ventricular tachycardia, and Brugada syndrome.<sup>58.4-8</sup> Drowning/near drowning events are particularly associated with LQT1 and catecholaminergic polymorphic ventricular tachycardia; genetic mutations in long QT syndrome and catecholaminergic polymorphic ventricular tachycardia have been identified in 23% of patients with unexplained near-drowning episodes.<sup>58.4-15</sup> In 1 study,<sup>58.4-6</sup> exertion-related cardiac arrest, particularly in children, may be related to long QT syndrome, catecholaminergic polymorphic ventricular tachycardia, or to calmodulin/triadin-mediated long QT syndrome/catecholaminergic polymorphic ventricular tachycardia mutations, which may require additional specialized genetic testing.<sup>58.4-1,58.4-2,58.4-4,58.4-16-58.4-18</sup> Single-driver auto crashes should prompt the consideration of arrhythmic causes. The yield of genetic testing is higher if a family history of SCD at a young age is present. Referral to specialized genetic testing centers is important if local expertise is unavailable.
2. VF in the absence of identifiable structural heart disease or known genetic arrhythmia syndromes such as catecholaminergic polymorphic ventricular tachycardia, long QT syndrome, short QT syndrome, Brugada syndrome, or J wave syndromes is usually the result of short coupled PVCs arising from the Purkinje system in either the right or left ventricles or, less commonly, from the ventricular myocardium.<sup>58.4-9-58.4-13</sup> The recurrence risk after resuscitation of idiopathic VF is very high.<sup>58.4-12</sup> Among 38 consecutive patients from 6 different centers who underwent ablation of primary idiopathic VF initiated by short coupled PVC, 87% had experienced ≥2 VF episodes in the preceding year.<sup>58.4-12</sup> Because idiopathic VF is associated with

### 8.4. Idiopathic Polymorphic VT/VF

Recommendations for Idiopathic Polymorphic VT/VF		
References that support the recommendations are summarized in Online Data Supplement 49.		
COR	LOE	Recommendations
I	B-NR	1. In young patients (<40 years of age) with unexplained SCA, unexplained near drowning, or recurrent exertional syncope, who do not have ischemic or other structural heart disease, further evaluation for genetic arrhythmia syndromes is recommended. <sup>58.4-1-58.4-8</sup>

a very high risk of recurrent VF, an ICD is indicated to prevent SCD. Catheter ablation of the triggering focus has proved to be highly effective in eliminating the repetitive PVCs which induce VF in these patients.<sup>58,4-11</sup> During a median post-procedural follow-up of 63 months, 7 (18%) of 38 patients undergoing catheter ablation of idiopathic VF induced by short coupled PVCs experienced VF recurrence at a median follow-up of 4 months. Five of these 7 patients underwent repeat ablation without VF recurrence. Thus, although catheter ablation is very effective in idiopathic VF, the recurrence risk remains substantial after an apparently successful procedure and the patient should be protected with an ICD. The subcutaneous ICD may not be a good therapy for these patients due to the higher risk of T-wave oversensing seen in this population; however, data are limited.<sup>58,4-10</sup>

- Idiopathic VF may be initiated by PVCs that arise from the outflow tracts or the His-Purkinje system within either the right ventricle or left ventricle.<sup>58,4-11,58,4-14,58,4-19-58,4-21</sup> Some patients have clusters of VF episodes (electrical storm) that typically present as PVCs initiating polymorphic VT/VF. The PVCs usually have a consistent QRS morphology and a short coupling interval and can be targeted for ablation to control the arrhythmia.<sup>58,4-11</sup> For PVCs from the Purkinje system, the ablation target is a high-frequency Purkinje potential preceding the PVCs. When episodes are induced by short-coupled PVCs arising from the outflow tracts, the ablation target is the site of earliest ventricular activation. Patients with idiopathic VF often have periods of frequent VT/VF interspersed with periods of relative quiescence.<sup>58,4-11,58,4-14</sup> To maximize the probability of successful ablation, the procedure is best performed during periods of frequent PVCs. Less-frequent episodes of VF may be amenable to ablation if frequent PVCs with a consistent QRS morphology are present. When the PVCs can be identified, ablation is highly successful, but late recurrences are observed in approximately 10% of patients such that implantation of an ICD is prudent even if ablation is acutely successful. The risks of catheter ablation include bleeding at the site of arterial or venous access and a small risk of pericardial tamponade. Therapy with quinidine acutely and chronically can suppress recurrent VF episodes in some patients.<sup>58,4-22</sup>

## 9. PVC-INDUCED CARDIOMYOPATHY

Recommendations for PVC-Induced Cardiomyopathy		
References that support the recommendations are summarized in Online Data Supplement 50.		
COR	LOE	Recommendations
I	B-NR	1. For patients who require arrhythmia suppression for symptoms or declining ventricular function suspected to be due to frequent PVCs (generally >15% of beats and predominately of 1 morphology) and for whom antiarrhythmic medications are ineffective, not tolerated, or not the patient's preference, catheter ablation is useful. <sup>59-1,59-2</sup>
Ila	B-NR	2. In patients with PVC-induced cardiomyopathy, pharmacological treatment (eg, beta blocker, amiodarone) is reasonable to reduce recurrent arrhythmias and improve symptoms and LV function. <sup>59-3,59-4</sup>

### Recommendation-Specific Supportive Text

- Frequent PVCs (usually >15% of the total number of beats) may produce a reversible form of LV dysfunction.<sup>59-5-59-18</sup> However, it is sometimes difficult to ascertain whether the PVCs caused LV dysfunction or whether progressive LV dysfunction caused frequent PVCs. LV dysfunction has been associated with greater PVC burden (>10% and usually >20%), NSVT, a retrograde P-wave after the PVCs, and interpolated PVCs.<sup>59-6,59-15</sup> In a prospective study of catheter ablation for PVC-induced cardiomyopathy, ablation was completely successful in 80% of patients.<sup>59-19</sup> LV function normalized within 6 months in 82% of the 22 patients who had depressed ventricular dysfunction at baseline. Thus, frequent PVCs may be a reversible cause of LV dysfunction that can be effectively treated with catheter ablation. It is often difficult to determine if apparent LV dysfunction reflects impaired LV function or inability to accurately assess LV function due to the frequent ectopic activity. In patients who have a high density of PVCs with normal ventricular function, optimal treatment and surveillance for prevention and detection of decline in ventricular function have not been established.
- In a double-blind parallel study of 30 patients with or without ischemic heart disease with >30 PVCs per hour comparing sotalol to propranolol, proarrhythmic effects were present in 1 patient on sotalol. There was no significant difference in suppression of PVCs (sotalol 65%, propranolol 44%), with reduction in ventricular couplets being 99% for sotalol and 49% for propranolol. There was a significant increase in QTc in patients on sotalol.<sup>59-20</sup> In a double-blind, randomized,

placebo-controlled study of 674 patients with HF and LVEF <0.40 attributed to ischemic or NICM and  $\geq 10$  PVCs per hour, amiodarone significantly reduced VA, slowed heart rate, and was associated with an increase in LVEF by 42% at 2 years with a nonsignificant trend toward reduction in mortality.<sup>59-4</sup> Whether the VA was contributing to ventricular dysfunction in these patients is unknown.

## 10. VA AND SCD RELATED TO SPECIFIC POPULATIONS

### 10.1. Athletes

In athletes, VAs range from isolated PVCs, couplets, and NSVT, to sustained VT and SCA leading to SCD.<sup>510.1-1</sup> Infrequent PVCs and short runs of repetitive NSVT, especially in the absence of structural heart disease, are more common in nonathletes, but they are generally benign, requiring only a limited workup and rarely lead to disqualification for sports.<sup>510.1-2,510.1-3</sup> In contrast, longer runs of NSVT, especially when exercise-induced, and sustained VT and SCA/SCD are infrequent, but they have a higher incidence in athletes than that reported for the general population in the corresponding age groups. Reported estimates of SCD range from 1 per 53 703 athlete-years in the National Collegiate Athletic Association database<sup>510.1-4</sup> to <1 per 200 000 in Minnesota high school students.<sup>510.1-5</sup> Among those studies judged to have better epidemiological protocols, estimates were in the range of 1 per 40 000 to 1 per 80 000.<sup>510.1-6</sup> These figures compare with a general population risk of 1.0 to 1.9/100 000 in adolescents and young adults.<sup>510.1-7,510.1-8</sup> Moreover, there appears to be both sport and sex differences in the magnitude of risk, with males being at higher risk than females in most sports,<sup>510.1-7,510.1-9</sup> blacks at higher risk than whites, and male basketball players being the single highest risk group in the United States, 1 per 5200 athlete-years.<sup>510.1-4</sup>

A study that included both competitive and recreational athletes showed that both groups are at a higher risk for SCD than the general population, with recreational athletes having greater cumulative numbers,<sup>510.1-7</sup> SCD occurring at an older age, and a different distribution of diseases. Postmortem data on SCD in athletes reveal that 25% to 40% are autopsy-negative, suggesting a role for genetic molecular disorders in these victims<sup>510.1-4,510.1-10,510.1-11</sup> and for family members.<sup>510.1-12</sup>

Another limitation of SCD data analysis in athletes centers on noncardiac causes, some of which mimic cardiac events. Noncardiac causes include acute neurological disorders, drug abuse, heat stroke, rhabdomyolysis, sickle cell disorders, suicides, and

accidents.<sup>510.1-13,510.1-14</sup> Nonetheless, arrhythmias in athletes remain the most common medical cause of death and many occur as the first cardiac event.

The most common structural cause of SCAs and SCDs in athletes in the United States is HCM, followed by anomalous origins of coronary arteries, with myocarditis contributing a smaller but significant proportion.<sup>510.1-15</sup> Beyond these, the other inherited disorders contribute to the distribution of causes of a SCD in athletes, many of which can be suspected or identified by a careful family history and preparticipation ECGs.

In general, management of arrhythmias in athletes follows that in nonathletes. In regard to interventions, it is now generally recommended that AEDs be available at training and facilities for competitive athletes,<sup>510.1-16</sup> with less specific statements for AED availability at venues (eg, tennis courts) or circumstances (eg, jogging or small group runs) in which recreational athletics are occurring.

Many athletes who have had corrective procedures (repair of congenital or developmental defects such as anomalous origins of coronary arteries)<sup>510.1-17,510.1-18</sup> are on therapy for inherited disorders<sup>510.1-19</sup> or have ICD implants<sup>510.1-1</sup> and are able to participate in athletics depending on the nature and severity of the disease and with appropriate precautions and counseling regarding potential residual risks.<sup>510.1-19,510.1-20</sup> For example, athletes with acquired disorders such as myocarditis are advised against exercise for at least 3 to 6 months after disease resolution.

### 10.2. Pregnancy

Recommendations for Pregnancy		
References that support the recommendations are summarized in Online Data Supplement 51.		
COR	LOE	Recommendations
I	B-NR	1. In mothers with long QT syndrome, a beta blocker should be continued during pregnancy and throughout the postpartum period including in women who are breastfeeding. <sup>510.2-1</sup>
I	C-EO	2. In the pregnant patient with sustained VA, electrical cardioversion is safe and effective and should be used with standard electrode configuration. <sup>510.2-2,510.2-3</sup>
Ia	B-NR	3. In pregnant patients needing an ICD or VT ablation, it is reasonable to undergo these procedures during pregnancy, preferably after the first trimester. <sup>510.2-4,510.2-5</sup>

### Recommendation-Specific Supportive Text

1. Women with long QT syndrome should be counseled about maternal and fetal risks prior to

pregnancy to ensure ongoing beta-blocker therapy. The risk of SCA or SCD is significantly higher during the 9 months after delivery, most notably among women with LQT2.<sup>S10.2-1,S10.2-6,S10.2-7</sup> A large retrospective analysis from the long QT syndrome registry demonstrated an odds ratio of 40.8 for syncope, SCA, or SCD among women with long QT syndrome in the 9 months' postpartum; treatment with beta blockers during pregnancy was independently associated with decreased risk.<sup>S10.2-7</sup> Overall arrhythmic events during pregnancy are not increased among women receiving beta-blocker therapy.<sup>S10.2-1,S10.2-6,S10.2-7</sup> In a case-control study, women with LQT1 who did not receive beta blockers during pregnancy, particularly those with prior syncope, were at significantly increased risk of SCA or syncope.<sup>S10.2-8</sup> Frequency of events returned to prepregnancy levels after 9 months.<sup>S10.2-1</sup> Maternal use of beta blockers during pregnancy is associated with decreased newborn birth weight and hypoglycemia,<sup>S10.2-9</sup> but it is not associated with increased risk of miscarriage.<sup>S10.2-8,S10.2-10</sup> Fetal bradycardia is associated with fetal long QT syndrome and should not independently provoke discontinuation of beta-blocker therapy<sup>S10.2-11–S10.2-14</sup>; these infants are at increased risk of death and require careful neonatal monitoring and treatment.<sup>S10.2-13</sup> As 50% of offspring may be affected with long QT syndrome, with highest risk of adverse events in infancy and childhood, screening of the newborn at birth and during infancy for long QT syndrome is important.<sup>S10.2-8</sup>

- Available data on electrical fields associated with properly applied AED patches suggest that the fetus is safe; no observational data are available to the contrary. Anterolateral defibrillator pad placement is preferred with the lateral pad/paddle placed under the breast tissue, which is an important consideration in the pregnant patient.
- The ICD in pregnant women is safe and effective.<sup>S10.2-4</sup> For the rare circumstance of pregnant women with an immediate indication for an ICD, or less common indications for VT ablation during pregnancy, the radiation risk to the fetus is minimal.<sup>S10.2-5,S10.2-15</sup> The procedure is usually performed after the first trimester unless there are circumstances that demand an earlier procedure. Wearable cardioverter-defibrillators have been used in peripartum cardiomyopathy while awaiting repeat assessment of recovery of ventricular function.<sup>S10.2-16</sup> The subcutaneous implantable cardioverter-defibrillator is a potential alternative to conventional ICDs, although data are unavailable to support a recommendation.

