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ACC/AHA/ESC PRACTICE GUIDELINES

ACC/AHA/ESC 2006 Guidelines 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 and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Develop Guidelines for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death)

Developed in Collaboration With the European Heart Rhythm Association and the Heart Rhythm Society

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Single copies of the executive summary and the full-text guidelines are also available by calling 800-253-4636 or writing the American College of Cardiology Foundation, Resource Center, at 9111 Old Georgetown Road, Bethesda, MD 20814-1699. To purchase bulk reprints, Fax 212-633-3820 or e-mail reprints@elsevier.com.

PREAMBLE

It is important that the medical profession plays a significant role in critically evaluating the use of diagnostic procedures and therapies as they are introduced and tested in the detection, management, or prevention of disease states. Rigorous and expert analysis of the available data documenting absolute and relative benefits and risks of those procedures and therapies can produce helpful guidelines that improve the effectiveness of care, optimize patient outcomes, and favorably affect the overall cost of care by focusing resources on the most effective strategies.

The American College of Cardiology Foundation (ACCF) and the American Heart Association (AHA) have jointly engaged in the production of such guidelines in the area of cardiovascular disease since 1980. The ACC/AHA Task Force on Practice Guidelines, whose charge is to develop, update, or revise practice guidelines for important cardiovascular diseases and procedures, directs this effort. The Task Force is pleased to have this guideline developed in conjunction with the European Society of Cardiology (ESC). Writing committees are charged with the task of performing an assessment of the evidence and acting as an independent group of authors to develop or update written recommendations for clinical practice.

Experts in the subject under consideration have been selected from all 3 organizations to examine subject-specific data and write guidelines. The process includes additional representatives from other medical practitioner and specialty groups when appropriate. Writing committees are specifically charged to perform a formal literature review, weigh the strength of evidence for or against a particular treatment or procedure, and include estimates of expected health outcomes where data exist. Patient-specific modifiers, comorbidities, and issues of patient preference that might influence the choice of particular tests or therapies are considered as well as frequency of follow-up and cost effectiveness. When available, information from studies on cost will be considered; however, review of data on efficacy and clinical outcomes will constitute the primary basis for preparing recommendations in these guidelines.

The ACC/AHA Task Force on Practice Guidelines and the ESC Committee for Practice Guidelines make every effort to avoid any actual, potential, or perceived conflict of interest that might arise as a result of an industry relationship or personal interest of the writing committee. Specifically, all members of the Writing Committee, as well as peer reviewers of the document, were asked to provide disclosure statements of all such relationships that might be perceived as real or potential conflicts of interest. Writing Committee members are also strongly encouraged to declare a previous relationship with industry that might be perceived as relevant to guideline development. If a Writing Committee member develops a new relationship with industry during his or her tenure, he or she is required to notify guideline staff in writing. The continued participation of the Writing Committee member will be reviewed. These statements are reviewed by the parent Task Force, reported orally to all members of the Writing Committee at each meeting, and updated and reviewed by the Writing Committee as changes occur. Please refer to the methodology manuals for further description of the policies used in guideline development, including relationships with industry, which are available on the ACC, AHA and ESC World Wide Web sites (http://www.acc.org/clinical/manual/manual_introltr.htm, http://circ.ahajournals.org/manual, and http://www.escardio.org/knowledge/guidelines/Rules, respectively). Please see Appendix 1 for author relationships with industry and Appendix 2 for peer reviewer relationships with industry that are pertinent to these guidelines.

These practice guidelines are intended to assist health care providers in clinical decision making by describing a range of generally acceptable approaches for the diagnosis and management of specific diseases or conditions. These guidelines attempt to define practices that meet the needs of most patients in most circumstances. These guideline recommendations reflect a consensus of expert opinion after a thorough review of the available, current scientific evidence and are intended to improve patient care. If these guidelines are used as the basis for regulatory/payer decisions, the ultimate goal is quality of care and serving the patient's best interests. The ultimate judgment regarding care of a particular patient must be made by the health care provider and the patient in light of all of the circumstances presented by that patient. There are circumstances in which deviations from these guidelines are appropriate.

The guidelines will be reviewed annually by the ACC/AHA Task Force on Practice Guidelines and the ESC Committee for Practice Guidelines and will be considered current unless they are updated, revised, or sunsetted and withdrawn from distribution. The executive summary and recommendations are published in the September 5, 2006 issue of the *Journal of the American College of Cardiology*, September 5, 2006 issue of *Circulation*, and September 17, 2006 issue of the *European Heart Journal*. The full-text guideline is e-published in the same issues of the *Journal of the American College of Cardiology* and *Circulation* and published in the September 2006 issue of *Europace*, as well as posted on the ACC (www.acc.org), AHA (www.americanheart.org), and ESC (www.escardio.org) World Wide Web sites. Copies of the full text and the executive summary are available from all 3 organizations.

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1. INTRODUCTION

Several excellent guidelines already exist on treating patients who have ventricular arrhythmias (Table 1). The purpose of

Table 1. Clinical Practice Guidelines and Policy Statements That Overlap With ACC/AHA/ESC Guidelines for the Management of Patients with Ventricular Arrhythmias and the Prevention of SCD

Document	Sponsor	Citation
Guidelines		
SCD	ESC	Eur Heart J 2001;22:1374–450
Syncope	ESC	Eur Heart J 2004;25:2054–72
Exercise testing	ACC/AHA	Circulation 2002;106:1883–92
Cardiac pacemakers and antiarrhythmia devices	ACC/AHA/NASPE	Circulation 2002;106:2145–61
Echocardiography	ACC/AHA	J Am Coll Cardiol 2003;42:954–70
Supraventricular arrhythmias	ACC/AHA/ESC	Eur Heart J 2003;24:1857–97 J Am Coll Cardiol 2003;42:1493–531
SCD Update	ESC	Eur Heart J 2003;24:13–5
Congenital heart disease	ESC	Eur Heart J 2003;24:1035–84
European guidelines on CVD prevention	ESC	Eur J Cardiovasc Prev Rehab 2003;10 Suppl 1:S1–78
Infective endocarditis	ESC	Eur Heart J 2004;25:267–76
Pericardial disease	ESC	Eur Heart J 2004;25:587–610
Pulmonary arterial hypertension	ESC	Eur Heart J 2004;25:2243–78
AED use in Europe	ESC/ERC	Eur Heart J 2004;25:437–45
ST-elevation myocardial infarction	ACC/AHA	J Am Coll Cardiol 2004;44:e1–211
Chronic heart failure	ACC/AHA	J Am Coll Cardiol 2005;46:e1–82
Chronic heart failure	ESC	Eur Heart J 2005;26:1115–40
CPR and ECC	AHA/ILCOR	Circulation 2005;112:IV-1–203
Resuscitation	ERC	Resuscitation 2005;67 Suppl:539–86
Valvular heart disease	ACC/AHA	J Am Coll Cardiol 2006;48:e1–e148
Statements		
Invasive electrophysiology studies, catheter ablation, and cardioversion	ACC/AHA	J Am Coll Cardiol 2000;36:1725–36
Hypertrophic cardiomyopathy	ACC/ESC	Eur Heart J 2003;24:1965–91 J Am Coll Cardiol 2003;42:1687–713
Cardiovascular disease during pregnancy	ESC	Eur Heart J 2003;24:761–81
Physical activity and recreational sports AHA for young patients with genetic CVD		Circulation 2004;109:2807–16
36th Bethesda Conference: Eligibility recommendations for competitive athletes with cardiovascular abnormalities	ACC	J Am Coll Cardiol 2005;45:1318–75

The guidelines from the ACC, AHA, and ESC are available at www.acc.org, www.americanheart.org, and www.escardio.org, respectively.

ACC = American College of Cardiology; AHA = American Heart Association; CVD = cardiovascular disease; CPR = cardiopulmonary resuscitation; ECC = emergency cardiovascular care; ERC = European Resuscitation Council; ESC = European Society of Cardiology; ILCOR = International Liaison Committee on Resuscitation; NASPE = Heart Rhythm Society (formerly North American Society for Pacing and Electrophysiology); SCD = sudden cardiac death.

this document is to update and combine the previously published recommendations into one source approved by the major cardiology organizations in the United States and Europe. We have consciously attempted to create a streamlined document, not a textbook, that would be useful specifically to locate recommendations on the evaluation and treatment of patients who have or may be at risk for ventricular arrhythmias. Thus, sections on epidemiology, mechanisms and substrates, and clinical presentations are brief, because there are no recommendations for those sections. For the other sections, the wording has been kept to a minimum, and clinical presentations have been confined to those aspects relevant to forming recommendations.

1.1. Organization of Committee and Evidence Review

Writing Committee members were selected with attention to cardiovascular subspecialties, broad geographical representation, and involvement in academic medicine and clinical practice. The Writing Committee on the Management of Patients With Ventricular Arrhythmias and Prevention of Sudden Cardiac Death also included members of the ACC/AHA Task Force on Practice Guidelines, ESC Committee on Practice Guidelines, ACC Board of Trustees, ACC Board of Governors, ESC Board, the European Heart Rhythm Association (EHRA), and the Heart Rhythm Society (HRS).

The committee was co-chaired by A. John Camm, MD, FACC, FAHA, FESC, and Douglas P. Zipes, MD, MACC, FAHA, FESC. This document was reviewed by 2 official reviewers nominated by the ACC, 2 official reviewers nominated by the AHA, 2 official reviewers nominated by the ESC, 1 official reviewer from the ACC/AHA Task Force on Practice Guidelines, reviewers from the EHRA and HRS, and 18 content reviewers, including members from ACCF Clinical Electrophysiology Committee, AHA Council on Clinical Cardiology, Electrocardiography, and Arrhythmias, and AHA Advanced Cardiac Life Support Subcommittee.

The committee conducted comprehensive searching of the scientific and medical literature on ventricular arrhythmias and sudden cardiac death (SCD). Literature searching was limited to publications on humans and in English from 1990 to 2006. The search parameters were extended for selected topics when a historical reference was needed or if limited studies existed in English. In addition to broad-based searching on ventricular arrhythmias and SCD, specific targeted searches were performed on ventricular ar-

rhythmias and SCD and the following subtopics: mechanisms, substrates, clinical presentations, ECG, exercise testing, echocardiography, imaging, electrophysiological (EP) testing, drug therapy (antiarrhythmic and nonantiarrhythmic), implantable and external cardioverter devices, ablation, surgery, acute specific arrhythmias (e.g., acute coronary syndrome [ACS], heart failure [HF], stable sustained monomorphic ventricular tachycardia [VT], torsades de pointes), specific pathology (e.g., congenital heart disease, myocarditis, endocrine disorders, renal failure), cardiomyopathies, genetic arrhythmias, structurally normal hearts, athletes, elderly, gender, pediatric, and drug-induced arrhythmias. The complete list of keywords is beyond the scope of this section. The committee reviewed all compiled reports from computerized searches and conducted additional manual searching. Literature citations were generally restricted to published manuscripts appearing in journals in the Index Medicus. Because of the scope and importance of certain ongoing clinical trials and other emerging information, published abstracts were cited in the text when they were the only published information available.