### 10.3. Older Patients With Comorbidities

Recommendation for Older Patients With Comorbidities		
See Systematic Review Report. <sup>S10.3-1</sup>		
COR	LOE	Recommendation
Ia	B-NR <sup>SR</sup>	1. For older patients and those with significant comorbidities, who meet indications for a primary prevention ICD, an ICD is reasonable if meaningful survival of greater than 1 year is expected. <sup>S10.3-1</sup>

SR indicates systematic review.

#### Synopsis

Refer to the "Systematic Review for the 2017 ACC/AHA/HRS Guideline for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death" for the complete systematic evidence review for additional data and analyses.<sup>S10.3-1</sup> The results from the question "What is the impact of ICD implantation for primary prevention in older patients and patients with significant comorbidities? (Part 2)" and the writing committee's review of the totality of the literature were used to frame our decision-making. Recommendations are based on a body of evidence that includes the systematic review conducted by the ERC and are denoted by the superscript SR (eg, LOE: B-R<sup>SR</sup>). Comorbidities included various combinations of renal disease, chronic obstructive pulmonary disease, atrial fibrillation, and heart disease, among others.

#### Recommendation-Specific Supportive Text

- Older age is defined as  $\geq 75$  years.

The ERC's analyses are helpful in clearly demonstrating that neither age nor comorbidities alone should be exclusions for an ICD. However, the data included in the analysis are limited. Firstly, most data are from non-randomized studies and "both selection and unidentified confounding biases can never be fully adjusted for." It is likely that the more frail patients are already appropriately not offered ICDs and are thus not included. Secondly, because most of the studies are nonrandomized, these findings signify only an association and not causality.

Also, older adults are prone to higher complication rates, shorter life expectancies (and thus, fewer years during which they could derive benefit from an ICD), and varying preferences.<sup>S10.3-2</sup> For these reasons, it is important to take a particularly nuanced and patient-centered approach to treating these patients.

### 10.4. Chronic Kidney Disease

Patients with chronic kidney disease (CKD) are at an increased risk of SCD compared with the general popula-

tion, yet the risk versus benefit of primary prevention ICDs has been unclear; data from observational studies have been conflicting, and patients with moderate or severe CKD, especially patients with end-stage renal disease (ESRD) on dialysis were not included in the pivotal RCTs of ICDs.<sup>S10.4.1–S10.4.5</sup> Furthermore, prior data had significant limitations given that patients who received ICDs have been compared inconsistently with a control group with CKD that did not receive primary prevention ICDs and the degree of renal insufficiency likely influences survival benefit.<sup>S10.4.6</sup> Patients with CKD, especially ESRD on dialysis, appear to be at increased risk of ICD-related complications. A significant number of sudden deaths are unassociated with VA in this population.<sup>S10.4.7</sup> Therefore, the ERC was asked to address the impact of ICDs on mortality in patients with CKD.

The ERC conducted a specific analysis of 5 studies that explored renal dysfunction. A meta-analysis of these studies suggested that an association exists between ICD implantation and improved survival.<sup>S10.4.8</sup> An important limitation is that only 2 studies specifically studied patients with ESRD and most data analyzed were from observational studies.<sup>S10.4.8,S10.4.9</sup> In view of these limitations, the writing committee concluded there was not enough data to inform a recommendation on ICD implantation in patients with ESRD on dialysis. Decisions regarding ICDs in patients with CKD, especially those with ESRD, should be individualized and take into consideration the patient's functional status, number of comorbidities, and preferences, among other factors.

### 10.5. Valvular Heart Disease

Patients with valvular heart disease should be evaluated and treated according to GDMT for valvular heart disease and, when LVEF is depressed, GDMT that applies to NICM to reduce the risk of SCD.<sup>S10.6.23</sup> VA in patients with valvular heart disease can be caused by any of the mechanisms responsible for VA in other cardiac disease including ischemic heart disease, MI, severe LV hypertrophy, adrenergic-dependent rhythm disturbances, or an inherited molecular abnormality. Patients with valvular heart disease and VA are generally evaluated and treated using current recommendations for each disorder.<sup>S10.6.1</sup> The presence of a VA alone does not constitute an indication for valve repair or replacement. In general, there is more knowledge on the risk for SCD in patients with aortic stenosis than other valvular lesions with a risk of 1% to 1.5% per year.<sup>S10.6.2</sup> Most patients who die suddenly have been symptomatic from their valve disease.<sup>S10.6.3,S10.6.4</sup> Although recurrent NSVT may place a patient with severe aortic stenosis at risk for syncope, the management of such a patient is guided by the severity of the valvular lesion.

Mitral valve prolapse has been implicated as a cause of SCD, although a study of 18 786 patients found no increased risk of SCA for patients with bileaflet mitral valve prolapse versus single leaflet mitral valve prolapse or no mitral valve prolapse.<sup>S10.6.5</sup> LV fibrosis in the papillary muscles has been described in some mitral valve prolapse patients with VA or SCD.<sup>S10.6.6</sup> Further, a possible syndrome for SCD has been described that includes bileaflet mitral valve prolapse, female sex, T wave abnormality, and complex ventricular ectopy.<sup>S10.6.7</sup> Guidance for treatment of patients with NICM, whether valvular or otherwise in origin, is provided in the current guideline (see Sections 7.2.1 and 7.2.2 for primary and secondary prevention).

### 10.6. Sex-Related Differences in the Risk of SCD

The information on associations between sex and VA and SCD is largely limited to epidemiological, cohort, and observational studies. Various population studies, primarily focused on SCD due to ischemic heart disease, have demonstrated age gradients in SCD risk among men and women.<sup>S10.6.8–S10.6.10</sup> These include a 10-year lag in SCD incidence in women compared with men. However, risk factor burden among women has the same proportional effect as in men, with a 17-fold increase in risk from the lowest to highest deciles.<sup>S10.6.9</sup> Importantly, 69% of the SCDs in women were first cardiac events.<sup>S10.6.8</sup> A study of lifetime risk of SCD stratified at 45, 55, 65, and 75 years of age identified persistently lower and similar proportions of lifetime risk of SCD among women versus men in each of the strata.<sup>S10.6.10</sup> The difference between women and men is somewhat smaller at ages below and above 75 years, largely because of a reduced risk in men. The overall lifetime risk of SCD was 1 in 9 among men and 1 in 30 among women.<sup>S10.6.10</sup>

In studies of outcomes after out-of-hospital cardiac arrest, women were older, had more SCAs in homes, and fewer shockable rhythms (VT/VF) than men.<sup>S10.6.11,S10.6.12</sup> This was associated with a somewhat lower probability of survival overall; however, women with VT/VF and those with pulseless electrical activity had better outcomes than men.<sup>S10.6.12</sup> A retrospective analysis of out-of-hospital cardiac arrest reported that survival improved over a 10-year period, with more favorable outcomes in men as well as younger women.<sup>S10.6.13</sup> Two studies demonstrated better outcomes in women with VT/VF, despite adverse risk factor profiles in women.<sup>S10.6.14,S10.6.15</sup> Another large study demonstrated that despite similar prehospital return of spontaneous circulation and survival to discharge, younger women had lower 1-month neurologically intact survival than the 50 to 60 age group.<sup>S10.6.16</sup> A 17-year retrospective analysis

did not demonstrate any difference between men and women, although total outcomes improved.<sup>S10.6-17</sup>

The proportion of ischemic heart disease-associated SCAs among women surviving out-of-hospital cardiac arrest was significantly lower than in men, but ischemic heart disease remained the most powerful predictor etiologically,<sup>S10.6-18</sup> and women were also significantly less likely to have severe LV dysfunction (LVEF  $\leq$ 35%) or previously recognized ischemic heart disease.<sup>S10.6-19</sup> Women appear to be less likely to benefit from therapeutic hypothermia postcardiac arrest; however, in the younger age group, neurologic recovery in women was better than in older women.<sup>S10.6-20</sup> Women are less likely to have SCA during competitive athletic events. A large study including both recreational and competitive athletes across a large age range noted that SCA in women during athletic events was 1 in 20 of that in men.<sup>S10.6-21</sup>

A large literature review from 1980 to 1992 demonstrated that women accounted for 70% of recorded cases of cardiovascular medication-related arrhythmias.<sup>S10.6-22</sup> This is consistent with QT interval differences among men and women. A retrospective analysis of quinidine discontinuation reported a significant difference in discontinuation between men and women (66% versus 84%) largely due to prolonged QT.<sup>S10.6-23</sup> A study of catheter ablation for VT reported that overall outcome was similar between men and women.<sup>S10.6-24</sup> The only sex difference was the greater probability of women having RVOT VT and a greater probability of men having LV outflow tract VT.

## 10.7. Medication-Induced Arrhythmias

Recommendations for Medication-Induced Arrhythmias		
References that support the recommendations are summarized in Online Data Supplements 52 and 53.		
Digoxin		
COR	LOE	Recommendation
I	B-NR	1. Administration of digoxin antibodies is recommended for patients who present with sustained VA potentially due to digoxin toxicity. <sup>S10.7-1,S10.7-2</sup>
Medication-induced QT prolongation and torsades de pointes		
COR	LOE	Recommendations
I	B-NR	2. In patients with recurrent torsades de pointes associated with acquired QT prolongation and bradycardia that cannot be suppressed with intravenous magnesium administration, increasing the heart rate with atrial or ventricular pacing or isoproterenol are recommended to suppress the arrhythmia. <sup>S10.7-3</sup>
I	C-LD	3. For patients with QT prolongation due to a medication, hypokalemia, hypomagnesemia, or other acquired factor and recurrent torsades de pointes, administration of intravenous magnesium sulfate is recommended to suppress the arrhythmia. <sup>S10.7-4,S10.7-5</sup>

Recommendations for Medication-Induced Arrhythmias (Continued)		
COR	LOE	Recommendations
I	C-LD	4. For patients with torsades de pointes associated with acquired QT prolongation, potassium repletion to 4.0 mmol/L or more and magnesium repletion to normal values (eg, $\geq$ 2.0 mmol/L) are beneficial. <sup>S10.7-6,S10.7-7</sup>
Sodium channel blocker–related toxicity		
COR	LOE	Recommendations
IIa	C-LD	5. In patients taking sodium channel blockers who present with elevated defibrillation or pacing thresholds, discontinuing the presumed responsible medication or reprogramming the device can be useful to restore effective device therapy. <sup>S10.7-8,S10.7-9</sup>
III: Harm	B-NR	6. In patients with congenital or acquired long QT syndrome, QT-prolonging medications are potentially harmful. <sup>S10.7-10</sup>

## Recommendation-Specific Supportive Text

1. Typical arrhythmias related to digoxin toxicity include enhanced atrial, junctional, or ventricular automaticity (with ectopic beats or tachycardia) often combined with atrioventricular block.<sup>S10.7-11</sup> VT that is fascicular or bidirectional in origin is suggestive of digoxin toxicity.<sup>S10.7-12</sup> Severe digoxin overdose causes hyperkalemia and cardiac standstill. The diagnosis is established by the combination of characteristic rhythm disturbances, ancillary symptoms (visual disturbances, nausea, changes in mentation), and elevated serum concentrations. Potentiating factors may include hypothyroidism, hypokalemia, or renal dysfunction.<sup>S10.7-12</sup> Treatment of digoxin toxicity is based on the severity. In mild cases, discontinuing the medication, monitoring rhythm, and maintaining normal serum potassium may be sufficient.<sup>S10.7-11</sup> Intravenous magnesium is often administered if VAs are present.<sup>S10.7-12</sup> Occasionally, temporary pacing may be needed for atrioventricular block or asystole.<sup>S10.7-13</sup> For more severe intoxication (serum digoxin concentrations exceeding 4 ng/mL and with serious arrhythmias such as VT), the treatment of choice is digoxin-specific Fab antibody.<sup>S10.7-1</sup> In 1 series of 150 severely intoxicated patients, response was rapid (30 minutes to 4 hour), and 54% of patients presenting with a cardiac arrest survived hospitalization.<sup>S10.7-1</sup> Adverse effects include worsening of the underlying disease (increased ventricular rate during AF, exacerbation of HF) and hypokalemia. Doses lower (and less expensive) than the full neutralizing dose are sufficient as long as cardiac arrest is not imminent.<sup>S10.7-2</sup>