The final recommendations for indications for a diagnostic procedure, a particular therapy, or an intervention for management of patients with ventricular arrhythmias and prevention of SCD summarize both clinical evidence and expert opinion. Once recommendations were written, a Classification of Recommendation and Level of Evidence grade was assigned to each recommendation.

Classification of Recommendations and Level of Evidence are expressed in the ACC/AHA/ESC format as follows:

Classification of Recommendations

- **Class I:** Conditions for which there is evidence and/or general agreement that a given procedure or treatment is beneficial, useful, and effective.
- **Class II:** Conditions for which there is conflicting evidence and/or divergence of opinion about the usefulness/efficacy of a procedure or treatment.
  - **Class IIa:** Weight of evidence/opinion is in favor of usefulness/efficacy.
  - **Class IIb:** Usefulness/efficacy is less well established by evidence/opinion.
- **Class III:** Conditions for which there is evidence and/or general agreement that a procedure/treatment is not useful/effective and in some cases may be harmful.

Level of Evidence

- **Level of Evidence A:** Data derived from multiple randomized clinical trials or meta-analyses.
- **Level of Evidence B:** Data derived from a single randomized trial or nonrandomized studies.
- **Level of Evidence C:** Only consensus opinion of experts, case studies, or standard-of-care.

The schema for classification of recommendations and level of evidence is summarized in Table 2, which also illustrates how the grading system provides an estimate of the size of treatment effect and an estimate of the certainty of the treatment effect.

Recommendations with respect to therapy have considered the following:

1. The therapy to be offered (implantable cardioverter-defibrillator [ICD], antiarrhythmic drugs, surgery, and miscellaneous other treatments)
2. The point at which therapy is offered (primary prevention for those who are at risk but have not yet had a life-threatening ventricular arrhythmia or sudden cardiac "death" episode, or secondary for those patients who have already experienced such arrhythmias or events)
3. The purpose of therapy (life preservation or symptom reduction/improved quality of life)
4. The etiology of the arrhythmia substrate (coronary heart disease [CHD], cardiomyopathy, or other conditions)
5. The functional status of the patient (New York Heart Association [NYHA] functional class)
6. The state of left ventricular (LV) function (LV ejection fraction [LVEF])
7. The specific arrhythmia concerned (e.g., sustained monomorphic VT, polymorphic VT, and ventricular fibrillation [VF])

Not all therapeutic combinations are clinically relevant, and many have no evidence base and probably will not have one in the future because of the lack of clinical relevance or the relative rarity of the particular grouping. In many instances, the probable value of therapy may be reasonably inferred by the response of similar patients to specific therapies.

1.2. Prophylactic Implantable Cardioverter-Defibrillator Recommendations Across Published Guidelines

The ACC/AHA/NASPE 2002 Guidelines Update for Implantation of Cardiac Pacemakers and Antiarrhythmia Devices (1), the ACC/AHA 2004 Guidelines for the Management of Patients With ST-Elevation Myocardial Infarction (2), the ESC 2001 and 2003 Guidelines on Prevention of Sudden Cardiac Death (3,4), the ESC 2005 Guidelines for the Diagnosis and Treatment of Chronic Heart Failure (5a), and the ACC/AHA 2005 Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult (6) include a large number of recommendations on ICD therapy that merit attention.

Recommendations for prophylactic ICD implantation based on ejection fractions (EFs) have been inconsistent because clinical investigators have chosen different EFs for enrollment in trials of therapy, average values of the EF in such trials have been substantially lower than the cutoff value for enrollment, and subgroup analyses of clinical trial populations based on EF have not been consistent in their

Table 2. Applying Classification of Recommendations and Level of Evidence†

"Estimate of Certainty (Precision) of Treatment Effect"	"SIZE of TREATMENT EFFECT"			
	Class I ***Benefit >>> Risk*** **Procedure/Treatment SHOULD be performed/administered**	**Class IIa** ***Benefit >> Risk*** **Additional studies with focused objectives needed** **IT IS REASONABLE to perform procedure/administer treatment**	**Class IIb** ***Benefit ≥ Risk*** ***Additional studies with broad objectives needed; Additional registry data would be helpful*** **Procedure/Treatment MAY BE CONSIDERED**	**Class III** ***Risk ≥ Benefit*** ***No additional studies needed*** **Procedure/Treatment should NOT be performed/administered SINCE IT IS NOT HELPFUL AND MAY BE HARMFUL**
Level A ***Multiple (3-5) population risk strata evaluated**** ***General consistency of direction and magnitude of effect***	• Recommendation that procedure or treatment is useful/effective • Sufficient evidence from multiple randomized trials or meta-analyses	• Recommendation in favor of treatment or procedure being useful/effective • Some conflicting evidence from multiple randomized trials or meta-analyses	• Recommendation's usefulness/efficacy less well established • Greater conflicting evidence from multiple randomized trials or meta-analyses	• Recommendation that procedure or treatment not useful/effective and may be harmful • Sufficient evidence from multiple randomized trials or meta-analyses
Level B ***Limited (2-3) population risk strata evaluated****	• Recommendation that procedure or treatment is useful/effective • Limited evidence from single randomized trial or non-randomized studies	• Recommendation in favor of treatment or procedure being useful/ effective • Some conflicting evidence from single randomized trial or non-randomized studies	• Recommendation's usefulness/efficacy less well established • Greater conflicting evidence from single randomized trial or non-randomized studies	• Recommendation that procedure or treatment not useful/effective and may be harmful • Limited evidence from single randomized trial or non-randomized studies
Level C ***Very limited (1-2) population risk strata evaluated****	• Recommendation that procedure or treatment is useful/effective • Only expert opinion, case studies, or standard-of-care	• Recommendation in favor of treatment or procedure being useful/ effective • Only diverging expert opinion, case studies, or standard-of-care	• Recommendation's usefulness/efficacy less well established • Only diverging expert opinion, case studies, or standard-of-care	• Recommendation that procedure or treatment not useful/effective and may be harmful • Only expert opinion, case studies, or standard-of-care

*Data available from clinical trials or registries about the usefulness/efficacy in different subpopulations, such as gender, age, history of diabetes, history of prior MI, history of heart failure, and prior aspirin use. †A recommendation with a Level of Evidence of B or C does not imply that the recommendation is weak. Many important clinical questions addressed in the guidelines do not lend themselves to clinical trials. Even though randomized trials are not available, there may be a very clear consensus that a particular therapy is useful or effective.

implications. Substantial differences between guidelines have resulted. However, no trial has randomized patients with an intermediate range of EFs. For instance, there is no trial that has specifically studied patients with an LVEF between 31% and 35%, yet recommendations have been set for such patients on the basis of data derived from trials that studied groups with EFs less than or equal to 30%, others that enrolled patients with an EF less than or equal to 35%, and one trial that enrolled patients with an EF less than or equal to 40%. Recognizing these inconsistencies, this Guideline Writing Committee decided to construct recommendations to apply to patients with an EF less than or equal to a range of values. The highest appropriate class of recommendation was then based on all trials that recruited patients with EFs within this range. In this way, potential conflicts between guidelines were reduced and errors due to drawing false conclusions relating to unstudied patient groups were minimized (Table 3).

It is important to note that experts can review the same data and arrive at different interpretations. Attempting to homogenize heterogeneous trials invariably leads to varying interpretations of the trial data. Furthermore, differences between the United States and Europe may modulate how recommendations are implemented. Guidelines are composed of recommendations on the basis of the best available medical science; however, *implementation* of these recommendations will be affected by the financial, cultural, and societal differences between individual countries.

1.3. Classification of Ventricular Arrhythmias and Sudden Cardiac Death

This classification table is provided for direction and introduction to the guidelines (Table 4).

2. EPIDEMIOLOGY

The epidemiology of ventricular arrhythmias spans a range of risk descriptors and clinical applications, ranging from premature ventricular complexes (PVCs) and nonsustained ventricular tachycardia (NSVT) in normal subjects to SCD due to ventricular tachyarrhythmias in patients with and without structural heart disease (9). Epidemiological patterns have implications that help improve profiling risk based on individual subject characteristics and for efficient designs of clinical trials (10). Techniques include identification of clinical and lifestyle risk factors for disease development, measurement of risk among subgroups of patients with established disease, and the newly emerging field of genetic epidemiology (9,11).

2.1. Ventricular Arrhythmias

2.1.1. Premature Ventricular Complexes and Nonsustained Ventricular Tachycardia

Single and repetitive forms of PVCs have been studied for their role in risk prediction in several contrasting clinical circumstances, including implications in apparently normal subjects compared with those with identified disease states,

Table 3. Inconsistencies Between ACC/AHA/ESC Guidelines for the Management of Patients With Ventricular Arrhythmias and the Prevention of SCD and Other Published ACC/AHA and ESC Guidelines With Respect to ICD Therapy for Primary Prevention to Reduce Total Mortality by a Reduction in SCD

	Guideline and Class of Recommendation with Level of Evidence* for Each Group				
Group Addressed in Recommendation	**2005 ACC/AHA HF**	**2005 ESC HF**	**2004 ACC/AHA STEMI**	**2002 ACC/ AHA/NASPE PM and ICD**	**Comment from the ACC/AHA/ESC VA and SCD Guidelines**
LVD d/t MI, LVEF 30% or less, NYHA II, III	*Class I; LOE: B*	*Class I; LOE: A*	*Class IIa; LOE: B*	*Class IIa; LOE: B*	VA and SCD has combined all trials that enrolled patients with LVD d/t MI into one recommendation, *Class I; LOE: A*
LVD d/t MI, LVEF 30% to 35%, NYHA II, III	*Class IIa; LOE: B*	*Class I; LOE: A*	N/A	N/A	
LVD d/t MI, LVEF 30% to 40%, NSVT, positive EP study	N/A	N/A	*Class I; LOE: B*	*Class IIb; LOE: B*	
LVD d/t MI, LVEF 30% or less, NYHA I	*Class IIa; LOE: B*	N/A	N/A	N/A	VA and SCD has expanded the range of LVEF to 30% to 35% or less for patients with LVD d/t MI and NYHA functional class I into one recommendation, *Class IIa; LOE: B*
LVD d/t MI, LVEF 31% to 35% or less, NYHA I	N/A	N/A	N/A	N/A	
NICM, LVEF 30% or less, NYHA II, III	*Class I; LOE: B*	*Class I; LOE: A*	N/A	N/A	VA and SCD has combined all trials of NICM, NYHA II, III into one recommendation, *Class I; LOE: B*
NICM, LVEF 30% to 35%, NYHA II, III	*Class IIa; LOE: B*	*Class I; LOE: A*	N/A	N/A	
NICM, LVEF 30% or less, NYHA I	*Class IIb; LOE: C*	N/A	N/A	N/A	VA and SCD has expanded the range of LVEF to 30% to 35% or less for patients with NICM and NYHA functional class I into one recommendation, *Class IIb; LOE: B*
NICM, LVEF 31% to 35% or less, NYHA I	N/A	N/A	N/A	N/A	

*For an explanation of Class Recommendation and Level of Evidence, see Table 2. For further discussion, please see the Introduction.