- Digoxin concentration monitoring is unreliable after antidigoxin antibody administration.
- Monitoring high-risk patients during initiation of QT-prolonging antiarrhythmic medications and recognition of the syndrome when it occurs are the first steps. Temporary pacing is highly effective in managing torsades de pointes that is recurrent after potassium and magnesium supplementation.<sup>S10.7-3</sup> Isoproterenol can also be used to increase heart rate and abolish postectopic pauses.<sup>S10.7-3</sup>
  - Intravenous magnesium can suppress episodes of torsades de pointes without necessarily shortening QT, even when serum magnesium is normal.<sup>S10.7-4, S10.7-5</sup> Repeated doses may be needed, titrated to suppress ectopy and nonsustained VT episodes while precipitating factors are corrected.<sup>S10.7-4</sup> Magnesium toxicity (areflexia progressing to respiratory depression) can occur at high serum concentrations, but this risk is very small with the doses usually used to treat torsades de pointes, 1 to 2 g intravenously.<sup>S10.7-14</sup>

Allelic variants in clinical long QT disease genes have been identified in patients with medication-induced torsades de pointes.<sup>S10.7-7, S10.7-15–S10.7-18</sup> Further, whole exome sequencing implicates an increased burden of rare potassium channel variants in the risk of medication-induced torsades de pointes.<sup>S10.7-17, S10.7-19</sup> These findings do not yet support general genetic screening for prediction of medication-induced torsades de pointes. In long QT syndrome, genetic testing may be performed in the index case who experienced medication-induced torsades de pointes and, if he/she did not survive that event, electrocardiographic screening of first-degree relatives may be performed.

- Maintaining serum potassium between 4.5 mEq/L and 5 mEq/L shortens QT and may reduce the chance of recurrent torsades de pointes.<sup>S10.7-6, S10.7-7</sup>
- In large clinical trials, sodium channel blockers increased mortality among patients convalescing from MI,<sup>S10.7-20</sup> but similar trends were also seen with earlier trials of mexiletine<sup>S10.7-21</sup> and disopyramide.<sup>S10.7-22</sup> Based on CAST, flecainide is contraindicated in patients with ischemia, prior MI, and is avoided in patients with other structural heart diseases.<sup>S10.7-20</sup>

Sodium channel blockers increase defibrillation energy requirement and pacing thresholds<sup>S10.7-8, S10.7-9</sup>; as a consequence, patients may require reprogramming or revision of pacing or ICD systems or changes in their medication regimens (although modern pacing systems that provide automatic pacing threshold testing and adjustment of pacing output have mitigated the risk of loss of capture). Sodium channel blockers can “convert” AF to slow atrial flutter, which can show 1:1 atrioventricular conduction with wide QRS complexes that can be confused with VT.<sup>S10.7-23</sup>

Sodium channel blockers, like procainamide and flecainide, can occasionally precipitate the typical Brugada syndrome ECG.<sup>S10.7-24, S10.7-25</sup> This has been reported not only with antiarrhythmic medications but also with tricyclic antidepressants<sup>S10.7-26</sup> and cocaine<sup>S10.7-27</sup> ([www.brugadadrugs.org](http://www.brugadadrugs.org)).<sup>S10.7-28</sup> Whether this represents unmasking individuals with clinically unapparent Brugada syndrome (see Section 7.9.1.3) or one end of a broad spectrum of responses to sodium channel blockers is unknown.

In the setting of sodium-channel blocker toxicity, limited animal data suggest that administration of sodium, as sodium chloride or sodium bicarbonate, may improve conduction slowing or suppress frequent or cardioversion-resistant VT.<sup>S10.7-29</sup> Successful treatment with beta blockers<sup>S10.7-30</sup> and intravenous fat emulsion and/or extracorporeal membrane oxygenation has also been reported.<sup>S10.7-31</sup>

- QT-prolonging medications ([www.crediblemeds.org](http://www.crediblemeds.org))<sup>S10.7-32</sup> are not used in patients with congenital or acquired long QT syndrome unless there is no suitable alternative or the benefit greatly exceeds the risk. Episodes of torsades de pointes can be precipitated by exposure to a QT-prolonging medication, and underlying prolongation of the QT (from genetic and clinical risk factors) increases this risk.<sup>S10.7-10</sup> Medications implicated in torsades de pointes are found in several medication classes, including antiarrhythmics, antihistamines, antibiotics, antifungals, antidepressants, antipsychotics, opiates, and anticancer agents<sup>S10.7-10</sup> (Table 10).

## 10.8. Adult Congenital Heart Disease

### Recommendations for Adult Congenital Heart Disease

References that support the recommendations are summarized in Online Data Supplement 54.

COR	LOE	Recommendations
I	B-NR	1. Adult patients with repaired complex congenital heart disease presenting with frequent, complex, or sustained VA, or unexplained syncope should undergo evaluation for potential residual anatomic or coronary abnormalities. <sup>S10.8-1–S10.8-6</sup>
I	B-NR	2. In patients with adult congenital heart disease and complex or sustained VA in the presence of important residual hemodynamic lesions, treatment of hemodynamic abnormalities with catheter or surgical intervention as feasible is indicated prior to consideration of ablation or an ICD. <sup>S10.8-3, S10.8-7–S10.8-12</sup>
I	B-NR	3. In patients with adult congenital heart disease and hemodynamically unstable VT, an ICD is recommended after evaluation and appropriate treatment for residual lesions/ventricular dysfunction if meaningful survival of greater than 1 year is expected. <sup>S10.8-13–S10.8-17</sup>

Recommendations for Adult Congenital Heart Disease (Continued)		
COR	LOE	Recommendations
I	B-NR	4. In patients with adult congenital heart disease with SCA due to VT or VF in the absence of reversible causes, an ICD is recommended if meaningful survival of greater than 1 year is expected. <sup>S10.8-13-S10.8-17</sup>
IIa	B-NR	5. In adults with repaired tetralogy of Fallot physiology with high-risk characteristics and frequent VA, an electrophysiological study can be useful to evaluate the risk of sustained VT/VF. <sup>S10.8-18,S10.8-19</sup>
IIa	B-NR	6. In adults with repaired tetralogy of Fallot physiology and inducible VT/VF or spontaneous sustained VT, implantation of an ICD is reasonable if meaningful survival greater than 1 year is expected. <sup>S10.8-1,S10.8-3-S10.8-6,S10.8-18,S10.8-34-S10.8-36</sup>
IIa	B-NR	7. In patients with adult congenital heart disease with recurrent sustained monomorphic VT or recurrent ICD shocks for VT, catheter ablation can be effective. <sup>S10.8-21-S10.8-25</sup>
IIa	B-NR	8. In adults with repaired severe complexity adult congenital heart disease and frequent or complex VA, a beta blocker can be beneficial to reduce the risk of SCA. <sup>S10.8-26</sup>
IIa	B-NR	9. In patients with repaired moderate or severe complexity adult congenital heart disease with unexplained syncope and at least moderate ventricular dysfunction or marked hypertrophy, either ICD implantation or an electrophysiological study with ICD implantation for inducible sustained VA is reasonable if meaningful survival of greater than 1 year is expected. <sup>S10.8-5,S10.8-16,S10.8-27-S10.8-29</sup>
IIb	B-NR	10. In patients with adult congenital heart disease and severe ventricular dysfunction (LVEF <35%) and symptoms of heart failure despite GDMT or additional risk factors, ICD implantation may be considered if meaningful survival of greater than 1 year is expected. <sup>S10.8-14-S10.8-16,S10.8-20</sup>
III: Harm	B-NR	11. In patients with adult congenital heart disease who have asymptomatic VA, prophylactic antiarrhythmic therapy with class Ic medications (ie, flecainide, propafenone) or amiodarone is potentially harmful. <sup>S10.8-30-S10.8-32</sup>

## Synopsis

Tetralogy of Fallot (TOF) is defined as, congenital heart disease with RVOT obstruction and ventricular septal defect, often requiring right ventricle to pulmonary artery conduit placement or pulmonary valve replacement; includes TOF and double-outlet right ventricle. Moderate complexity congenital heart disease is defined as congenital heart disease requiring intracardiac surgical repair, other than isolated atrial and ventricular septal defects; includes TOF, aortic stenosis, coarctation of aorta, and Ebstein anomaly of the tricuspid valve. Severe complexity congenital heart disease is defined as cyanotic congenital heart disease requiring intracardiac repair in infancy, often with staging procedures;

includes transposition of the great arteries, truncus arteriosus, and single ventricle anatomy (Figure 16).

## Recommendation-Specific Supportive Text

1. The association of VT with RV hemodynamic abnormalities was first established in patients with repaired TOF.<sup>S10.8-33</sup> Multiple studies since that time have demonstrated the correlation of hemodynamic residue and ventricular dysfunction with risk of VT or SCD in patients with congenital heart disease.<sup>S10.8-1,S10.8-3-S10.8-6,S10.8-18,S10.8-34-S10.8-36</sup> Presentation with frequent or complex VA may indicate worsening hemodynamic function, coronary artery compromise, or decreased perfusion in the setting of ventricular hypertrophy. Evaluation may also include exercise testing to assess functional capacity.<sup>S10.8-35</sup> Careful evaluation of hemodynamic status for optimization of management is important.<sup>S10.8-9</sup> Potentially treatable residual hemodynamic problems may be identified during hemodynamic evaluation, such as outflow tract stenosis or significant regurgitation, which may benefit from either catheter or surgical intervention.<sup>S10.8-3,S10.8-7,S10.8-10,S10.8-12,S10.8-37</sup> Patients with markedly reduced ventricular function, elevated end-diastolic pressures, or pulmonary hypertension should be treated for underlying hemodynamic problems as part of their arrhythmia management.
2. The correlation of residual hemodynamic abnormalities with VA has been most extensively studied in patients with repaired TOF, where RV hypertension, residual pulmonary outflow tract obstruction or regurgitation, and RV dilation are risk factors for VT/SCD.<sup>S10.8-1,S10.8-2,S10.8-4,S10.8-8,S10.8-33,S10.8-34,S10.8-36</sup> In these studies, frequent PVCs correlated with risk of clinical or inducible sustained VT. A combined approach of surgery for structural abnormalities with map-guided arrhythmia surgery has been used with success,<sup>S10.8-3,S10.8-8,S10.8-10,S10.8-12</sup> but elimination of VT circuits may be limited by deep endocardial or LV origin of VT and limitations of operative mapping; an empiric approach to VT surgery is generally not recommended as it has limited effectiveness and carries risk of ventricular proarrhythmia.<sup>S10.8-38</sup> Pulmonary valve replacement in patients with TOF may result in improved hemodynamics and functional status, but it may not eliminate the risk of VT.<sup>S10.8-3,S10.8-12</sup>; postoperative reassessment for the need for an ICD is performed after the early recovery period.
3. Correction of residual hemodynamic/structural abnormalities contributing to VT may improve ventricular function and reduce symptoms, but



**Table 11. Congenital Heart Disease: Risk Factors for VA/SCD**

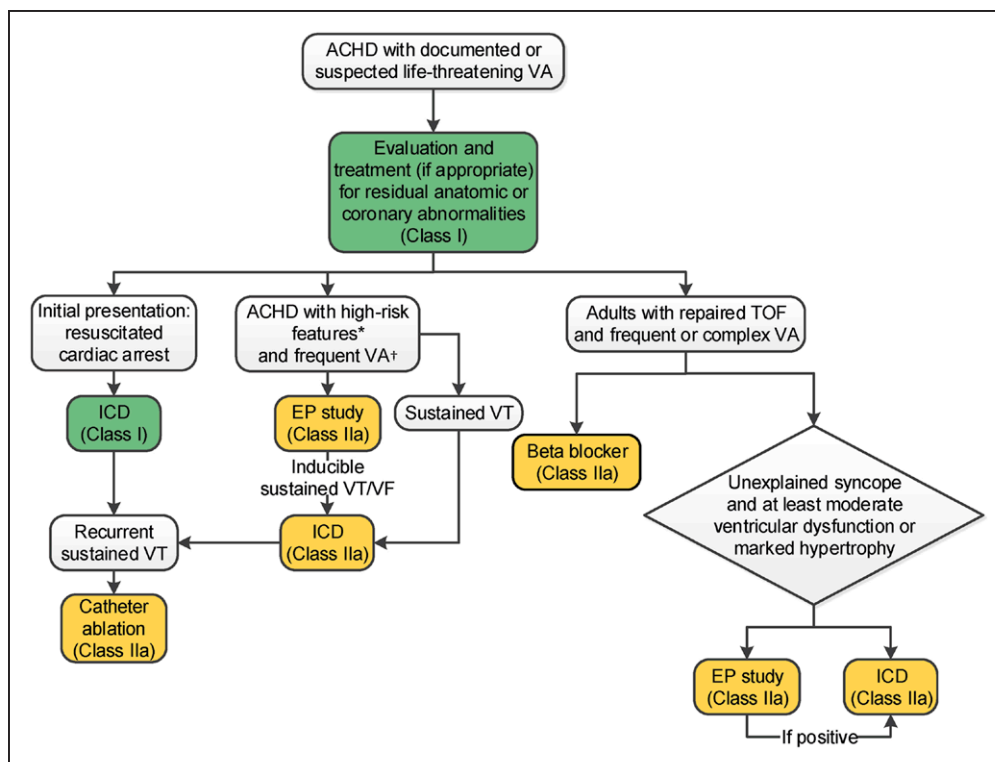
Congenital Heart Disease	Incidence of VA	Incidence of SCD	Higher Risk Characteristics
<b>Simple complexity</b>			
ASD <sup>S10.8-44,S10.8-47,S10.8-57—S10.8-62</sup>	2%–6%	<1.5%	Ventricular pacing RV dilatation Pulmonary hypertension NKX2.5 gene
VSD <sup>S10.8-27,S10.8-44,S10.8-47,S10.8-57—S10.8-63</sup>	3%–18%	<3%	
<b>Moderate complexity</b>			
Tetralogy of Fallot <sup>S10.8-1,S10.8-2,S10.8-5,S10.8-6,S10.8-28,S10.8-34,S10.8-36,S10.8-44,S10.8-46,S10.8-47,S10.8-54—S10.8-56,S10.8-62—S10.8-65</sup>	14%–31%	1.4%–8.3%	Unexplained syncope Frequent or complex VA Sustained VT QRS duration ≥180 ms Inducible sustained VT Atrial tachycardia Decreased LVEF Dilated right ventricle Severe PR Severe PS
Aortic stenosis <sup>S10.8-27,S10.8-44,S10.8-56</sup>	10%–34%	3%–20%	Unexplained syncope Severe LV hypertrophy Aortic stenosis mean pressure gradient >40 mm Hg Ventricular dysfunction
Coarctation of aorta <sup>S10.8-28,S10.8-29, S10.8-44,S10.8-46,S10.8-56,S10.8-62</sup>	2%	2%	Aneurysm at repair site Aortic stenosis Systemic hypertension Premature coronary artery disease
Ebstein's anomaly <sup>S10.8-45,S10.8-47,S10.8-55</sup>	2%	3%–6%	Cardiomegaly Atrial fibrillation Wide complex tachycardia Mitral regurgitation Dilated RVOT
<b>Severe complexity</b>			
Transposition of the great arteries <sup>S10.8-27,S10.8-44—S10.8-48,S10.8-51,S10.8-55,S10.8-56,S10.8-62</sup>			Atrial switch
Atrial switch	2%	3%–9.5%	Mustard repair
Arterial switch	2%	1%	Prior VSD closure
cc-TGA	10%	17%–25%	Unexplained syncope Atrial tachycardia Coronary orifice stenosis Systemic ventricular dysfunction Severe tricuspid regurgitation
Truncus arteriosus <sup>S10.8-66,S10.8-67</sup>	10%	4%	Multiple surgical repairs Coronary anomalies Ventricular dysfunction and/or hypertrophy
Fontan repair for univentricular physiology* <sup>S10.8-27,S10.8-37, S10.8-44,S10.8-45,S10.8-47,S10.8-55,S10.8-68</sup>	5%–17%	2.8%–5.4%	Atrial tachycardia Longer duration of follow-up Ascites Protein-losing enteropathy

\*Univentricular physiology includes: Tricuspid atresia, Double inlet left ventricle, Mitral atresia, Hypoplastic left heart, Unbalanced AV septal defect.

ASD indicates atrial septal defect; cc-TGA, congenitally corrected transposition of the great arteries; LV, left ventricular; LVEF, left ventricular ejection fraction; PR, pulmonary regurgitation; PS, pulmonary stenosis; RV, right ventricular; RVOT, right ventricular outflow tract; SCD, sudden cardiac death; VA, ventricular arrhythmia; VSD, ventricular septal defect; and VT, ventricular tachycardia.

it may inadequately prevent the risk of subsequent VT or SCA. The use of ICDs in adult congenital heart disease patients for secondary prevention accounts for approximately 50% of implantations presently, at a mean age of 36 to

41 years.<sup>S10.8-13–S10.8-17</sup> Patients with adult congenital heart disease experience appropriate shock rates of 3% to 6% per year, with equivalent or slightly increased frequency of appropriate shocks for secondary prevention indications.<sup>S10.8-14,S10.8-15,S10.8-17</sup>



**Figure 16. Prevention of SCD in patients with adult congenital heart disease.**

Colors correspond to Class of Recommendation in Table 1. See Section 10.8 for discussion. \*High-risk features: prior palliative systemic to pulmonary shunts, unexplained syncope, frequent PVC, atrial tachycardia, QRS duration  $\geq 180$  ms, decreased LVEF or diastolic dysfunction, dilated right ventricle, severe pulmonary regurgitation or stenosis, or elevated levels of BNP. †Frequent VA refers to frequent PVCs and/or nonsustained VT. ACHD indicates adult congenital heart disease; BNP, B-type natriuretic peptide; EP, electrophysiological; ICD, implantable cardioverter-defibrillator; LVEF, left ventricular ejection fraction; PVC, premature ventricular complexes; SCD, sudden cardiac death; TOF, tetralogy of Fallot; VA, ventricular arrhythmia; and VT, ventricular tachycardia.

Patients with adult congenital heart disease experience a higher rate of complications and inappropriate shocks compared with other adult populations.<sup>510.8-13–510.8-17,510.8-39</sup>

- Challenges of ICD implantation in patients with adult congenital heart disease may include anatomic complexity, intracardiac shunts, and limited vascular access to the ventricle. Patients with adult congenital heart disease receiving an ICD have an increased rate of complications of 26% to 45%, as well as inappropriate shocks in 15% to 25% of patients.<sup>510.8-13–510.8-16,510.8-40</sup> Limited studies on the use of subcutaneous implantable cardioverter-defibrillator implantation, particularly in patients with single ventricle anatomy,<sup>510.8-41</sup> report improved success by using right in addition to left parasternal lead positioning for screening.<sup>510.8-42</sup> Patients with a single ventricle or a systemic right ventricle may not tolerate defibrillation threshold testing, resulting in multiorgan system failure. Patients with complex anatomy, such as older patients with univentricular physiology, or patients with significantly reduced ventricular function, marked hypertrophy, or multiple prior

surgeries, may benefit from earlier consideration of heart transplantation before renal or liver dysfunction progresses.

- Patients with repaired TOF who are at an increased risk of sustained VT include those with prior palliative systemic to pulmonary shunts, unexplained syncope, frequent PVCs, atrial tachycardia, QRS duration  $\geq 180$  ms, decreased LVEF or diastolic dysfunction, dilated right ventricle, severe pulmonary regurgitation or stenosis, or elevated levels of BNP. Patients with TOF physiology and suboptimal hemodynamic status are more likely to have inducible sustained VT,<sup>510.8-18,510.8-19,510.8-33,510.8-35</sup> and inducible sustained VT correlated with an increased risk of SCA in a multicenter cohort study.<sup>510.8-19</sup> Evaluation of hemodynamics for residual abnormalities is important, with catheter or surgical treatment of important lesions prior to consideration of ICD implantation.
- In a multicenter cohort, inducible sustained VT in patients with TOF was an independent risk factor for subsequent clinical VT or SCD<sup>510.8-19</sup>; patients in that early study had cardiomegaly and prior palliative shunts. Patients with repaired

TOF account for approximately 50% of ICD implantations in adult congenital heart disease.<sup>S10.8-13–S10.8-16,S10.8-40</sup> Appropriate ICD shocks occur in up to 7.7% per year of patients with TOF receiving the ICD for primary prevention, compared with 9.8% per year in patients with a secondary prevention ICD.<sup>S10.8-20</sup> In another study including patients with TOF as well as other lesions, inducible sustained VT did not correlate with subsequent appropriate ICD shocks.<sup>S10.8-14</sup> Because of the high incidence of inappropriate shocks in 20% to 30% and complications in at least 30% of patients with adult congenital heart disease,<sup>S10.8-14–S10.8-17,S10.8-39,S10.8-40,S10.8-43</sup> in addition to financial and psychological burdens, shared decision-making regarding primary prevention ICDs is essential.

7. In patients with recurrent sustained monomorphic VT, catheter ablation of VT can be effective.<sup>S10.8-21–S10.8-25</sup> Hemodynamic repair, at the time that an arrhythmia is being ablated surgically, should be considered. For patients with complex adult congenital heart disease, care should be provided at experienced centers. After successful catheter ablation of VT, implantation of an ICD for those who do not have an ICD is an individualized decision based on overall functional and physiological status and shared decision making. Careful monitoring during follow-up for recurrent arrhythmias is essential.
8. The highest risk of SCD associated with repaired congenital heart disease reported from large contemporaneous cohorts is in patients with transposition of the great arteries with atrial baffle repair, Ebstein anomaly of the tricuspid valve, aortic stenosis, and univentricular physiology.<sup>S10.8-44–S10.8-47</sup> Patients with Senning or Mustard atrial baffle repairs are at an increased risk for SCA, particularly during exertion.<sup>S10.8-48</sup> The atrial baffle is noncompliant restricting ability to augment volume and may be associated with pulmonary vein stenosis and increased end-diastolic pressures. RV ischemia and infarction occur, with perfusion defects identified by myocardial perfusion studies in >40% of patients in this population.<sup>S10.8-49,S10.8-50</sup> Risk factors for cardiac arrest in patients with transposition and atrial baffle repairs include prior ventricular septal defect closure, symptoms of HF, atrial arrhythmia, RVEF <30% to 35%, and QRS duration ≥140 ms.<sup>S10.8-48,S10.8-51</sup> In the single multicenter study assessing outcomes after implantation of an ICD in patients with prior atrial baffle repair of transposition of the great arteries, the lack of beta blockers was associated with a high risk of appropriate ICD therapy.<sup>S10.8-26</sup> Atrial arrhythmias frequently precede VT in transposition patients, and treatments for atrial tachycardia including catheter ablation, antitachycardia pacing algorithms,

and beta blockers are important to reduce ICD shocks.<sup>S10.8-26,S10.8-52,S10.8-53</sup>

9. The risk of SCD is increased among patients with adult congenital heart disease compared with the general population, with the median age at death ranging from 30 to 49 years of age.<sup>S10.8-27,S10.8-44,S10.8-47,S10.8-54,S10.8-55</sup> The risk of SCD is highest among patients with moderate or severe complexity congenital heart disease, and accounts for approximately 25% of cardiac causes of death.<sup>S10.8-5,S10.8-27,S10.8-28,S10.8-44–S10.8-46,S10.8-55,S10.8-56</sup> Patients with septal defects and a positive family history of septal defects, cardiomyopathy, or bundle-branch block/conduction defects may have the gene mutation *NKX2.5*, which portends an increased risk of early SCD; genetic testing and early consideration of ICD implantation if positive is warranted.<sup>S10.8-57–S10.8-59</sup> Patients with repaired complex forms of congenital heart disease have undergone multiple intracardiac surgeries in the first few decades of life with resultant hypertrophy and risk for subendocardial ischemia as well as scar formation contributing to VT/VF. Risk factors for SCD include increasing complexity of heart disease, VA, SVT, progressive increase in QRS duration, systemic ventricular dysfunction, and subpulmonary ventricular dysfunction.<sup>S10.8-1,S10.8-5,S10.8-6,S10.8-14,S10.8-28,S10.8-29,S10.8-36,S10.8-45–S10.8-47,S10.8-55</sup> Extrapolation of data regarding specific measures of ventricular function warranting implantation of primary prevention ICDs from adult patients with NICM is unrealistic. The development of unexplained syncope in patients with moderate or severe complexity adult congenital heart disease may be a harbinger of risk for SCD; electrophysiological study with consideration for an ICD as primary prevention can be beneficial.
10. ICDs implanted in patients with adult congenital heart disease, who are in their 40s and 50s, for primary prevention indications now account for >40% to 67% of implanted devices in patients with adult congenital heart disease.<sup>S10.8-13,S10.8-15,S10.8-16,S10.8-41</sup> In these patients, appropriate shocks are delivered in 14% to 22% of patients in the first 3 to 5 years of follow-up.<sup>S10.8-13,S10.8-15,S10.8-16</sup> In patients with congenital heart disease and severely depressed ventricular function, or single ventricle anatomy, defibrillation threshold testing may pose excessively high risk. In patients without vascular access or prior Fontan repairs, the risk of reoperation with sternotomy for epicardial ICD implantation may outweigh the potential benefits, and consideration for transplant evaluation may be preferable. Subcutaneous implantable

cardioverter-defibrillator implantation may be an appropriate option for some patients.<sup>S10.8-42,S10.8-53</sup>