ACC/AHA HF = ACC/AHA 2005 Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult (6); ACC/AHA/NASPE PM and ICD = ACC/AHA/NASPE 2002 Guidelines Update for Implantation of Cardiac Pacemakers and Antiarrhythmia Devices (1); ACC/AHA STEMI = ACC/AHA 2004 Guidelines for the Management of Patients With ST-Elevation Myocardial Infarction (2); EP = electrophysiological; ESC HF = ESC 2005 Guidelines for the Diagnosis and Treatment of Chronic Heart Failure (5); LOE = level of evidence; LVD d/t MI = left ventricular dysfunction due to prior myocardial infarction; LVEF = left ventricular ejection fraction; N/A = populations not addressed; NICM = nonischemic cardiomyopathy; NSVT = nonsustained ventricular tachycardia; NYHA = New York Heart Association functional class; SCD = sudden cardiac death; VA = ventricular arrhythmias.

Table 4. Classification of Ventricular Arrhythmias

Classification by Clinical Presentation			**Reference**
Hemodynamically stable	Asymptomatic	The absence of symptoms that could result from an arrhythmia.	(7)
	Minimal symptoms, e.g., palpitations	Patient reports palpitations felt in either the chest, throat, or neck as described by the following: ■ Heartbeat sensations that feel like pounding or racing ■ An unpleasant awareness of heartbeat ■ Feeling skipped beats or a pause	(7)
Hemodynamically unstable	Presyncope	Patient reports presyncope as described by the following: ■ Dizziness ■ Lightheadedness ■ Feeling faint ■ "Graying out"	(7)
	Syncope	Sudden loss of consciousness with loss of postural tone, not related to anesthesia, with spontaneous recovery as reported by the patient or observer. Patient may experience syncope when supine.	(7)
	Sudden cardiac death	Death from an unexpected circulatory arrest, usually due to a cardiac arrhythmia occurring within an hour of the onset of symptoms.	(7a)
	Sudden cardiac arrest	Death from an unexpected circulatory arrest, usually due to a cardiac arrhythmia occurring within an hour of the onset of symptoms, in whom medical intervention (e.g., defibrillation) reverses the event.	(7)
Classification by Electrocardiography			
Nonsustained VT		Three or more beats in duration, terminating spontaneously in less than 30 s. VT is a cardiac arrhythmia of three or more consecutive complexes in duration emanating from the ventricles at a rate of greater than 100 bpm (cycle length less than 600 ms)	(7)
	Monomorphic	Nonsustained VT with a single QRS morphology.	(7)
	Polymorphic	Nonsustained VT with a changing QRS morphology at cycle length between 600 and 180 ms.	(7)
Sustained VT		VT greater than 30 s in duration and/or requiring termination due to hemodynamic compromise in less than 30 s.	(7)
	Monomorphic	Sustained VT with a stable single QRS morphology.	(7)
	Polymorphic	Sustained VT with a changing or multiform QRS morphology at cycle length between 600 and 180 ms.	(7)
Bundle-branch re-entrant tachycardia		VT due to re-entry involving the His-Purkinje system, usually with LBBB morphology; this usually occurs in the setting of cardiomyopathy.	(7)
Bidirectional VT		VT with a beat-to-beat alternans in the QRS frontal plane axis, often associated with digitalis toxicity.	(7)
Torsades de pointes		Characterized by VT associated with a long QT or QTc, and electrocardiographically characterized by twisting of the peaks of the QRS complexes around the isoelectric line during the arrhythmia: ■ "Typical," initiated following "short-long-short" coupling intervals. ■ Short coupled variant initiated by normal-short coupling.	(7)
Ventricular flutter		A regular (cycle length variability 30 ms or less) ventricular arrhythmia approximately 300 bpm (cycle length—200 ms) with a monomorphic appearance; no isoelectric interval between successive QRS complexes.	(7)
Ventricular fibrillation		Rapid, usually more than 300 bpm/200 ms (cycle length 180 ms or less), grossly irregular ventricular rhythm with marked variability in QRS cycle length, morphology, and amplitude.	(7)
Classification by Disease Entity			
Chronic coronary heart disease			
Heart failure			
Congenital heart disease			
Neurological disorders			
Structurally normal hearts			
Sudden infant death syndrome			
Cardiomyopathies			
	Dilated cardiomyopathy		
	Hypertrophic cardiomyopathy		
	Arrhythmogenic right ventricular cardiomyopathy		

LBBB = left bundle-branch block; VT = ventricular tachycardia.

in steady-state pathophysiology versus transient events, and in inactive subjects versus those under physical stress. The epidemiological implications vary for each of these contingencies.

2.1.1.1. Premature Ventricular Complexes in the Absence of Heart Disease

Among presumably normal individuals, estimates of the prevalence of PVCs and NSVT vary according to the

sampling technique used and the source of data. PVCs were recorded on standard 12-lead electrocardiograms (ECGs) in 0.8% of subjects in a healthy military population, with a range of 0.5% among those under the age of 20 y to 2.2% of those over 50 y of age (12). In a study of middle-aged men, both with and without known heart disease, a 6-h monitor sampling technique identified a 62% incidence of asymptomatic ventricular arrhythmias, more than one half of which were infrequent single PVCs (13). The incidence, frequency, and complexity of ventricular arrhythmias were greater in the presence of known or suspected heart disease, and mortality risk implications were absent in those without heart disease (13,14). In contrast to PVCs and monomorphic patterns of NSVT, polymorphic ventricular tachyarrhythmias in the absence of structural heart disease are indicators of risk (15). Many nonsustained polymorphic VT events occurring in individuals free of grossly evident structural abnormalities of the heart are due to abnormalities at a molecular level or a consequence of electrolyte disturbances or adverse drug effects.

In the Tecumseh, Michigan, communitywide cardiovascular epidemiology study, PVCs in subjects with structurally normal hearts carried no adverse prognostic significance under the age of 30 y, but in those older than 30 y, PVCs and short runs of NSVT began to influence risk (16). More recent studies provide conflicting implications regarding risk in asymptomatic subjects. In one study (17), asymptomatic ventricular arrhythmias in the absence of identifiable heart disease predicted a small increase in risk, while another study (18) suggested no increased risk.

In contrast to the apparently non–life-threatening implication of PVCs at rest, PVCs elicited during exercise testing, even in apparently normal individuals, appear to imply risk over time. In one study (19), PVCs and NSVT induced during exercise correlated with increased risk of total mortality, while in another study (20), both exercise- and recovery-phase PVCs correlated with risk, with the greater burden associated with recovery-phase arrhythmias. A selection bias, based on indications for stress testing, may have influenced these observations (21).

2.1.1.2. Premature Ventricular Complexes in the Presence of Established Heart Disease

PVCs and runs of NSVT in subjects with structural heart disease contribute to an increased mortality risk, the magnitude of which varies with the nature and extent of the underlying disease. Among survivors of myocardial infarction (MI), frequent and repetitive forms of ventricular ectopic activity, accompanied by a reduced EF, predict an increased risk of SCD during long-term follow-up (21–23). Most studies cite a frequency cutoff of 10 PVCs per hour and the occurrence of repetitive forms of ventricular ectopy as thresholds for increased risk. Several investigators have emphasized that the most powerful predictors among the various forms of PVCs are runs of NSVT (21,22). Although the specificity of this relationship is now questioned. The power of risk prediction conferred by the presence of PVCs and NSVT appears to be directly related to the extent of structural disease as estimated by EF and to cardiovascular limitations as estimated by functional capacity (24).

Ventricular arrhythmias during ambulatory recording in patients with HF do not specifically predict risk for SCD (25). Risk is already high because of the underlying disease. Suppression of ambient ventricular arrhythmias is no longer considered a therapeutic target for prevention of death in the post-MI or nonischemic cardiomyopathy subgroups.

2.1.2. Ventricular Tachycardia and Ventricular Fibrillation During Acute Coronary Syndromes

Observations of both post-MI patients (26) and survivors of cardiac arrest that occurred during the acute phase of transmural MI (27) suggest that life-threatening ventricular tachyarrhythmias occurring during the first 24 to 48 h of MI do not imply continuing risk over time. A study done on follow-up after in-hospital VF does suggest an adverse prognosis over the ensuing 6 mo (28), but the patients were not selected for acute-phase arrhythmias. Later in-hospital VF has previously been reported to confer long-term risk (29). In contrast, patients presenting with non–ST-elevation myocardial infarction (NSTEMI) are at increased long-term risk of SCD (30), possibly related in part to a persistent propensity for ventricular tachyarrhythmias (31). Such patients have generally been excluded from clinical trials for interventions targeting long-term arrhythmic death risk because of low absolute risk, but it remains unclear whether the magnitude of risk is modulated by the extent of myocardial damage that occurs during the acute event. The long-term risk implications of sustained VT and VF during the acute phase of MI may also be applied to frequent PVCs and runs of NSVT (32). It is important to stress that the clinician's ability to recognize individuals with reversible or transient causes of ventricular tachyarrhythmias is limited (33).

2.2. Sudden Cardiac Death

2.2.1. Incidence of Sudden Cardiac Death

The geographical incidence of SCD varies as a function of CHD prevalence in different regions (3). Estimates for the United States (34–38) range from less than 200,000 to more than 450,000 SCDs annually, with the most widely used estimates in the range of 300,000 to 350,000 SCDs annually (39). The variation is based, in part, on the inclusion criteria used in individual studies. Overall, event rates in Europe are similar to those in the United States (3), with significant geographic variations reported.

The temporal definition of SCD strongly influences epidemiological data (40). The proportion of all natural deaths due to SCD is 13% when a definition of 1 h from onset of symptoms is used. In contrast, the communitywide study in Maastricht, the Netherlands, reported that 18.5% of all deaths were SCD, using a 24-h definition (41). The

application of a 24-h definition of SCD increases the fraction of all natural deaths falling into the "sudden" category but reduces the proportion of all sudden natural deaths that are due to cardiac causes (40).

Approximately 50% of all CHD deaths are sudden and unexpected, occurring shortly (instantaneous to 1 h) after the onset of a change in clinical status, with some geographical variation in the fraction of coronary deaths that are sudden (42). The decreasing age-adjusted CHD mortality does not imply a decrease in absolute numbers of cardiac or sudden deaths (43,44) because of the growth and aging of the U.S. and European populations and the increasing prevalence of chronic heart disease (45).

2.2.2. Population Subgroups and Risk Prediction

Three factors affect the ability to identify subjects and population subgroups at risk and consideration of strategies for prevention of SCD:

- Absolute numbers and event rates (incidence) among population subgroups (Fig. 1)
- Clinical subgroups in which SCDs occur
- Time dependence of risk (39).