11. Adult patients with complex adult congenital heart disease typically have hypertrophy and ventricular dysfunction of varying degrees, increasing their risk for worsening ventricular function with antiarrhythmic medications. In the only large study of antiarrhythmic medications for congenital heart disease, the use of flecainide was associated with proarrhythmia in 5.8% of patients and SCA in 3.9% of patients.<sup>S10.8-30</sup> The use of amiodarone is generally reserved for refractory symptomatic VA or asymptomatic VA that can aggravate ventricular dysfunction, due to the high risk of adverse effects including thyroid dysfunction, particularly among females and patients with univentricular physiology.<sup>S10.8-31,S10.8-32</sup>

## 11. DEFIBRILLATORS OTHER THAN TRANSVENOUS ICDS

### 11.1. Subcutaneous Implantable Cardioverter-Defibrillator

Recommendations for Subcutaneous Implantable Cardioverter-Defibrillator		
References that support the recommendations are summarized in Online Data Supplement 55.		
COR	LOE	Recommendations
I	B-NR	1. In patients who meet criteria for an ICD who have inadequate vascular access or are at high risk for infection, and in whom pacing for bradycardia or VT termination or as part of CRT is neither needed nor anticipated, a subcutaneous implantable cardioverter-defibrillator is recommended. <sup>S11.1-1-S11.1-5</sup>
IIa	B-NR	2. In patients who meet indication for an ICD, implantation of a subcutaneous implantable cardioverter-defibrillator is reasonable if pacing for bradycardia or VT termination or as part of CRT is neither needed nor anticipated. <sup>S11.1-1-S11.1-4</sup>
III: Harm	B-NR	3. In patients with an indication for bradycardia pacing or CRT, or for whom antitachycardia pacing for VT termination is required, a subcutaneous implantable cardioverter-defibrillator should not be implanted. <sup>S11.1-1-S11.1-4,S11.1-6-S11.1-8</sup>

### Synopsis

In patients being considered for a subcutaneous implantable cardioverter-defibrillator, a preimplant ECG to establish QRS-T wave morphology is needed to reduce the risk of under sensing of VT/VF and the risk of inappropriate shocks.<sup>S11.1-9-S11.1-11</sup> The subcutaneous implantable cardioverter-defibrillator is implanted using primarily anatomical landmarks, thereby minimizing the

need for fluoroscopy. The subcutaneous implantable cardioverter-defibrillator consists of a pulse generator that is placed at the midaxillary line between the fifth and sixth intercostal spaces and a lead with 2 sensing electrodes and a shocking coil, positioned subcutaneously adjacent to the sternum. As with the transvenous ICD, the pulse generator housing serves as an electrode for defibrillation but, in addition, it can also serve as an optional electrode for sensing. The subcutaneous implantable cardioverter-defibrillator cannot achieve adequate arrhythmia sensing for all patients, and electrocardiographic screening to assess sensing is required prior to implantation.<sup>S11.1-10,S11.1-11</sup> Some advocate exercise testing after device implantation to ensure proper sensing with exercise.

Both transvenous and subcutaneous implantable cardioverter-defibrillators have SVT-VT discriminators that can be programmed to facilitate discrimination of SVT from VT; however, these discriminators do not always work. If sustained VT is confirmed, therapy to terminate the arrhythmia is delivered. All ICDs provide shocks to terminate VT or VF, but shocks in an awake patient are painful and associated with decreased QoL. Transvenous ICDs are capable of bradycardia pacing as well as antitachycardia pacing that can terminate many VTs painlessly. Subcutaneous implantable cardioverter-defibrillators provide limited postshock bradycardia pacing but do not provide either bradycardia or antitachycardia pacing.

The subcutaneous implantable cardioverter-defibrillator recommendations supplant, but do not nullify, the need for waiting periods and other requirements to be satisfied for ICD/CRT implantation specified in other parts of this document.

### Recommendation-Specific Supportive Text

1. The subcutaneous implantable cardioverter-defibrillator was designed to avoid the need for venous access and some of the complications of inserting transvenous lead(s)<sup>S11.1-1-S11.1-4</sup> that include pneumothorax, hemothorax, and cardiac tamponade.<sup>S11.1-12</sup> Difficulties in achieving venous access can prolong the implantation procedure and occasionally result in failed ICD implantation. These difficulties are more likely to be encountered in patients with limited venous access such as patients with ESRD. In a study of 27 patients with ESRD, the subcutaneous implantable cardioverter-defibrillator was not associated with an increased risk of procedural complications or inappropriate shocks.<sup>S11.1-5</sup> The risk of infection appears to be lower with subcutaneous implantable cardioverter-defibrillators than with transvenous ICDs.<sup>S11.1-1-S11.1-4</sup> Therefore, a subcutaneous

implantable cardioverter-defibrillator may be preferred in patients who are at high risk of infection, such as those with a prior device infection, ESRD, diabetes mellitus, or who are chronically immunosuppressed.

- Nonrandomized studies show that the subcutaneous implantable cardioverter-defibrillator reliably detects and converts VF during defibrillation threshold testing and successfully terminates spontaneous sustained VT that occurs during follow-up.<sup>S11.1-1,S11.1-13</sup> In 1 study of 314 patients, the 180-day complication-free rate was 99%, and the success of VF termination with first shock was >90%.<sup>S11.1-2</sup> All spontaneous episodes of VT/VF recorded in 21 patients (6.7%) were successfully converted, and there were no lead failures, endocarditis or bacteremia, tamponade, cardiac perforation, pneumothorax, or hemothorax associated with the subcutaneous implantable cardioverter-defibrillator.<sup>S11.1-2</sup> In 472 patients enrolled in the EFFORTLESS (Evaluation of Factors Impacting Clinical Outcome and Cost Effectiveness of the S-ICD) registry,<sup>S11.1-3</sup> the complication-free rate was 94%, at 360 days. First shock conversion efficacy was 88% with 100% overall successful clinical conversion after a maximum of 5 shocks. In 882 patients enrolled in investigational device exemption trials and the EFFORTLESS registry,<sup>S11.1-4</sup> 111 spontaneous VT/VF events were treated in 59 patients; 90.1% were terminated with 1 shock, and 98.2% were terminated within the 5 available shocks. The estimated 3-year inappropriate shock rate was 13.1% most due to oversensing of cardiac signals, and mortality was 4.7%. Device-related complications occurred in 11.1% of patients. An ongoing trial will compare the effect of the subcutaneous implantable cardioverter-defibrillator with that of the transvenous ICD on the outcomes of inappropriate shocks, complications, shock efficacy, and mortality.<sup>S11.1-13</sup>
- The subcutaneous implantable cardioverter-defibrillator is incapable of bradycardia pacing, biventricular pacing, or antitachycardia pacing. Therefore, patients who need any of these types of pacing from an ICD should not be offered a subcutaneous implantable cardioverter-defibrillator.<sup>S11.1-6</sup> Some clinical scenarios may come up in which a transvenous pacemaker for bradycardia pacing in a patient with a subcutaneous implantable cardioverter-defibrillator which is needed; this can be performed as long as the pacing is not unipolar. Leadless pacing devices for patients who require bradycardia pacing will be evaluated with the subcutaneous implantable cardioverter-defibrillator in the near future.

## 11.2. Wearable Cardioverter-Defibrillator

### Recommendations for Wearable Cardioverter-Defibrillator

References that support the recommendations are summarized in Online Data Supplement 56.

COR	LOE	Recommendations
Ia	B-NR	1. In patients with an ICD and a history of SCA or sustained VA in whom removal of the ICD is required (as with infection), the wearable cardioverter-defibrillator is reasonable for the prevention of SCD. <sup>S11.2-1-S11.2-4</sup>
Iib	B-NR	2. In patients at an increased risk of SCD but who are not ineligible for an ICD, such as awaiting cardiac transplant, having an LVEF of 35% or less and are within 40 days from an MI, or have newly diagnosed NICM, revascularization within the past 90 days, myocarditis or secondary cardiomyopathy or a systemic infection, the wearable cardioverter-defibrillator may be reasonable. <sup>S11.2-1-S11.2-5</sup>

### Synopsis

The wearable cardioverter-defibrillator is a vestlike device worn under the clothing that continuously monitors the heart rhythm and automatically delivers an electric shock when VF or VT is detected. This device is intended to be worn continuously, 24 hours per day, except when the wearer is bathing or showering. The wearable cardioverter-defibrillator has been approved in the United States by the US Food and Drug Administration for patients who are "at risk for SCA and are not candidates for or refuse an implantable defibrillator."<sup>S11.2-6</sup> A science advisory from the AHA summarizes the data and recommendations for the use of the wearable cardioverter-defibrillator.<sup>S11.2-4</sup> Effectiveness of the wearable cardioverter-defibrillator in recognition and defibrillation of VF has been demonstrated in a number of studies, although no RCTs support the use of the wearable cardioverter-defibrillator. Among 3569 patients who received the device for various reasons, for at least 1 day in the US manufacturer registry, there were 80 VT/VF events in 59 patients, with a frequency of 1.7% per patient-year. First shock efficacy was 99%, with postshock survival of 90%. Overall, 2% of the patients received an inappropriate shock.<sup>S11.2-1</sup>

### Recommendation-Specific Supportive Text

- Removal of an ICD for a period of time, most commonly due to infection, exposes the patient to risk of untreated VT/SCD unless monitoring and access to emergency external defibrillation is maintained. In 1 series of 354 patients who received the wearable cardioverter-defibrillator, the indication was infection in 10%.<sup>S11.2-3</sup> For patients with a history of SCA or sustained VA,

the wearable cardioverter-defibrillator may allow the patient to be discharged from the hospital with protection from VT/SCA until the clinical situation allows reimplantation of an ICD.

2. The patients listed in this recommendation are represented in clinical series and registries that demonstrate the safety and effectiveness of the wearable cardioverter-defibrillator. Patients with recent MI, newly diagnosed NICM, recent revascularization, myocarditis, and secondary cardiomyopathy are at increased risk of VT/SCA. However, the wearable cardioverter-defibrillator is of unproven benefit in these settings, in part because the clinical situation may improve with therapy and time. In patients awaiting transplant, even with anticipated survival <1 year without transplant, and depending on clinical factors such as use of intravenous inotropes and ambient VA, a wearable cardioverter-defibrillator may be an alternative to an ICD.

### 11.3. Automated External Defibrillator

External defibrillation can save lives when used within minutes of the onset of VF. The AED is an efficient method of delivering defibrillation to persons experiencing out-of-hospital cardiac arrest, and its use by first responders is safe and effective.<sup>511.3-1-511.3-3</sup> Federal efforts have been effective in placing AEDs in airports/airplanes and federal buildings, while varying efforts at the state and community levels have been effective in placing AEDs in many, but not all, schools, sporting events, high-density residential sites, and airports as well as in police and fire department vehicles.<sup>511.3-4-511.3-7</sup> Resuscitation protocols with or without AED placement are required in most states for fitness clubs, although alternate indoor exercise facilities may have higher rates of arrest and provide for increased survival over other indoor public sites.<sup>511.3-8</sup> In a study population of 21 million, survival to hospital discharge was nearly twice as high when an AED was applied for out-of-hospital cardiac arrest.<sup>511.3-9</sup> Expanded and coordinated placement of AEDs in the community, including in high-risk geographic locations such as schools and organized sports arenas, can substantially increase the proportion of patients with cardiac out-of-hospital cardiac arrest who receive AED therapy.<sup>511.3-10</sup> The US Food and Drug Administration has approved over-the-counter sales of AEDs. Approximately 70% of SCAs occur in the home, and the rate of survival to hospital discharge after AED placement by emergency medical services is significantly lower for arrest at home (12%) versus public settings (34%).<sup>511.3-11</sup> However, in an RCT of AEDs, home AED placement did not improve the survival of patients recovering from an anterior MI.<sup>511.3-12</sup> Appropriate device location to reduce time delay after onset of SCA is criti-

cal. In addition to prevention, critical components of survival from SCA include immediate recognition and activation of the emergency response system, early high-quality CPR, and rapid defibrillation for shockable rhythms.<sup>511.3-13</sup>

## 12. SPECIAL CONSIDERATIONS FOR CATHETER ABLATION

### Recommendations for Catheter Ablation

References that support the recommendations are summarized in Online Data Supplement 57.