The overall incidence of SCD in the United States is 1 to 2 per 1000 population (0.1% to 0.2%) annually, with some variations in estimates based on differences in various sources of data. This large population base includes those in whom SCD occurs as a first cardiac event, as well as those for whom SCDs can be predicted with greater accuracy because they are included in higher risk subgroups (Fig. 1). Higher levels of risk resolution can be achieved by identification of more specific subgroups. However, the corresponding absolute number of deaths becomes progressively smaller as the subgroups become more focused, limiting the potential impact of interventions to a much smaller fraction of the total population (10). At least 50% of all SCDs due to CHD occur as a first clinical event or among subgroups of patients thought to be at relatively low risk for SCD (43).

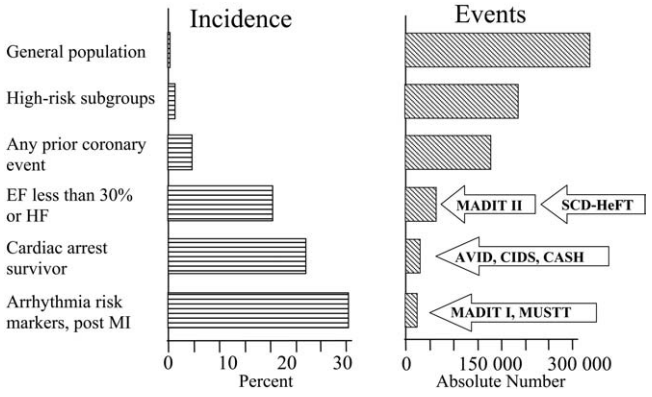

Figure 1. Absolute numbers of events and event rates of SCD in the general population and in specific subpopulations over 1 y. General population refers to unselected population age greater than or equal to 35 y, and high-risk subgroups to those with multiple risk factors for a first coronary event. Clinical trials that include specific subpopulations of patients are shown in the right side of the figure. AVID = Antiarrhythmics Versus Implantable Defibrillators; CASH = Cardiac Arrest Study Hamburg; CIDS = Canadian Implantable Defibrillator Study; EF = ejection fraction; HF = heart failure; MADIT = Multicenter Automatic Defibrillator Implantation Trial; MI = myocardial infarction; MUSTT = Multicenter UnSustained Tachycardia Trial; SCD-HeFT = Sudden Cardiac Death in Heart Failure Trial. Modified with permission from Myerburg RJ, Kessler KM, Castellanos A. SCD. Structure, function, and time-dependence of risk. Circulation 1992;85:I2–10.

2.2.3. Time-Dependent Risk

The risk of SCD after a clinical event is not linear as a function of time (39,46). Survival curves after major cardiovascular events, which identify risk for both sudden and total cardiac death, demonstrate that the most rapid rate of attrition usually occurs during the first 6 to 18 mo after the index event. Curves with these characteristics have been generated from data on survivors of out-of-hospital cardiac arrest, new onset of HF, and unstable angina and on high-risk subgroups of patients with recent MI. In contrast to inherent (baseline) risk patterns over time, however, benefit patterns from controlled trials may show divergence of curves early (e.g., post-MI beta-blocker therapy, clopidogrel in ACSs) or later (e.g., angiotensin-converting enzyme [ACE] inhibitors and statins). Mortality is highest in the first month after acute MI (AMI) in patients with EF of less than 30% (47).

2.2.4. Age, Heredity, Gender, and Race

The incidence of SCD increases as a function of advancing age (48), in parallel with the age-related increase in the incidence of total CHD deaths, but may undergo a relative decrease in the eighth decade and beyond because of competing causes of death. The incidence is 100-fold less in adolescents and adults younger than 30 y (1 in 100 000 per year) than it is in adults older than 35 y (49–51). The proportion of coronary deaths and of all cardiac causes of death that are sudden is highest in the younger age groups.

Hereditary factors that contribute to CHD risk have been thought to operate nonspecifically for the SCD syndrome. However, several studies have identified mutations and relevant polymorphisms along multiple steps of the cascade from atherogenesis to plaque destabilization, thrombosis, and arrhythmogenesis, each of which is associated with a risk of a coronary event (52–55). Integration of these individual markers may provide more powerful individual risk prediction in the future (56). In addition, 2 population studies suggest that SCD, as an expression of CHD, clusters in specific families (57,58). There is a large preponderance of SCD in males compared with females during the young adult and early middle-age years because of the protection females enjoy from coronary atherosclerosis before menopause (59–61). As coronary event risk increases in postmenopausal women, SCD risk increases proportionately. Even though the overall risk is much lower in younger women, the established coronary risk factors are still predictive of events (59,61–63).

Studies comparing racial differences in risk of SCD among whites and African Americans with CHD in the

United States have yielded conflicting and inconclusive data. However, some studies have demonstrated excess risk of cardiac arrest and SCD among African Americans compared with whites (61,64). SCD rates among Hispanic populations were lower (61).

2.2.5. Risk Profiles and Sudden Cardiac Death

Biological and behavioral risk profiling for coronary artery disease, using the conventional risk factors for coronary atherogenesis (65), is useful for identifying levels of population risk but has limited value for distinguishing individual patients at risk for SCD. Multivariate analyses of selected risk factors for atherogenesis have determined that approximately one half of all SCDs occur among the 10% of the population in the highest risk decile. Thus, the cumulative risk associated with conventional risk factors for coronary atherosclerosis exceeds the simple arithmetic sum of the individual risks (65). The comparison of risk factors in the victims of SCD with those in people who developed any manifestations of coronary artery disease does not provide useful patterns. In addition, certain angiographic and hemodynamic patterns discriminate SCD risk from non-SCD risk only under limited conditions (66).

Markers of risk that move beyond the direct lipid deposition concept of atherogenesis into more complex pathobiology are now being identified, largely focusing on mechanisms responsible for destabilization of lipid-laden plaques. Inflammatory markers, such as C-reactive protein and other indicators of inflammation and destabilization (67), have entered into risk formulations, offering potentially useful additions to conventional risk markers (68,69). In addition, familial clustering of SCD as a specific manifestation of the disease (57,58) may lead to identification of specific genetic abnormalities that predispose to SCD (52–54,70).

Hypertension is an established risk factor for CHD and also emerges as a risk factor for SCD (71). Both the ECG pattern of left ventricular hypertrophy (LVH) and echocardiographic evidence or LVH are associated with a higher proportion of sudden and unexpected cardiac death. Intraventricular conduction abnormalities such as left bundle-branch block (LBBB) are also suggestive of a disproportionate number of SCD (72,73).

There are also meaningful associations between cigarette smoking, obesity, diabetes, and lifestyle and SCD. The Framingham Study demonstrates that cigarette smokers have a 2- to 3-fold increase in SCD risk; this is one of the few risk factors in which the proportion of CHD deaths that are sudden increases in association with the risk factor (72). In addition, in a study of 310 survivors of out-of-hospital cardiac arrest, the recurrent cardiac arrest rate was 27% at 3 y of follow-up among those who continued to smoke after their index event, compared with 19% in those who stopped (74). Obesity is a second factor that appears to influence the proportion of coronary deaths that occur suddenly (72).

Associations between levels of physical activity and SCD have been studied, with varying results (75). A high resting heart rate with little change during exercise and recovery is a risk factor for SCD. Epidemiological observations have suggested a relationship between sedentary activity and increased CHD death risk. The Framingham Study, however, showed an insignificant relationship between low levels of physical activity and incidence of SCD but a high proportion of sudden to total cardiac deaths at higher levels of physical activity (72). An association between acute physical exertion and SCD demonstrated a 17-fold relative increase for the risk of SCD during vigorous exercise for the entire populations (active and inactive). For the habitually inactive, the relative risk was 74 (76). Habitual vigorous exercise attenuates risk (76,77). Therefore, these data indicate that, while the risk of cardiac arrest is higher during vigorous exercise (especially among individuals who are usually sedentary), habitual exercise attenuates the risk of cardiac arrest, both during exercise and at rest (78).

The magnitude of recent life changes in the realms of health, work, home, and family and personal and social factors have been related to MI and SCD (79–82). There is an association between significant elevations of life-change scores during the 6 mo before a coronary event, and the association is particularly striking in victims of SCD. After controlling for other major prognostic factors, the risk of SCD and total mortality is increased by social and economic stresses (83), and alteration of modifiable lifestyle factors has been proposed as a strategy for reducing risk of SCD in patients with CHD (84). Acute psychosocial stressors have been associated with risk of cardiovascular events, including SCD (85,86). The risk appears to cluster around the time of the stress and appear to occur among victims at preexisting risk, with the stressor simply advancing the time of an impending event (85). The possibility of physical stress–induced coronary plaque disruption has also been suggested (87).

3. MECHANISMS AND SUBSTRATES

3.1. Substrate for Ventricular Arrhythmias

The substrate for SCD varies depending on the underlying structural heart disease, if any, and ranges from no obvious evidence of structural damage to advanced cardiomyopathic states. Most studies suggest that three quarters of the patients dying of SCD have CHD. Extensive coronary atherosclerosis is generally found, with a high proportion of hearts having 3- or 4-vessel coronary disease involvement. Anatomical findings at autopsy include acute changes in coronary plaque morphology, such as thrombus, plaque disruption, or both, in more than 50% of cases of sudden coronary death. Hearts that have myocardial scars and no acute infarction show active coronary lesions in approximately 50% of cases (88). Erosion of proteoglycan- and smooth muscle cell–rich plaques lacking a superficial lipid core, or plaque rupture, is a frequent pathological finding (89). Plaque rupture appears to be more common in older women (90). However, these anatomical abnormalities are not represented by specific clinical risk factors different from

those that identify patients with CHD in general. Naturally, the substrate will be different depending on the nature of the heart disease. As noted in Section 2, other diseases predisposing to SCD include both hypertrophic cardiomyopathy (HCM) and dilated cardiomyopathy (DCM), right ventricular (RV) cardiomyopathy, congenital abnormalities (especially coronary artery anomalies), coronary artery spasm, and other less common problems (44,46,91). Obesity, hypertension, lipid abnormalities, and diabetes are important risk factors (92–95). The heritable abnormalities of RV cardiomyopathy and HCM are the major substrates found in the sudden deaths of pre–coronary artery age groups (96–98). The cumulative risk of SCD has been estimated at 15% to 20% of adults with aortic stenosis, with the risk being higher in symptomatic patients and equal to or less than 5% in asymptomatic patients (99). Mitral valve prolapse is usually non–life threatening, and its link with SCD has never been conclusively demonstrated (3). Reported SCD rates in patients with Wolff-Parkinson-White (WPW) syndrome have been 0.15%, due in most to the development of atrial fibrillation (AF) with a rapid ventricular response that degenerates to VF (100,101).