COR	LOE	Recommendations
I	C-LD	1. In patients with bundle-branch reentrant VT, catheter ablation is useful for reducing the risk of recurrent VT and ICD shocks. <sup>512-1-512-3</sup>
Ia	B-NR	2. In patients with structural heart disease who have failed endocardial catheter ablation, epicardial catheter ablation can be useful for reducing the risk of recurrent monomorphic VT. <sup>512-4-512-6</sup>

### Synopsis

Bundle-branch reentrant VT is due to reentry involving the bundle branches. Catheter ablation is the preferred therapy for this VT, which is encountered in <10% of patients with recurrent sustained monomorphic VT and structural heart disease (see Section 7.2.3).

### Recommendation-Specific Supportive Text

1. Bundle-branch reentrant VT can occur in any form of heart disease associated with slow infra-Hisian conduction. The most common mechanism involves antegrade conduction over the right bundle branch and retrograde conduction over the left bundle branch, thereby producing left bundle-branch block QRS morphology during VT, which is often rapid and poorly tolerated. Catheter ablation of the right or left bundle branch interrupts the circuit and is usually curative.<sup>512-1-512-3</sup> After ablation, severely impaired atrioventricular conduction can be present, requiring permanent pacing, which can have hemodynamic consequences.<sup>512-4,512-6</sup> Many patients have other inducible scar related VTs or meet eligibility for an ICD due to severity of associated heart disease.
2. Endocardial catheter ablation failure can be due to location of the arrhythmia substrate in the midmyocardium or epicardium, and this is more likely in patients with nonischemic rather than ischemic cardiomyopathy, and in arrhythmogenic right ventricular cardiomyopathy.<sup>512-7-512-9</sup> In the

HELP-VT trial,<sup>512-4</sup> epicardial ablation was required in 30% of patients with VT related to NICM compared with 1.2% of patients with ischemic cardiomyopathy. A wide QRS with marked slurring of the initial portion of the QRS and a QS complex in the lateral or inferior leads during VT suggests an epicardial circuit in NICM, but the ECG does not reliably predict epicardial VT locations in patients with prior MI. Preprocedural cardiac MRI and intraprocedural electroanatomic mapping are useful tools to guide the localization of epicardial scar that may be the source of reentrant VT.<sup>512-8,512-10</sup> Pericardial adhesions prevent percutaneous access in some patients, notably many with prior cardiac surgery. Percutaneous pericardial access for mapping and ablation is associated with a serious complication rate of approximately 5% and tamponade from RV puncture or laceration that can require emergent surgery or be fatal, coronary artery injury and phrenic nerve injury can occur.<sup>512-11,512-12</sup> Reported experience is from tertiary referral centers.

### 13. POSTMORTEM EVALUATION OF SCD

Recommendations for Postmortem Evaluation of SCD		
References that support the recommendations are summarized in Online Data Supplement 58.		
COR	LOE	Recommendations
I	B-NR	1. In victims of SCD without obvious causes, a standardized cardiac-specific autopsy is recommended. <sup>513-1,513-2</sup>
I	B-NR	2. In first-degree relatives of SCD victims who were 40 years of age or younger, cardiac evaluation is recommended, with genetic counseling and genetic testing performed as indicated by clinical findings. <sup>513-3</sup>
IIa	B-NR	3. In victims of SCD with an autopsy that implicates a potentially heritable cardiomyopathy or absence of structural disease, suggesting a potential cardiac channelopathy, postmortem genetic testing is reasonable. <sup>513-4-513-7</sup>
IIa	C-LD	4. In victims of SCD with a previously identified phenotype for a genetic arrhythmia-associated disorder, but without genotyping prior to death, postmortem genetic testing can be useful for the purpose of family risk profiling. <sup>513-8</sup>

#### Recommendation-Specific Supportive Text

1. A comprehensive postmortem protocol has been recommended for the routine evaluation of subjects (typically <40 years of age) who die suddenly without a prior diagnosis of a condition and

circumstances of death that could be reasonably implicated in the cause of unexpected SCD.<sup>513-1</sup> One study documented the added value of post-mortem examination at a specialized cardiac pathology center,<sup>513-2</sup> with particular value for clarifying an apparent overdiagnosis of cardiomyopathy by nonspecialized centers. Pathological findings limited to the specialized conduction system were demonstrated in 22% of cases.<sup>513-9</sup> A misdiagnosis of cardiomyopathy was reported in 37% of referred cases that were ultimately determined to be structurally normal. The etiologic data for specialized cardiac evaluation are not generalizable to the overall population because of skewing of age at the time of SCD. In another study of SCD patients at ages ranging from <1 year to >80 years (mean, 38.2 years; median, 38 years), the peak incidence of SCD occurred between the ages of 31 and 60 years, with a 5- to 7-fold excess of males/females in that age range.<sup>513-10</sup> For the overall group, 42% of SCD were due to ischemic heart disease, 12% viral myocarditis, and 5% cardiomyopathy, with 15% being unexplained by autopsy. For the subgroup <35 years of age, 13.5% were attributed to ischemic heart disease and 24.9% were unexplained. In the subgroup >55 years of age, only 0.8% were unexplained. In patients who die suddenly despite an ICD, interrogation of the ICD is important to confirm proper device functioning and can provide information on the mechanism of death.

2. Comprehensive cardiac screening including 12-lead ECG, possible signal averaged ECG, echocardiogram, and ambulatory rhythm monitoring or exercise testing of first-degree relatives of decedents with sudden unexpected death may identify a probable heritable cardiac cause of death in up to 30% of cases.<sup>513-11-513-13</sup> Genetic testing should be targeted based on the results of initial evaluation.<sup>513-3</sup> Genetic testing in selected first-degree relatives may result in identification of inherited conditions including long QT syndrome, catecholaminergic polymorphic ventricular tachycardia, Brugada syndrome, arrhythmogenic right ventricular cardiomyopathy, and HCM in 4% to 30% of families.<sup>513-11,513-12,513-14</sup>
3. For the purpose of family risk profiling, it is important to use the disease-specific genetic test panel that corresponds to the autopsy findings. Risk profiling of family members of an SCD victim suspected of having an inherited cardiomyopathy at autopsy is important. Although phenotyping of surviving family members is crucial, genotyping of the SCD proband provides a mechanism for efficient follow-up evaluation of those relatives with the disease-causing mutation found

in the proband. To be able to harvest quality DNA for such testing, medical examiners, hospital pathologists, and private pathologists need standards for harvesting and storing samples for later genetic testing. Family members of SCD probands who died suddenly (first cardiac event, death from natural causes, last seen alive and well within 12 hours), with autopsy findings showing structural abnormalities of uncertain significance (eg, ventricular hypertrophy, myocardial fibrosis, or minor ischemic heart disease [n=41]) had a 51% prevalence of genetic variants associated with sudden arrhythmic deaths, compared with 47% among a comparison group in which proband autopsies were completely negative.<sup>513-15</sup>

4. Identification of the genotype can facilitate family screening.<sup>513-16</sup>

## 14. TERMINAL CARE

Recommendations for Terminal Care		
References that support the recommendations are summarized in Online Data Supplement 59.		
COR	LOE	Recommendations
I	C-EO	1. At the time of ICD implantation or replacement, and during advance care planning, patients should be informed that their ICD shock therapy can be deactivated at any time if it is consistent with their goals and preferences.
I	C-EO	2. In patients with refractory HF symptoms, refractory sustained VA, or nearing the end of life from other illness, clinicians should discuss ICD shock deactivation and consider the patients' goals and preferences.

### Synopsis

A particularly challenging area of medicine is recognizing when life-prolonging therapies may become burdensome or even harmful. This is particularly true near the end of life for patients with ICDs in whom once life-prolonging shocks may only cause unnecessary morbidity and distress to both patients and loved ones.

### Recommendation-Specific Supportive Text

1. Current evidence suggests that many patients are unaware of the possibility that their ICD can be deactivated without surgery.<sup>514-1-514-3</sup> During decision-making, clinicians do not routinely inform patients about ICD deactivation.<sup>514-4</sup> Clinicians even disagree on whether discussions of deactivation should occur when patients are making a decision about an ICD-related procedure.<sup>514-5</sup> As a result, patients often do not include wishes

about deactivation in advance care planning documents.<sup>514-6</sup> Consequently, surrogates usually make decisions about ICD deactivation without any prior discussions with the patient.<sup>514-6</sup> In hypothetical scenarios, patients with ICDs were able to identify scenarios in which they might choose to deactivate their ICD.<sup>514-1,514-7</sup> This discussion can occur at any time, but it is particularly important to have it at the time of initial ICD implantation, at the time of reimplantation, and during preparation of advance care plans.

2. When ICDs are not deactivated at the end of life, patients and families suffer unnecessarily. Families have had unpleasant experiences of watching their loved one die while getting shocked repeatedly by an ICD.<sup>514-8</sup> In 1 survey of hospice staff, half of those surveyed noted that a deceased patient had been shocked by an ICD during the year prior to the survey.<sup>514-9</sup> This is unnecessary and easily preventable by having caring, patient-centered discussions with patients and their loved ones. In general, patients want their clinicians to initiate these discussions,<sup>514-2,514-10</sup> so this recommendation is carefully worded to put the responsibility of initiating the discussion on the clinician. Ethically, patients and surrogates are free to choose to deactivate antitachycardia function.<sup>514-11-514-13</sup> Most patients only elect deactivation of the antitachycardia functions while leaving the pacing function on. Even at the end of life, pacing (either for bradycardia or for resynchronization therapy) may be an important aspect of the patient's QoL and may facilitate more alert and meaningful personal interactions. These differences are easily misunderstood, so they need careful explanation.

## 15. SHARED DECISION-MAKING

Recommendations for Shared Decision-Making		
References that support the recommendations are summarized in Online Data Supplement 60.		
COR	LOE	Recommendations
I	B-NR	1. In patients with VA or at increased risk for SCD, clinicians should adopt a shared decision-making approach in which treatment decisions are based not only on the best available evidence but also on the patients' health goals, preferences, and values. <sup>515-1-515-5</sup>
I	B-NR	2. Patients considering implantation of a new ICD or replacement of an existing ICD for a low battery should be informed of their individual risk of SCD and nonsudden death from HF or noncardiac conditions and the effectiveness, safety, and potential complications of the ICD in light of their health goals, preferences, and values. <sup>515-1-515-5</sup>



## Synopsis

During most of their lives, people prefer to do everything possible to prevent SCD and prolong life. However, many people may get to a point in their lives where SCD is not the worst outcome. Patients may report a desire to die in their sleep.<sup>515-6</sup> Decisions related to SCD can be quite emotional; according to the patient's wishes, shared decision regarding end-of-life therapy making may involve caregivers such as family members or friends.

## Recommendation-Specific Supportive Text

1. Consideration of patient preferences is important for VA diagnosis and management decisions. Patient preferences for invasive therapies and acceptance of SCD risk vary and may evolve throughout the course of their illness. The writing committee endorses a shared decision-making approach as part of the general care for patients at risk for VA and SCD. A commonly accepted definition of the shared decision-making<sup>515-7</sup> includes 4 components: 1) at least 2 participants, the clinician and patient, be involved; 2) both parties share information; 3) both parties take steps to build a consensus about the preferred treatment; and 4) an agreement is reached on the treatment to implement. Sharing a decision does not mean giving a patient a list of risks and benefits and telling them to make a decision—a practice some authors have called “abandonment.”<sup>515-8</sup> Notably, a recommendation based on evidence or guidelines alone is not shared decision-making. Rather, a recommendation based both on the evidence as well as an understanding of the patients' health goals, preferences, and values is essential to achieving true shared decision-making. Also, the possibility of deactivation of an existing ICD should be discussed with patients who have terminal illnesses.
2. ICDs prolong lives as highlighted in many places within this guideline. However, a patient with HF or advanced noncardiac illness may elect to forgo replacement of an ICD when faced with the prospect of continual decline in health and functional status from either progressive HF or some other competing morbidity.