Genetic influences modulate the risk of SCD in the setting of coronary (and likely other) heart disease (3,55,102). The Paris Prospective Study I, analyzing more than 7000 men followed for an average of 23 y, found that a parental history of SCD increased the relative risk of SCD for offspring to 1.8, without elevating the risk for MI. When both parents had SCD, the relative risk for SCD in offspring was 9.4 (58). A retrospective study performed on cardiac arrest survivors in King County, Washington, also reported family history to be a significant, independent risk for SCD, with an odds ratio of 1.57 (57). Genetic influences may act through multiple, though, not necessarily exclusive mechanisms: by modulating the fixed substrate, atherothrombosis, electrogenesis impulse propagation, neural control and regulation.

In 5% to 10% of cases, SCD occurs in the absence of CHD or cardiomyopathy. There exists a group of inherited abnormalities such as the long QT syndrome (LQTS), short QT syndrome (SQTS), Brugada syndrome, and catecholaminergic VT, which can precipitate SCD without overt structural changes in the heart (103–105). Abnormalities in potassium and sodium channels, in ankyrin B, and in the ryanodine receptor of the sarcoplasmic reticulum which is responsible for release of the calcium required for cardiac muscle contraction, can disrupt the normal electrical processes of the heart to cause life-threatening ventricular arrhythmias. It is important to stress that some individuals can have inherited abnormalities that are not manifest until triggered by an external event. For example, autonomic modulation associated with certain types of activity, as well as drugs that affect cardiac repolarization, can convert a subclinical genetic abnormality to SCD. It is highly likely that additional genetic causes of SCD will be found in the future (56).

Among the genetic factors, the most common are DNA variants called "polymorphisms" that may be present in a large proportion of the population and create susceptibility for SCD. Single nucleotide polymorphisms (SNPs) are DNA variants that can be associated with a functional consequence. For example, a polymorphism identified in the alpha 2b adrenergic receptor is associated with an increased risk of MI and SCD (106). Studies such as these require validation before they enter clinical practice. Nevertheless, because millions of SNPs are present in the DNA of each individual, a specific combination of polymorphisms in different genes, interacting with a specific trigger or substrate, may be required to create a risk for SCD (56).

3.2. Mechanisms of Sudden Cardiac Death

The rhythm most often recorded at the time of sudden cardiac arrest is VF. Previous studies suggest that 75% to 80% occur via this mechanism and 15% to 20% are attributed to bradyarrhythmias, including advanced atrioventricular (AV) block and asystole (107). Bayes de Luna et al. (108) noted that in 157 ambulatory patients who had SCD while undergoing Holter recording, 62.4% had VF, 16.5% had bradyarrhythmias, 12.7% had torsades de pointes, and 8.3% had primary VT. The true incidence of bradyarrhythmias is not clear because a rhythm beginning as VF may appear to be asystole when the first ECG is recorded. However, a study reported by Cobb et al. (37) suggests that VF accounts for a smaller proportion of events than previously thought. Advanced AV block or significant bradycardia can cause VF. It is difficult to identify accurately the EP mechanism(s) responsible for SCD. The reason for this is that the mechanisms may be multifactoral and are quite likely to be different depending on the specific cardiac abnormality and a rhythm can start via one mechanism and be perpetuated via another. It is also important to remember that while many studies have investigated EP mechanisms responsible for the onset of VT and VF and their continuation, no class I or III antiarrhythmic agent (109) has clearly been demonstrated to reduce total and SCD mortality in patients at risk for SCD (7a,109). In fact, it is the drugs without direct EP actions on cardiac muscle or specialized conducting tissue that have been shown effective for prevention of SCD. These drugs include beta blockers, ACE inhibitors, angiotensin receptor–blocking agents, lipid-lowering agents, spironolactone, and fibrinolytic and antithrombotic agents; some data also suggest a protective effect of n-3 fatty acids (110), although this remains to be confirmed (111) (see Section 6.4).

Because SCD is for the most part the result of a ventricular tachyarrhythmia, these drugs must be acting on the fundamental biochemical, ischemic, fibrotic, or other processes that underlie the onset or maintenance of the life-threatening ventricular arrhythmias. Thought of in this fashion, VF can be considered a final common pathway for the expression of an electrically unstable heart. The fundamental mechanisms of cardiac arrest include electromechan-

ical dissociation, asystole and heart block, and VF, with VF being the most common. It is the "upstream" events triggering the electrical instability upon which these drugs probably act. While we unquestionably need to pursue investigations into the electrophysiology of these ventricular tachyarrhythmias, more study needs to be applied to the drugs affecting upstream events, because these events appear to yield the greatest dividends, at least for the present, and must be the reason why the asymptomatic, apparently stable, individual suddenly develops SCD at a particular time on a particular day. It must be that a dynamic factor or factors, possibly transient, interact with a fixed substrate to precipitate the arrhythmia. The possibilities fill a long list and include such things as physical activity, transient ischemia, pH and electrolyte changes, inflammation, hypoxia, stretch, ion channel abnormalities, neuroendocrine actions, drugs, and so forth, all of which are capable of modulating conduction in ways we mostly do not understand. More permanent changes could also occur, such as plaque rupture, as mentioned earlier (112).

4. CLINICAL PRESENTATIONS OF PATIENTS WITH VENTRICULAR ARRHYTHMIAS AND SUDDEN CARDIAC DEATH

Ventricular arrhythmias can occur in individuals with or without a cardiac disorder. There is a great deal of overlap between clinical presentations (Table 5) and the severity and type of heart disease. For example, stable and well-tolerated VT can occur in the individual with previous MI and impaired ventricular function. The prognosis and management are individualized according to symptom burden and severity of underlying heart disease, in addition to the clinical presentation.

4.1. Asymptomatic

Ventricular arrhythmias may be detected as an incidental finding during ECG monitoring or physical examination. They may also be uncovered during an attempt to further define prognosis in an individual with known heart disease.

Table 5. Clinical Presentations of Patients With Ventricular Arrhythmias and Sudden Cardiac Death

- Asymptomatic individuals with or without electrocardiographic abnormalities
- Persons with symptoms potentially attributable to ventricular arrhythmias
  - Palpitations
  - Dyspnea
  - Chest pain
  - Syncope and presyncope
- Ventricular tachycardia that is hemodynamically stable
- Ventricular tachycardia that is not hemodynamically stable
- Cardiac arrest
  - Asystolic (sinus arrest, atrioventricular block)
  - Ventricular tachycardia
  - Ventricular fibrillation
  - Pulseless electrical activity

In general, treatment is indicated to prevent potential morbidity (e.g., "tachycardia-induced cardiomyopathy"), reduce symptom burden, or reduce the risk of SCD. There is no reason to treat asymptomatic ventricular arrhythmias in the absence of such potential benefit. The major determinants of risk of SCD are related more to the type and severity of associated cardiac disease and less to the frequency or classification of ventricular arrhythmia (44,113). Certain arrhythmias such as rapid polymorphic VT may be compelling to treat even in the asymptomatic individual without evident heart disease. Nonetheless, such arrhythmias are rarely asymptomatic and are probably related to ionic channel abnormalities yet to be elucidated (114,115). NSVT in the patient with previous MI and impaired LV function indicates increased risk of SCD and the need for further evaluation or treatment (116). The contribution of asymptomatic ventricular arrhythmias to the patient's management is not well established for other cardiac diseases such as DCM (117) or HCM (118).

4.2. Symptoms Potentially Related to Ventricular Arrhythmias

Palpitations or a perception of cardiac rhythm irregularity may be caused by the whole spectrum of arrhythmias and are also frequently reported in patients in the absence of any arrhythmia (119). Less frequently, patients with VT may present with symptoms of paroxysmal dyspnea or chest pain in the absence of a sensation of rapid heart beating. In such instances, the dyspnea or chest pain may be related to the hemodynamic consequences of tachycardia. "Presyncope" is a vague term that is poorly defined but probably is interpreted by most as a feeling of impending syncope (120). It is not specific as a symptom. VT may be a cause of undiagnosed syncope, especially in patients with structural heart disease (121). Patients with poor ventricular function and inducible VT or VF have a high incidence of subsequent appropriate therapies when implanted with an ICD (122–128). Similar patients with poor ventricular function may be at risk of SCD (129). Patients with sudden onset of very rapid VT such as torsades de pointes with the repolarization syndromes will typically present with syncope or seizure rather than an awareness of rapid heart beating or palpitations (130).

4.2.1. Hemodynamically Stable Ventricular Tachycardia

Patients with slower, stable VT may be asymptomatic but more frequently present with a sensation of rapid heart beating possibly accompanied by dyspnea or chest discomfort. The stability or tolerance of VT is related to the rate of tachycardia, presence of retrograde conduction, ventricular function, and the integrity of peripheral compensatory mechanisms. A presentation with stable, relatively well-tolerated VT does not suggest the absence of heart disease and can be observed in patients with very poor LV function. Even patients with poor ventricular function may not be aware of palpitations during VT. Presentation with stable

VT does not in itself indicate a benign prognosis in patients with significant heart disease (131). Incessant VT, although hemodynamically stable, can be a cause of hemodynamic deterioration leading to HF (132). In patients with an ICD, the VT rate can fall below the lower rate of VT detection, causing underdetection of VT that can prevent arrhythmia termination. Immediate reinitiation of the VT following proper ICD therapy can also result in hemodynamic deterioration and an early battery depletion (132,133).

4.2.2. Hemodynamically Unstable Ventricular Tachycardia

The term "hemodynamically unstable" has not been rigidly defined but is widely used. It connotes a tachycardia associated with hypotension and poor tissue perfusion that is considered to have the imminent potential to lead to cardiac arrest or shock if left untreated. Hemodynamically unstable VT is usually, but not exclusively, observed in patients with poor ventricular function. Patients with normal ventricular function can have unstable VT or VF if the tachycardia is rapid enough, as in the LQTS and other abnormal repolarization syndromes (103). Some patients with a normal heart and idiopathic monomorphic VT or even supraventricular tachycardia (SVT) can become hypotensive during the arrhythmia because of a vasovagal reaction.

4.3. Sudden Cardiac Arrest

Rapid sustained VT or VF results in presentation with markedly impaired tissue perfusion and loss of consciousness as a result of inadequate cardiac output, leading to SCD if not expediently reversed. Sudden cardiac arrest may be the presenting symptom with any cardiac disease or even in individuals with no apparent heart disease (44). The initiating mechanism of sudden cardiac arrest may or may not be related to arrhythmia.