Unfortunately, research suggests that patients are ill-informed when faced with understanding the risks, benefits, and downstream burdens of their ICDs. Patients with an ICD tend to overestimate the benefit of this therapy and underestimate its risks.<sup>515-1-515-3</sup> Likewise, patients who decline an ICD also frequently underestimate their personal risk of VA and SCD.<sup>515-4,515-5</sup> Stud-

ies of clinician decision-making demonstrate that clinicians often overestimate the benefits while downplaying the potential harms.<sup>515-3</sup>

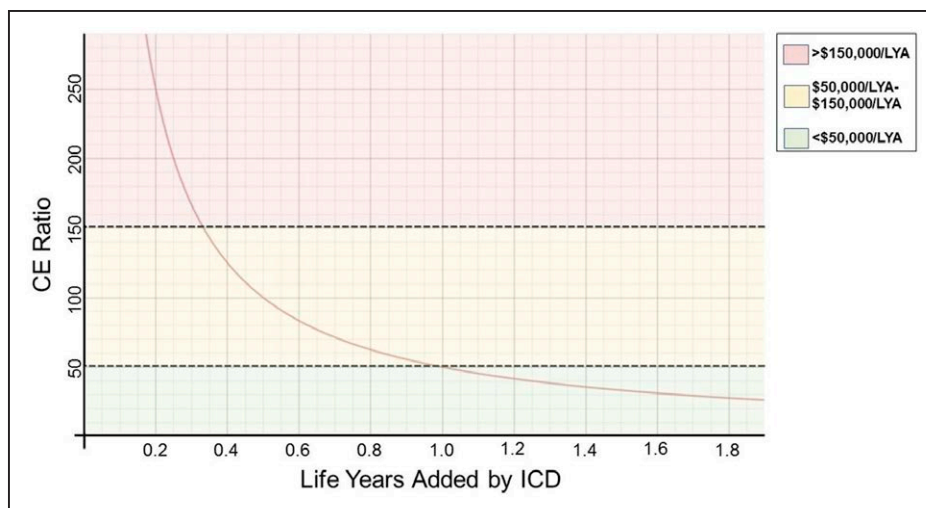
In kind, ICD replacement is also an important point in time where patients and clinicians should discuss whether replacing an ICD is still consistent with the patients' goals. What made sense at 70 years of age may not make sense at 80 years of age. Patients may have had progressive disease or developed poor QoL. These factors can all change the risk/benefit ratio of the ICD and the patients' preferences.

## 16. COST AND VALUE CONSIDERATIONS

The key principles of value assessment as part of clinical practice guidelines have been discussed in detail.<sup>516-1</sup> Economic outcomes of clinical management strategies can be documented empirically using the same research designs as used in establishing clinical outcomes, including RCTs and observational comparisons. In addition, simulation models are often used to assess the value of management strategies, because the standard for cost-effectiveness studies is to compare life-time outcomes, and clinical studies usually have follow-up of a few years at most. Standards for economic modeling in health care have been published by an expert group.<sup>516-2</sup>

Economic assessments of alternative management strategies for VA and prevention of SCD have primarily evaluated ICDs, including several RCTs<sup>516-3-516-7</sup> and observational studies,<sup>516-8,516-9</sup> and simulation models.<sup>516-10-516-14</sup> In all studies, patients who received ICDs had higher long-term costs. The high initial cost of the ICD device and the implantation procedure leads to higher long-term costs, because there are few, if any, subsequent cost-savings from implanting an ICD. ICDs without resynchronization capability do not reduce hospital readmissions and may increase late costs due to device monitoring, complications, and replacement. However, the cost of the device and the procedure may change significantly over time.

The trial based assessments of the cost-effectiveness of the ICD are based on 3 to 6 years of follow-up, which is considerably shorter than the lifetime perspective that is standard in cost-effectiveness models. Because most of the incremental cost of the ICD is incurred immediately, while most of the potential effectiveness (life-years of survival added by the ICD) is accrued over many years, estimates of ICD cost-effectiveness based on limited trial follow-up have a systematic bias toward showing lower value. Trial based economic studies that projected long-term ICD outcomes have consistently found more favorable cost-effectiveness ratios than estimates restricted to the duration of trial follow-up.<sup>516-4-516-7</sup> A



**Figure 17. Incremental cost-effectiveness of ICD by years of life added\* (example).**

\*Figure based on formula: Incremental cost-effectiveness ratio =  $\$50,000/\text{QALYs}$ . CE indicated cost effectiveness, ICD, implantable cardioverter-defibrillator; LYA, life year added; and QALYs, quality-adjusted life-years.

lifetime simulation model applied to each major trial of primary prevention ICDs also reported consistently more favorable estimates of cost-effectiveness than the estimates based on limited trial follow-up.<sup>516-11</sup> Because the framework proposed for assessing value in ACC/AHA clinical practice guidelines uses benchmarks based on lifetime estimates,<sup>516-1</sup> we have generally relied on the model-based estimates of ICD cost-effectiveness in applying value ratings to recommendations in this guideline.

The initial cost of an ICD device is similar regardless of the clinical indication, so variations in ICD cost-effectiveness are driven primarily by potential differences in clinical effectiveness in extending survival in different patient populations. The effect of the years of life added by an ICD on its incremental cost-effectiveness ratio is illustrated in Figure 17: the cost-effectiveness ratio becomes rapidly unfavorable as the extension in survival time falls below 1 year, particularly below 0.5 year. This inverse relation strongly suggests that the value provided by an ICD will be highest when the risk of arrhythmic death due to VT/VF is relatively high and the risk of nonarrhythmic death (either cardiac or noncardiac) is relatively low, such that a meaningful increase in survival can be expected from the ICD. Thus, appropriate patient selection is fundamental to high value care in using the ICD to prevent SCD. It should also be recognized that cost-effectiveness is also influenced by the costs for the ICD and implantation procedure, which are likely to change significantly over time.

The empirical evidence suggests that ICDs are not effective for primary prevention of SCD when implanted early after CABG<sup>516-15</sup> or an acute myocardial infarction.<sup>516-16,516-17</sup> An analysis of individual patient lev-

el data from 3 secondary prevention trials<sup>516-18</sup> showed a significant variation ( $P=0.011$ ) in the clinical effectiveness of ICDs between patients with an LVEF  $\leq 35\%$  (hazard ratio: 0.66) and an LVEF  $>35\%$  (hazard ratio: 1.2). Some studies and simulation models suggest that ICDs might prolong life expectancy to a greater extent when used in higher-risk patients than in lower-risk patients.<sup>516-19</sup> In contrast, there is little evidence of variation in the effectiveness or cost-effectiveness of the ICD based on factors such as age or sex.<sup>516-20</sup> Most studies of ICD effectiveness and value have been performed on patients with reduced LV function due to prior MI or NICM. There are few data on the effectiveness or value of an ICD for other potential clinical indications, such as cardiac channelopathies or HCM, although studies have suggested that their potential cost effectiveness in such patients will depend on their underlying risk of SCD, with little evidence of value in low-risk patients.<sup>516-14</sup>

## 17. QUALITY OF LIFE

ICD implantation has not had a significant effect on QoL in the overall population of patients enrolled in RCTs.<sup>517-1-517-3</sup> Several studies have, however, demonstrated that the subset of patients who receive inappropriate ICD shocks have worse QoL than patients who have an ICD but have not had inappropriate shocks.<sup>517-2</sup> Because an ICD is designed to prevent SCD rather than to reduce symptoms, it would not be expected to improve QoL or functional status directly, but may have indirect, negative effects in some patients due to device complications, or indirect, positive effects in some patients due to reassurance of having a protective device in place.

## 18. EVIDENCE GAPS AND FUTURE RESEARCH NEEDS

Despite the numerous advances in risk stratification for SCD and prevention and treatment of SCD and VA, many gaps in knowledge remain. These gaps include:

- Identification of patients who are most likely to benefit from an ICD among all ICD-eligible patients. The role of novel markers (including genetic and imaging markers) and combinations of markers should be studied.
- Characterizing the role of the ICD in patient subgroups not well-represented in the pivotal ICD trials. Such subgroups include patients  $\geq 80$  years of age and those with kidney disease, especially patients with ESRD on dialysis, or multiple comorbidities.
- Methods to identify and treat patients at high individual risk for SCD who are not identified by current ICD eligibility criteria, including those who are within 40 days of an MI.
- Defining the role of the ICD in patients with HCM, arrhythmogenic right ventricular cardiomyopathy, cardiac sarcoidosis, and inherited cardiac channelopathies in prospective studies (preferably RCT).
- Determining the best approach to patients due for elective ICD generator replacement due to battery depletion, but who may now be at low risk for SCA, such as if significant LVEF improvement has occurred.
- Obtaining more data on the efficacy and effectiveness of the subcutaneous implantable cardioverter-defibrillator, compared with transvenous ICDs and on the extent of testing required, and its use with other novel technologies, including leadless pacemakers.
- Conducting RCTs on catheter ablation of VT in ischemic heart disease and cardiomyopathies that evaluates procedural end points, mortality, arrhythmia suppression, QoL, and costs.
- Improving identification of individuals without significant ventricular dysfunction who are at risk of SCD.
- Identifying mechanisms and risk factors for SCD in patients with HFpEF.
- Improving emergency response to out-of-hospital cardiac arrest.
- Developing better methods for identifying and ablating the arrhythmia substrate in structural heart disease.
- Developing better risk stratification of diseases and syndromes associated with sudden death, including ischemic heart disease, NICM, adult congenital heart disease, and Brugada syndrome.
- Identifying what causes different types of long QT syndrome, catecholaminergic polymorphic ventricular tachycardia, Brugada syndrome, HCM, and

arrhythmogenic right ventricular cardiomyopathy and advancing the genotype-phenotype relationships, genotype-dependent risk, and genotype-based tailoring of therapies for patients with inherited cardiomyopathies and inherited channelopathies.

- Defining the most appropriate and beneficial use of wearable cardioverter-defibrillators.
- Developing methods to identify and treat patients at high personal risk for SCD who are not identified by current ICD eligibility criteria.
- Defining the role of CMR in enhancing risk stratification for SCD.

Increasing research funding in this area, through existing and new mechanisms is critically important. Some have proposed research funding strategies that would offer business incentives to the insurance industries, while providing support for unresolved research goals. Such approaches should be tested.

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## ARTICLE INFORMATION

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## 5. THERAPIES FOR TREATMENT OR PREVENTION OF VA

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## 7. ONGOING MANAGEMENT OF VA AND SCD RISK RELATED TO SPECIFIC DISEASE STATES

### 7.1. Ischemic Heart Disease

#### 7.1.1. Secondary Prevention of SCD in Patients With Ischemic Heart Disease

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**Appendix 1. Author Relationships With Industry and Other Entities (Relevant)—2017 AHA/ACC/HRS Guideline for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death (October 2017)**

Committee Member	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness	Voting Recusals by Section*
Sana M. Al-Khatib, Chair	Duke Clinical Research Institute; Duke University—Professor of Medicine	None	None	None	None	None	None	None
William G. Stevenson, Vice Chair	Vanderbilt University Medical Center—Professor; Brigham and Women’s Hospital—Director of Clinical Cardiac EP	• St. Jude Medical	• Boston Scientific	• Biosense Webster‡	None	None	None	4.1, 4.2.2, 4.2.3, 5, 10.1, 5.4, 5.6, 6, 7, 8, 9 (except 9.7), 13, 15
Michael J. Ackerman	Mayo Clinic—Professor of Medicine, Pediatrics, and Pharmacology; Long QT Syndrome/Genetic Heart Rhythm Clinic and the Mayo Clinic Windland Smith Rice Sudden Death Genomics Laboratory—Director	• Audentes Therapeutics • Boston Scientific • Gilead Sciences • Invitae • Medtronic • MyoKardia • St. Jude Medical	None	None	None	• Transgenomic (Familion)† • Blue Ox Health Corporation‡ • AliveCor‡ • Stemonix‡	None	4.1, 4.2.2, 4.2.3, 5 (except 5.1.5.2, 5.5), 6, 7, 8, 9, 10 (except 10.2) 11, 13, 15
William J. Bryant	Dominick Feld Hyde—Attorney at Law	None	None	None	None	None	None	None
David J. Callans	University of Pennsylvania Health System—Professor of Medicine; Associate Director of EP	• Biosense Webster† • Biotronik • Boston Scientific† • Medtronic • St. Jude Medical	None	None	• Biosense Webster (PI)‡ • Endosense (PI)‡	• Acutus	None	4.1, 4.2.2, 4.2.3, 5.3, 5.4, 5.5.1, 5.6, 6, 7, 8, 9 (except 9.7), 10 (except 10.3), 13, 15
Anne B. Curtis	University at Buffalo—SUNY Distinguished Professor; Charles and Mary Bauer Professor and Chair	• Medtronic • St. Jude Medical	None	None	None	None	None	4.1, 4.2.2, 4.2.3, 5.1.1, 5.1.2, 5.1.3, 5.1.4, 5.2, 5.4, 5.6, 6, 7, 8, 9, 10, 12, 13, 15
Barbara J. Deal	Getz Professor of Cardiology Feinberg School of Medicine Northwestern University	None	None	None	None	None	None	None
Timm Dickfeld	University of Maryland—Associate Professor of Medicine	• Biosense • St. Jude Medical • Siemens	None	None	• Biosense† • General Electric†	• Impulse Dynamics‡ • Siemens†	None	4.1, 4.2 (except 4.2.6), 4.3, 5.3, 5.4, 5.6, 6, 7, 8, 9 (except 9.7), 10.1, 11, 13, 15
Anne M. Gillis	University of Calgary—Professor of Medicine	None	None	None	• Medtronic	None	None	4.2, 5.2.2, 5.3.2, 6.4.1, 6.4.2, 6.4.4, 6.5, 6.7, 7, 8, 9, 10, 11 (except 11.7), 13, 15
Christopher B. Granger	Duke Clinical Research Institute; Duke University—Professor of Medicine; Director, Cardiac Care Unit	• AstraZeneca† • Gilead Sciences† • GlaxoSmithKline† • Janssen Pharmaceuticals† • Medtronic† • Pfizer† • Sanofi-aventis†	None	None	• AstraZeneca† • GlaxoSmithKline† • Janssen Pharmaceuticals† • Medtronic† • Pfizer† • Sanofi-aventis†	• GE Healthcare† • Medtronic† • ZOLL Medical† • Spacelabs† • Phillips†	None	4, 5.1 (except 5.1.5), 5.2, 5.3, 5.4, 5.6, 6, 7, 8, 9, 12, 13, 15
Stephen C. Hammill	Mayo Clinic—Professor Emeritus of Medicine	None	None	None	None	None	None	None
Mark A. Hlatky	Stanford University School of Medicine—Professor of Health and Research Policy, and of Cardiovascular Medicine	None	None	None	None	None	None	None
José A. Joglar	UT Southwestern Medical Center—Professor of Internal Medicine; Clinical Cardiac EP—Fellowship Program Director	None	None	None	None	None	None	None
G. Neal Kay	University of Alabama at Birmingham—Professor Emeritus	None	None	None	None	None	None	None
Michael E. Field	University of Wisconsin School of Medicine and Public Health—Director, Clinical EP and Cardiac Arrhythmia Service, Associate Professor of Medicine	None	None	None	None	None	None	None