5. GENERAL EVALUATION OF PATIENTS WITH DOCUMENTED OR SUSPECTED VENTRICULAR ARRHYTHMIAS

5.1. History and Physical Examination

Palpitations, presyncope, and syncope are the 3 most important symptoms requiring further characterization in patients suspected of having ventricular arrhythmias. Palpitations are usually of a sudden onset/offset pattern and may be associated with presyncope and/or syncope. Sudden episodes of collapse with loss of consciousness without any premonition that usually last for a few seconds must raise the suspicion of conduction defects or ventricular arrhythmias. Other symptoms related to underlying structural heart disease may also be present, especially chest discomfort, dyspnea, and fatigue. A thorough drug history including dosages used must be included in the evaluation of patients suspected of having ventricular arrhythmias. Two important studies (57,58) have confirmed that a positive family history of SCD is a strong independent predictor of susceptibility to ventricular arrhythmias and SCD, as noted earlier. Physical examination is often unrevealing in patients suspected of having ventricular arrhythmias unless the arrhythmia occurs while the patient is being examined or has other findings indicative of structural heart disease.

5.2. Noninvasive Evaluation

5.2.1. Resting Electrocardiogram

Recommendations

Class I

Resting 12-lead ECG is indicated in all patients who are evaluated for ventricular arrhythmias. *(Level of Evidence: A)*

A standard resting 12-lead ECG allows not only identification of various congenital abnormalities associated with ventricular arrhythmias and SCD (e.g., LQTS, SQTS, Brugada syndrome, ARVC) but also identification of various other ECG parameters, such as those due to electrolyte disturbances, or evidence suggesting underlying structural disease, such as bundle-branch block, AV block, ventricular hypertrophy, and Q waves indicative of ischemic heart disease or infiltrative cardiomyopathy. QRS duration and repolarization abnormalities are both independent predictors of SCD. A prolonged QRS duration greater than 120 to 130 ms has been shown in a number of studies to be associated with increased mortality in patients with a reduced LVEF (equal to or less than 30%). Prospective studies have also reported an association between ST-segment depression or T-wave abnormalities and increased risk of cardiovascular death and SCD in particular. These studies have demonstrated a risk ratio for cardiovascular death of 2.16 (95% confidence interval [CI] 1.30 to 3.58) to 2.4 (95% CI 1.70 to 3.53) in the presence of an "ischemic" ECG (134) and 4.4 (95% CI 2.6 to 7.4) for SCD in the presence of an abnormal T-wave axis (135,136). A prolonged QTc interval is also an independent predictor of SCD. QTc greater than 420 ms has been shown to have a higher risk of cardiovascular death relative to a shorter QTc. And a QTc greater than 440 ms significantly predicted cardiovascular death with adjusted relative risk of 2.1 (137). Although a prolonged QTc interval predicts SCD, it is worth noting that some data suggest that the correlation between QTc and survival may be "J-shaped." In other words, relatively short QTc intervals have also been associated with increased risk. For instance, it has been reported that patients with a mean QTc shorter than 400 ms during 24-h ECG have a more than 2-fold risk of dying suddenly than do patients with a mean QTc between 400 and 440 ms after a 2-y follow-up (138). A QTc less than 300 ms is often used to define the SQTS, which is an independent predictor of SCD (139,140).

5.2.2. Exercise Testing

Recommendations

Class I

1. **Exercise testing is recommended in adult patients with ventricular arrhythmias who have an intermediate or greater probability of having CHD by age, gender, and symptoms* to provoke ischemic changes or ventricular arrhythmias.** ***(Level of Evidence: B) *See Table 4 in the ACC/AHA 2002 Guideline Update for Exercise Testing (141) for further explanation of CHD probability.***
2. **Exercise testing, regardless of age, is useful in patients with known or suspected exercise-induced ventricular arrhythmias, including catecholaminergic VT, to provoke the arrhythmia, achieve a diagnosis, and determine the patient's response to tachycardia.** ***(Level of Evidence: B)***

Class IIa

Exercise testing can be useful in evaluating response to medical or ablation therapy in patients with known exercise-induced ventricular arrhythmias. ***(Level of Evidence: B)***

Class IIb

1. **Exercise testing may be useful in patients with ventricular arrhythmias and a low probability of CHD by age, gender, and symptoms.*** ***(Level of Evidence: C) *See Table 4 in the ACC/AHA 2002 Guideline Update for Exercise Testing (141) for further explanation of CHD probability.***
2. **Exercise testing may be useful in the investigation of isolated premature ventricular complexes (PVCs) in middle-aged or older patients without other evidence of CHD.** ***(Level of Evidence: C)***

Class III

See Table 1 in the ACC/AHA 2002 Guideline Update for Exercise Testing (141) for contraindications. ***(Level of Evidence: B)***

Exercise-ECG is commonly used in the evaluation of patients with ventricular arrhythmias. Its most common application is for detection of silent ischemia in patients suspected of having underlying CHD (141). In patients with known or silent CHD or cardiomyopathies, the presence of frequent PVCs during or after exercise has been associated with greater risk for serious cardiovascular events but not specifically SCD (19,20,24). Exercise-induced PVCs in apparently normal individuals should not be used to dictate therapy unless associated with documented ischemia or sustained VT. With the exception of beta blockers, at the present time the use of antiarrhythmic drugs to abolish exercise-induced PVCs has not been proved to be effective in reducing SCD.

Exercise testing in adrenergic-dependent rhythm disturbances, including monomorphic VT and polymorphic VT, may be useful in evaluating symptomatic subjects and evaluating response to therapy. Ambulatory ECG or event monitoring may fail to capture the arrhythmia, particularly if the patient is relatively sedentary. Moreover, exercise testing may provide prognostic information in these patients, given that the presence of exercise-induced ventricular ectopy increases mortality at 12 mo by 3-fold relative to patients with ectopy at rest only (142). Patients with exercise-induced paired ventricular complexes or VT have a lower survival rate than those with exercise-induced simple ventricular ectopy (143).

Although the safety of supervised exercise testing is well established, less data are available in patients at risk for serious ventricular arrhythmias. In one series, exercise testing in patients with life-threatening ventricular arrhythmias was associated with a 2.3% incidence of arrhythmias requiring cardioversion, intravenous drugs, or resuscitation (144). Such an exercise study may still be warranted because it is better to expose arrhythmias and risk under controlled circumstances. Exercise testing should be performed where resuscitation equipment and trained personnel are immediately available.

5.2.3. Ambulatory Electrocardiography

Recommendations

Class I

1. **Ambulatory ECG is indicated when there is a need to clarify the diagnosis by detecting arrhythmias, QT-interval changes, T-wave alternans (TWA), or ST changes, to evaluate risk, or to judge therapy.** ***(Level of Evidence: A)***
2. **Event monitors are indicated when symptoms are sporadic to establish whether or not they are caused by transient arrhythmias.** ***(Level of Evidence: B)***
3. **Implantable recorders are useful in patients with sporadic symptoms suspected to be related to arrhythmias such as syncope when a symptom-rhythm correlation cannot be established by conventional diagnostic techniques.** ***(Level of Evidence: B)***

The use of continuous or intermittent ambulatory recording techniques can be very helpful in diagnosing a suspected arrhythmia, establishing its frequency, and relating symptoms to the presence of the arrhythmia. Silent myocardial ischemic episodes may also be detected. A 24- to 48-h continuous Holter recording is appropriate whenever the arrhythmia is known or suspected to occur at least once a day. For sporadic episodes producing palpitations, dizziness, or syncope, conventional event monitors are more appropriate because they can record over extended periods of time (145).

New implantable recorders are capable of monitoring the rhythm and can record on patient activation or automatically for prespecified criteria. Although these devices require surgical implantation, they have been shown to be extremely useful in diagnosing serious tachyarrhythmias and bradyarrhythmias in patients with life-threatening symptoms such as syncope (120,146).

5.2.4. Electrocardiographic Techniques and Measurements

Recommendations

Class IIa

It is reasonable to use TWA to improve the diagnosis and risk stratification of patients with ventricular arrhythmias or who are at risk for developing life-threatening ventricular arrhythmias. ***(Level of Evidence: A)***

Class IIb

ECG techniques such as signal-averaged ECG (SAECG), heart rate variability (HRV), baroflex sensitivity, and heart rate turbulence may be useful to improve the diagnosis and risk stratification of patients with ventricular arrhythmias or who are at risk of developing life-threatening ventricular arrhythmias. ***(Level of Evidence: B)***

ICD trials, especially Multicenter Automatic Defibrillator Implantation Trial (MADIT) II, have highlighted the need to develop novel tools in order to identify patients at highest risk of ventricular arrhythmias and SCD. Numerous modalities exist at present for assessing this risk but only 2 are currently approved by the U.S. Food and Drug Administration (FDA): SAECG and TWA. However, HRV and baroflex sensitivity also show considerable promise. SAECG improves the signal-to-noise ratio of a surface ECG, permitting the identification of low-amplitude (microvolt level) signals at the end of the QRS complex referred to as "late potentials." Late potentials indicate regions of abnormal myocardium demonstrating slow conduction, a substrate abnormality that may allow for reentrant ventricular arrhythmias, and they are believed to serve as a marker for the presence of an EP substrate for reentrant ventricular tachyarrhythmias. The presence of an abnormal SAECG was shown to increase the risk of arrhythmic events by 6- to 8-fold in a post-MI setting (147). However, the restoration of patency to the infarct-related coronary artery with fibrinolysis or angioplasty and the widespread use of surgical revascularization have modified the arrhythmogenic substrate, leading to a noticeable reduction in the predictive power of this tool. SAECG in isolation, therefore, is no longer useful for the identification of post-MI patients at risk of ventricular arrhythmias. However, a high negative predictive value of 89% to 99% rendered the SAECG a useful tool with which to exclude a wide-complex tachycardia as a cause of unexplained syncope (148,149).

TWA, which is a fluctuation in the amplitude or morphology of the T wave that alternates every other beat assessed during exercise testing or atrial pacing, has been shown to be an effective tool for identifying high-risk patients post-MI (150) and in the presence of ischemic or nonischemic cardiomyopathy. This association appears to be independent of EF and equally strong in patients with ischemic and nonischemic cardiomyopathy. TWA appears to have a very high negative predictive accuracy (151–153). TWA may also be used to identify risk of arrhythmic mortality in patients with LV dysfunction due to prior MI (154). In a small study of patients with MADIT II characteristics (post-MI with EF less than or equal to 30%), a microvolt TWA test was found to be better than QRS duration at identifying a high-risk group and also a low-risk group unlikely to benefit from ICD therapy (155).

HRV, which is a beat-to-beat variation in cardiac cycle length resulting from autonomic influence on the sinus node of patients in sinus rhythm, has been shown to independently predict the risk of SCD and total mortality in patients post-MI (156) both with and without impaired LV function (157–159). Observational studies also suggest its usefulness in the presence of nonischemic cardiomyopathy, but this has to be confirmed with large clinical trials. There are many different forms of heart rate analysis, some of which, such as heart rate turbulence, may be more productive than others. Reduced baroflex sensitivity, a quantitative assessment of the ability of the autonomic nervous system to react to acute stimulation involving primarily vagal reflexes, compared with a continuous assessment of basal sympathovagal information provided by HRV, has also proved successful in assessing the risk of SCD both alone (increased inducibility of arrhythmic events including VT during EP testing) (160,161) and when used in combination with HRV (increased risk of cardiac mortality post-MI) (157) and TWA (increased risk of arrhythmic events if both parameters are abnormal in a cohort of patients with ICDs) (162). Additional prospective studies are needed to further clarify the role of these ECG parameters in assessing risk in differing clinical settings.