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Committee Member	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness	Voting Recusals by Section*
Gregg C. Fonarow	Ahmanson-UCLA Cardiomyopathy Center—Director; UCLA Division of Cardiology—Co-Chief	<ul style="list-style-type: none"> <li>• Amgen</li> <li>• Janssen Pharmaceuticals</li> <li>• Medtronic</li> <li>• ZS Pharma</li> </ul>	None	None	<ul style="list-style-type: none"> <li>• Medtronic—IMPROVE-HF (Steering Committee)†</li> <li>• Medtronic‡</li> </ul>	None	None	4.1, 4.2.2, 4.2.3, 5.1 (except 5.1.5.1), 5.2, 5.3, 5.4, 5.6, 6, 7, 8, 9, 10, 12, 13, 15
Daniel D. Matlock	University of Colorado School of Medicine—Associate Professor of Medicine	None	None	None	None	None	None	None
Robert J. Myerburg	University of Miami Miller School of Medicine—Professor of Medicine and Physiology	None	None	None	None	None	None	None
Richard L. Page	University of Wisconsin Hospital and Clinics—Chair, Department of Medicine	None	None	None	None	None	None	None

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

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

\*Writing committee members are required to recuse themselves from voting on sections to which their specific relationships with industry and other entities may apply.

†Significant relationship.

‡No financial benefit.

ACC indicates American College of Cardiology; AHA, American Heart Association; EP, Electrophysiology; HRS, Heart Rhythm Society; IMPROVE-HF, Improve the Use of Evidence-Based Heart Failure Therapies in the Outpatient Setting; PI, principal investigator; SUNY, State University of New York; and UT, University of Texas.

**Appendix 2. Reviewer Relationships With Industry and Other Entities (Comprehensive)—2017 AHA/ACC/HRS Guideline for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death (July 2017)**

Reviewer	Representation	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Salary	Expert Witness
Alfred E. Buxton	Content Reviewer	Professor of Medicine—Harvard Medical School—Beth Israel Deaconess Medical Center	None	None	None	• NHLBI (DSMB)†	• Medtronic† • Biosense Webster†	None	None
Andrew E. Epstein	Content Reviewer	Professor of Medicine—Cardiovascular Division University of Pennsylvania—Chief of Cardiology Section—Philadelphia VA Medical Center	• Zoll*	None	None	• Biotronik* • Boston Scientific* • Boston Scientific (DSMB)* • Medtronic* • Medtronic (DSMB) • St Jude Medical/ Abbott* • St Jude Medical/ Abbott (DSMB)*	None	None	• Defendant, Amiodarone pulmonary toxicity, 2016 • Defendant, Appropriateness of pacemaker implantation, 2016*
Brian Olshansky	Content Reviewer	Adjunct Professor of Medicine—Des Moines University—Professor Emeritus—University of Iowa	• Boehringer Ingelheim • Lundbeck Inc* • On-X/Cryolife	• Lundbeck Inc* • On-X/Cryolife	None	• Amarin (DSMB)*	None	None	• Plaintiff, Long QT sudden death, 2017
Bulent Gorenek	Content Reviewer—ACC EP Council	None	None	None	None	None	None	None	None
Charles I. Berul	Content Reviewer	Division Chief of Pediatric Cardiology—Children's National Medical Center	None	None	None	None	• Circulation*	None	None
Darren Sudman	Content Reviewer	Executive Director—Simon's Fund	None	None	None	None	None	None	None
George J. Klein	Content Reviewer	Chief of Cardiology—London Health Sciences Center	• Biotronik • Boston Scientific • Medtronic*	None	None	None	None	None	None
Glenn N. Levine	Content Reviewer—ACC/ AHA Task Force on Clinical Practice Guidelines	Professor of Medicine—Baylor College of Medicine Director—Cardiac Care Unit—Michael E. DeBakey Medical Center	None	None	None	None	None	None	• Defendant, Catheterization Laboratory Procedure, 2016 • Defendant, Out of hospital death, 2016
Gurusher S. Panjra	Content Reviewer—ACC Heart Failure and Transplant Council	Director Heart Failure and Mechanical Support Program—George Washington University	• Amgen Inc.*	None	None	None	• BEAT-HF‡ • ENDEAVOUR‡	None	None
James P. Daubert	Official Reviewer—AHA	Duke University Medical Center	• Biosense Webster • Boston Scientific • CardioFocus • Gilead • Heart Metabolics • Medtronic* • St. Jude Medical • Zoll	None	None	• ARCA biopharma • Biosense Webster* • Boston Scientific* • Gilead* • Gilead (DSMB) • Medtronic* • NHLBI* • NHLBI (DSMB) • Northwestern University • St. Jude Medical (DSMB) • VytronUS (DSMB)	• Biosense* • Biotronik* • Boston Scientific* • Gilead Sciences, Inc.* • Medtronic* • St. Jude Medical*	• ACC	None
James Tisdale	Content Reviewer—ACC EP Council	Professor—College of Pharmacy Purdue University—Adjunct Professor—School of Medicine Indiana University	None	None	None	• AHA* • HRS* • Indiana Clinical Translational Sciences Institute/ Strategic Research Initiative*	• ACC† • AHA† • AZCert† • QT drugs list, credible meds. org†	None	• Plaintiff, Drug-induced torsades de pointes, 2017*
John L. Sapp	Official Reviewer—HRS	Interim Head—Division of Cardiology QEII Health Sciences Centre—Professor of Medicine—Dalhousie University	• Biosense Webster* • Medtronic • St. Jude	None	None	• Biosense Webster* • Canadian Institute of Health Research* • DSMB† • Phillips healthcare* • St. Jude Medical*	• ARTESIA‡ • Medtronic‡ • Optisure Registry‡ • St. Jude‡	None	None

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Reviewer	Representation	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Salary	Expert Witness
Joseph Edward Marine	Official Reviewer—ACC	Associate Professor of Medicine—Johns Hopkins University School of Medicine	None	None	None	None	• UpToDate	None	None
Kathleen T. Hickey	Official Reviewer—AHA	Professor of Nursing—Columbia University Medical Center	None	None	None	None	None	None	None
Kenneth A. Ellenbogen	Content Reviewer	Chief of Cardiology—Virginia Commonwealth University Medical Center	<ul style="list-style-type: none"> <li>• AHA</li> <li>• AtriCure*</li> <li>• Biosense Webster*</li> <li>• Biotronik*</li> <li>• Boston Science*</li> <li>• Capricor</li> <li>• HRS</li> <li>• Janssen</li> <li>• Medtronic*</li> <li>• Pfizer*</li> <li>• Sentra heart</li> <li>• St. Jude Medical*</li> </ul>	None	None	<ul style="list-style-type: none"> <li>• AtriCure*</li> <li>• Biosense Webster*</li> <li>• Boston Science*</li> <li>• Daiichi Sankyo</li> <li>• Medtronic*</li> <li>• Medtronic (DSMB)*</li> <li>• NIH*</li> <li>• Pfizer*</li> </ul>	<ul style="list-style-type: none"> <li>• Biosense Webster*</li> <li>• Boston Science*</li> <li>• Circulation†</li> <li>• Heart Rhythm†</li> <li>• JACC†</li> <li>• Medtronic*</li> <li>• PACE†</li> <li>• Sanofi Aventis</li> </ul>	None	None
Kim K. Birtcher	Content Reviewer—ACC/AHA Task Force on Clinical Practice Guidelines	University of Houston—College of Pharmacology	• Jones and Bartlett Learning	None	None	None	• Accreditation Council for Clinical Lipidology	• University of Houston College of Pharmacology*	None
Kristen B. Campbell	Content Reviewer	Duke University Hospital	None	None	None	None	None	None	None
Kristen K. Patton	Content Reviewer	Professor of Medicine—University of Washington	None	None	None	None	<ul style="list-style-type: none"> <li>• ABIM</li> <li>• ACGME†</li> <li>• AHA†</li> <li>• FDA</li> <li>• HRS†</li> </ul>	None	None
L. Brent Mitchell	Content Reviewer	Professor—Department of Cardiac Sciences—Libin Cardiovascular Institute of Alberta—University of Calgary—Alberta Health Services	<ul style="list-style-type: none"> <li>• Boehringer Ingelheim*</li> <li>• Forest Pharmaceuticals</li> <li>• Guidnat Canada*</li> <li>• Medtronic Canada*</li> <li>• Medtronic Inc*</li> <li>• Merck</li> <li>• Pfizer*</li> <li>• Servier Canada*</li> </ul>	None	None	• Boston Scientific*	<ul style="list-style-type: none"> <li>• ARTESIA†</li> <li>• Health Protection Branch, Government of Canada</li> </ul>	None	None
Martin Borggreffe	Content Reviewer	I Medizinische Klinik/Klinikum Mannheim GmbH/Universitätsklinikum	<ul style="list-style-type: none"> <li>• Bayer Health Care</li> <li>• Boehringer Ingelheim</li> <li>• Impulse Dynamics</li> <li>• Sanofi Aventis</li> <li>• St. Jude Medical</li> </ul>	None	None	• German Centre for Cardiovascular Research*	None	None	None
Mathew D. Hutchinson	Official Reviewer—HRS	Professor of Medicine—University of Arizona College of Medicine—Tucson	• St. Jude Medical	None	None	None	None	None	None
Matthew W. Martinez	Content Reviewer—Sports and Exercise EP Council	Lehigh Valley Health Network	None	None	None	None	None	None	None
Melissa R. Robinson	Content Reviewer	Director—Complex Ablation Program—University of Washington	<ul style="list-style-type: none"> <li>• Medtronic*</li> <li>• Abbott*</li> <li>• Boston Scientific*</li> </ul>	None	None	None	None	None	None
Michael J. Silka	Content Reviewer	Children's Hospital Los Angeles	None	None	None	None	None	None	• Defendant, ICD implantation, 2017
Miguel A. Quinones	Content Reviewer	Methodist DeBakey Heart and Vascular Center	None	None	None	None	• Houston Methodist Hospital*	None	None
Mitchell T. Saltzberg	Organizational Reviewer—HFSA	Jefferson Medical College—Christiana Care Health System	None	None	<ul style="list-style-type: none"> <li>• Nephroceuticals*</li> <li>• Stem Cell Theranostics*</li> </ul>	None	None	None	None

(Continued)

Appendix 2. Continued

Reviewer	Representation	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Salary	Expert Witness
N.A. Mark Estes III	Content Reviewer	Professor of Medicine—Tufts University School of Medicine	<ul style="list-style-type: none"> <li>• Boston Scientific*</li> <li>• Medtronic*</li> <li>• St. Jude Medical*</li> </ul>	None	None	<ul style="list-style-type: none"> <li>• Boston Scientific*</li> <li>• International Board of Heart Rhythm Examiners†</li> <li>• Medtronic*</li> <li>• St. Jude Medical*</li> </ul>	None	None	None
Norma M. Keller	Official Reviewer—ACC	New York University Medical Center	None	None	None	None	None	None	None
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