5.2.5. Left Ventricular Function and Imaging

Recommendations

Class I

1. **Echocardiography is recommended in patients with ventricular arrhythmias who are suspected of having structural heart disease.** ***(Level of Evidence: B)***
2. **Echocardiography is recommended for the subset of patients at high risk for the development of serious ventricular arrhythmias or SCD, such as those with dilated, hypertrophic, or RV cardiomyopathies, AMI survivors, or relatives of patients with inherited disorders associated with SCD.** ***(Level of Evidence: B)***

3. **Exercise testing with an imaging modality (echocardiography or nuclear perfusion [single-photon emission computed tomography (SPECT)]) is recommended to detect silent ischemia in patients with ventricular arrhythmias who have an intermediate probability of having CHD by age, symptoms, and gender and in whom ECG assessment is less reliable because of digoxin use, LVH, greater than 1-mm ST-segment depression at rest, WPW syndrome, or LBBB.** ***(Level of Evidence: B)***
4. **Pharmacological stress testing with an imaging modality (echocardiography or myocardial perfusion SPECT) is recommended to detect silent ischemia in patients with ventricular arrhythmias who have an intermediate probability of having CHD by age, symptoms, and gender and are physically unable to perform a symptom-limited exercise test.** ***(Level of Evidence: B)***

Class IIa

1. **MRI, cardiac computed tomography (CT), or radionuclide angiography can be useful in patients with ventricular arrhythmias when echocardiography does not provide accurate assessment of LV and RV function and/or evaluation of structural changes.** ***(Level of Evidence: B)***
2. **Coronary angiography can be useful in establishing or excluding the presence of significant obstructive CHD in patients with life-threatening ventricular arrhythmias or in survivors of SCD, who have an intermediate or greater probability of having CHD by age, symptoms, and gender.** ***(Level of Evidence: C)***
3. **LF imaging can be useful in patients undergoing biventricular pacing.** ***(Level of Evidence: C)***

5.2.5.1. Echocardiograph

Echocardiography is the imaging technique that is most commonly used because it is inexpensive in comparison with other techniques such as MRI and cardiac CT, it is readily available, and it provides accurate diagnosis of myocardial, valvular, and congenital heart disorders associated with ventricular arrhythmias and SCD (163,164) (Table 6). In addition, LV systolic function and regional wall motion can be evaluated and, in a majority of patients, EF can be determined (165). Echocardiography is therefore indicated in patients with ventricular arrhythmias suspected of having structural heart disease and in the subset of patients at high risk for the development of serious ventricular arrhythmias or SCD, such as those with dilated, hypertrophic or RV cardiomyopathies, AMI survivors, or relatives of patients with inherited disorders associated with SCD. The combination of echocardiography with exercise or pharmacological stress (commonly known as "stress echo") is applicable to a selected group of patients who are suspected of having ventricular arrhythmias triggered by ischemia and who are unable to exercise or have resting ECG abnormalities that limit the accuracy of ECG for ischemia detection (164). Anomalous origin of coronary arteries can be detected by echocardiography or other imaging techniques.

Table 6. Conditions Associated With Ventricular Arrhythmias That Can Be Diagnosed With Echocardiography

Disease Entity	Diagnostic Accuracy
Dilated cardiomyopathy	High
Ischemic cardiomyopathy	High
Hypertension with moderate to severe LVH	High
Hypertrophic cardiomyopathy	High
Valvular heart disease	High
ARVC	Moderate
Brugada syndrome	Poor

ARVC = arrhythmogenic right ventricular cardiomyopathy; LVH = left ventricular hypertrophy.

5.2.5.2. Cardiac Magnetic Resonance Imaging

Advances in cardiac MRI have made possible the use of this imaging technique to evaluate both the structure and function of the beating heart. The excellent image resolution obtained with current techniques allows for the accurate quantification of chamber volumes, LV mass, and ventricular function (166–168). This is of particular value to patients with suspected arrhythmogenic RV cardiomyopathy (ARVC), in whom MRI provides excellent assessment of RV size, function, and regional wall motion and, importantly, may allow the detection of fatty infiltration within the RV myocardium (169,170). RV angiography may also be useful. Cardiac MRI increasingly is being applied and validated for the detection of ischemia (adenosine stress perfusion and dobutamine stress wall motion studies) and the detection and quantification of infarction/fibrosis, a substrate for VT. The cost and availability of cardiac MRI are becoming more competitive. Cardiac MRI can provide a comprehensive cardiac evaluation in a single study. It is important to stress that, as with all imaging modalities, accurate interpretation affects its usefulness (171).

5.2.5.3. Cardiac Computed Tomography

As with MRI, the field of CT has advanced greatly with the development of fast scanners with better resolution that allow tomographic imaging of the heart and coronary arteries. These systems allow precise quantification of LV volumes, EF, and LV mass with results comparable to MRI but in addition provide segmental images of the coronary arteries from which the extent of calcification can be quantified (172–176). The majority of cardiac disorders associated with serious ventricular arrhythmias or SCD are assessed well with echocardiography. Cardiac CT can be used in selected patients in whom evaluation of cardiac structures is not feasible with echocardiography and MRI is not available. There is currently no incremental clinical benefit derived from imaging the coronary arteries by cardiac CT in patients with ventricular arrhythmias.

5.2.5.4. Radionuclide Techniques

Myocardial perfusion SPECT using exercise or pharmacological agents is applicable for a selected group of patients

who are suspected of having ventricular arrhythmias triggered by ischemia and who are unable to exercise or have resting ECG abnormalities that limit the accuracy of ECG for ischemia detection. Myocardial perfusion SPECT can also be used to assess viability in patients with LV dysfunction due to prior MI (177). Accurate quantification of LVEF is possible with gated radionuclide angiography (multiple gated acquisition scan) and thus this technique may be helpful in patients for whom this measurement is not available with echocardiography.

5.2.5.5. Coronary Angiography

In patients with life-threatening ventricular arrhythmias or in survivors of SCD, coronary angiography plays an important diagnostic role in establishing or excluding the presence of significant obstructive coronary artery disease. It is common for these patients to undergo this procedure as part of their diagnostic evaluation, particularly if they have an intermediate or greater probability for CHD. Detailed recommendations regarding imaging and exercise testing can be found in the respective guidelines (141,164,177).

5.3. Electrophysiological Testing

EP testing with intracardiac recording and electrical stimulation at baseline and with drugs has been used for arrhythmia assessment and risk stratification for SCD. EP testing for the evaluation of VT was introduced in 1972 by Wellens et al. (178). The sensitivity, specificity, and predictive values of EP testing have been extensively assessed by various authors, usually in small patient groups. EP testing is used to document the inducibility of VT, guide ablation, evaluate drug effects, assess the risks of recurrent VT or SCD, evaluate loss of consciousness in selected patients with arrhythmias suspected as a cause, and assess the indications for ICD therapy (121,179–183). The yield of EP testing varies fundamentally with the kind and severity of the underlying heart disease, the presence or absence of spontaneous VT, concomitant drug therapy, the stimulation protocol, and the site of stimulation. Highest induction rates and reproducibility are observed in patients after MI (184–186).

To evaluate patients with ventricular arrhythmias, most centers use 8 ventricular stimuli at drive cycle lengths between 600 and 400 ms at the RV apex, at twice diastolic threshold and the pulse duration of 0.5 to 2 ms, delivering 1 to 3 ventricular extrastimuli at baseline. This test may be repeated during isoproterenol infusion (187–189). The prematurity of extrastimuli is increased until refractoriness or induction of sustained ventricular tachyarrhythmia is achieved. Long-short cycle sequences may be tested. Because premature ventricular stimulation with a very short coupling interval is more likely to induce VF as opposed to monomorphic VT, it may be reasonable to limit the prematurity of the extrastimuli to a minimum of 180 ms when studying patients for whom only inducible sustained monomorphic VT would be considered a positive endpoint (190). EP testing may be repeated at the RV outflow tract (RVOT) or LV (189). In some patients with rate-dependent induction of VT, rapid atrial or ventricular stimulation may induce VT (191).

5.3.1. Electrophysiological Testing in Patients With Coronary Heart Disease

Recommendations

Class I

1. **EP testing is recommended for diagnostic evaluation of patients with remote MI with symptoms suggestive of ventricular tachyarrhythmias, including palpitations, presyncope, and syncope. *(Level of Evidence: B)***
2. **EP testing is recommended in patients with CHD to guide and assess the efficacy of VT ablation. *(Level of Evidence: B)***
3. **EP testing is useful in patients with CHD for the diagnostic evaluation of wide-QRS-complex tachycardias of unclear mechanism. *(Level of Evidence: C)***

Class IIa

EP testing is reasonable for risk stratification in patients with remote MI, NSVT, and LVEF equal to or less than 40%. *(Level of Evidence: B)*

Drug testing for assessing antiarrhythmic drug efficacy has largely been abandoned. EP testing was required in the MADIT, Multicenter UnSustained Tachycardia Trial (MUSTT), and Beta-Blocker Strategy plus Implantable Cardioverter Defibrillator (BEST-ICD) trials and others, but not in the MADIT II, Sudden Cardiac Death in Heart Failure (SCD-HeFT), or Antiarrhythmics Versus Implantable Defibrillators (AVID) trials. Inducibility of VT in patients with NSVT on Holter monitoring identified a population at high risk for VT/VF and ICD use in the MADIT trial (192).

In a MUSTT trial substudy, the ECG characteristics of NSVT (rate, duration, frequency, occurrence in-hospital vs. out-of-hospital) did not correlate with inducibility (193–195). Survival was worse for in-hospital compared with out-of-hospital NSVT, (193) suggesting that different risk stratification criteria may be necessary in asymptomatic ambulatory patients. In a MADIT II substudy, inducibility was 36%. Lower heart rate, lower EF, and a longer interval between MI and an EP study correlates with higher inducibility (196).

In patients with CHD, asymptomatic NSVT, and an EF less than 40%, inducibility of sustained VT ranges between 20% and 40% (116). Inducibility conferred a worse prognosis. Inducibility identifies patients at high risk of subsequent VT and that the absence of inducibility indicated a low risk with MADIT-like patients (197). However, these patients had a high rate of percutaneous revascularization. In CHD patients with a low EF (less

than 30%), noninducibility does not portend a good prognosis (198). Persistent inducibility while receiving antiarrhythmic drugs predicts a worse prognosis (199). Patients in whom amiodarone suppressed VT inducibility or slowed VT to a mean cycle length of greater than 400 ms had 30% higher mortality compared with patients who did not respond to amiodarone and had an ICD placed instead (200). EP-guided antiarrhythmic drug effectiveness in patients with NSVT who had induced sustained VT conferred no benefit (195).

The prognostic value of inducible ventricular flutter and VF is still controversial. Limited data on the prognostic value of inducible ventricular flutter suggest that it may be an important endpoint (201,202).

5.3.2. Electrophysiological Testing in Patients With Dilated Cardiomyopathy

In DCM, EP testing plays a minor role in the evaluation and management of VT. This is related to low inducibility, reproducibility of EP study, and the predictive value of induced VT (203,204) (see Section 9.1).

5.3.3. Electrophysiological Testing in Repolarization Anomalies Due to Genetic Arrhythmia Syndromes

5.3.3.1. Long QT Syndrome

EP testing has not proved useful in LQTS (103,205) (see Section 11.1.1 for further discussion).

5.3.3.2. Brugada Syndrome

The role of EP testing for risk stratification in Brugada syndrome is debated (104,206–208), and it will probably remain undefined until prospective data are obtained in patients studied with a uniform protocol in a large population with adequate follow-up (see Section 11.1.3 for further discussion).

5.3.3.3. Hypertrophic Cardiomyopathy

The value of EP testing in HCM has been controversial (see Section 9.2 for further discussion).

5.3.3.4. Arrhythmogenic Right Ventricular Cardiomyopathy

The arrhythmic manifestations of ARVC are variable (96). The prognostic role of EP testing in patients presenting with isolated PVCs or NSVT is not known. The response to EP testing may be influenced by the severity of the disease. Progression of disease has to be considered (see Section 9.3 for further discussion).

5.3.4. Electrophysiological Testing in Patients With Outflow Tract Ventricular Tachycardia

EP testing for the evaluation of outflow tract VT is basically similar to that for other VT entities. It is motivated by the need to establish precise diagnosis to guide curative catheter ablation (209,210) (see Section 12.1 for further discussion).

5.3.5. Electrophysiological Testing in Patients With Syncope

Recommendations

Class I

EP testing is recommended in patients with syncope of unknown cause with impaired LV function or structural heart disease. ***(Level of Evidence: B)***

Class IIa

EP testing can be useful in patients with syncope when bradyarrhythmias or tachyarrhythmias are suspected and in whom noninvasive diagnostic studies are not conclusive. ***(Level of Evidence: B)***

Syncope is a transient symptom that may be caused by an underlying rhythm disorder with or without an associated cardiac disease. EP testing is used to document or exclude the arrhythmic cause of syncope (120,211). It is most useful in patients with CHD and LV dysfunction. EP testing is usually not the first evaluation step but rather is complementary to a full syncope work-up. Lack of correlation between symptoms and a documented arrhythmia elicited during EP testing may lead to overinterpretation or underinterpretation of the predictive value of the results. Transient drug effects that can provoke syncope may remain undetected. Other causes such as a neurological etiology need to be considered in some patients.

5.3.5.1. Electrophysiological Testing When Bradyarrhythmia Is Suspected

Syncope can be due to bradyarrhythmias from sinus node dysfunction or AV block. Antiarrhythmic drugs, beta-blocking agents, cardiac glycosides, and calcium channel blockers can induce symptomatic bradycardia. EP testing can be used to document or provoke bradyarrhythmias or AV block when other investigations have failed to provide conclusive information. The diagnostic yield varies greatly with the selected patient populations (212). EP testing is more useful in the presence of structural heart disease (213). The diagnostic yield in the absence of structural heart disease or abnormal ECG is low. False-positive results of EP testing can be present in up to 24% of the patients. In syncopal patients with chronic BBB and reduced EF (less than 45%), EP-induced VT is present in up to 42% (184,214,215). In patients with syncope and BBB, false-negative EP studies are common (216,217). EP testing in patients with sporadic bradycardia and syncope has limited sensitivity, even when adding electropharmacological stress such as intravenous procainamide or atropine (218). EP testing can provoke nonspecific tachyarrhythmic responses in patients with preserved LV function who do not have structural heart disease (219).

5.3.5.2. Electrophysiological Testing When Supraventricular Tachyarrhythmia Is Suspected

The role of EP testing is to document the type of tachyarrhythmia and to guide management of patients. In a mixed population, the diagnostic yield of EP testing was 5% (220). In supraventricular tachyarrhythmias, syncope is rarely the only symptom and palpitations are usually present as well. Vasodepressive reaction in a few patients with induced SVT, mainly AV node reentry (221), may be the cause of syncope. Syncope did not correlate with the rate or cycle length of preexcited R-R intervals in WPW syndrome during AF (221).

5.3.5.3. Electrophysiological Testing When Ventricular Tachycardia Is Suspected

Syncope in patients with structural heart disease and, in particular, significant LV dysfunction is ominous. NSVT on Holter monitoring, syncope, and structural heart disease are highly sensitive for predicting the presence of inducible VT (184). Syncope associated with heart disease and reduced EF has high recurrence and death rates (222,223), even when EP testing results are negative. EP testing is useful in patients with LV dysfunction due to prior MI (EF less than 40%) but not sensitive in patients with nonischemic cardiomyopathy (184). Induction of polymorphic VT or VF, especially with aggressive stimulation techniques, is not specific. In CHD, the diagnostic yield may reach 50% (222). In HCM, EP testing is not diagnostic in the majority of patients (224). Induction of nonspecific VTs in 23% of patients with slightly reduced EF has been observed (225).

6. THERAPIES FOR VENTRICULAR ARRHYTHMIAS

6.1. General Management

The selection of appropriate therapy for the management of ventricular arrhythmias (PVCs, NSVT, sustained monomorphic and polymorphic VT, and ventricular flutter/VF) necessitates an understanding of the etiology and mechanism of the arrhythmia, an appreciation of the associated medical conditions that may contribute to and/or exacerbate the arrhythmia, the risk posed by the arrhythmia, and risk-to-benefit aspects of the selected therapy (31,99,226–235). Management of the manifest arrhythmia may involve discontinuation of offending proarrhythmic drugs, specific antiarrhythmic therapy with drugs, implantable devices, ablation, and surgery.

6.2. Drug Therapy

With the exception of beta blockers, the currently available antiarrhythmic drugs have not been shown in randomized clinical trials to be effective in the primary management of patients with life-threatening ventricular arrhythmias or in the prevention of SCD. As a general rule, antiarrhythmic agents may be effective as adjunctive therapy in the management of arrhythmia-prone patients under special circumstances. Because of potential adverse side effects of the available antiarrhythmic drugs, these agents must be used with caution. This section provides general comments about drug and interventional therapy for life-threatening arrhythmias. The recommendations and level of evidence for specific therapy of ventricular arrhythmias that occur in various cardiac disease states are provided in other sections of these guidelines, with the exception of recommendations on ablation, which are located in Section 6.6.

Many marketed cardiac and noncardiac drugs prolong ventricular repolarization and have the potential to precipitate life-threatening ventricular tachyarrhythmias (202,236–239) (see Section 13.6). Some patients are more susceptible than others to the QT-prolonging effects of these drugs even at an ordinary dosage, possibly due to a genetic propensity or female gender. More commonly, the proarrhythmic effect of the agent is related to elevated drug blood levels as a result of excessive dosage, renal disease, or drug interactions. Once it is appreciated that a patient's ventricular arrhythmia may be due to QT prolongation from one or more prescribed medications, the possible offending therapies should be discontinued and appropriate follow-up monitoring of ventricular repolarization and cardiac rhythm should be carried out.

6.3. Antiarrhythmic Drugs

6.3.1. Value of Antiarrhythmic Drugs

Uses of antiarrhythmic drugs in the acute setting are described in Section 7.

The available antiarrhythmic drugs can be classified by the Vaughan Williams 4-level schema (type I: fast sodium channel blockers, type II: beta blockers, type III: repolarization potassium current blockers, type IV: calcium channel antagonists) (240) or by the more mechanistic and clinically relevant Sicilian Gambit (241). The Vaughan Williams schema is somewhat outdated because antiarrhythmic drugs have complex actions that do not easily fit into 1 of the 4 specified classes of drug effects. This classification is of limited usefulness when choosing an antiarrhythmic drug to manage a specific arrhythmia. The Sicilian Gambit, introduced in 1991, was an attempt to provide a classification of antiarrhythmic drugs based on their mechanism of action and on arrhythmogenic mechanisms.

6.3.1.1. Beta Blockers

These drugs are effective in suppressing ventricular ectopic beats and arrhythmias as well as in reducing SCD in a spectrum of cardiac disorders in patients with and without HF. Beta blockers are safe and effective antiarrhythmic agents that can be considered the mainstay of antiarrhythmic drug therapy (242,243). The mechanism of antiarrhythmic efficacy of this class of drugs involves competitive adrenergic-receptor blockade of sympathetically mediated triggering mechanisms, slowing of the sinus rate, and possibly inhibition of excess calcium release by the ryanodine receptor (244).

6.3.1.2. Amiodarone and Sotalol

Amiodarone has a spectrum of actions that includes block of potassium repolarization currents that can inhibit or terminate ventricular arrhythmias by increasing the wavelength for reentry. The overall long-term survival benefit from amiodarone is controversial, with most studies showing no clear advantage over placebo. A few studies and one meta-analysis of several large studies have shown reduction in SCD using amiodarone for LV dysfunction due to prior MI and nonischemic DCM (245–247), but the SCD-HeFT trial showed no survival benefit from amiodarone compared with placebo (7a,248). Chronic administration of amiodarone is associated with complex drug interactions and a host of adverse side effects involving the lung, liver, thyroid, and skin. As a general rule, the longer the therapy and the higher dose of amiodarone, the greater is the likelihood that adverse side effects will require discontinuance of the drug. Sotalol, like amiodarone, is effective in suppressing ventricular arrhythmias, but it has greater proarrhythmic effects and has not been shown to provide a clear increase in survival; worsening ventricular arrhythmias occur in 2% to 4% of treated patients (249).

6.3.1.3. Efficacy of Antiarrhythmic Drugs

Overall, the available antiarrhythmic drugs other than beta blockers should not be used as primary therapy in the management of ventricular arrhythmias and the prevention of SCD. The efficacy of non–beta-blocker antiarrhythmic drugs is equivocal at best, and each drug has significant potential for adverse events including proarrhythmia.

6.3.2. Special Considerations Where Antiarrhythmic Drugs May Be Indicated

Amiodarone therapy may be considered in special situations (109); secondary subset analyses indicate possible survival benefit when amiodarone is combined with beta blockers (250,251). However, the SCD-HeFT study showed no benefit in patients with NYHA functional class II HF and potential harm in patients with NYHA functional class III HF and EF equal to or less than 35% (8). Azimilide was shown to decrease the risk of appropriate and inappropriate shocks in patients with ICDs (252). Both sotalol and amiodarone have also been shown to reduce the frequency of ICD shock therapy (253,254).

6.3.2.1. Patients With Ventricular Tachyarrhythmias Who Do Not Meet Criteria for an Implantable Cardioverter-Defibrillator

Beta blockers are the first-line therapy, but if this therapy at full therapeutic dose is not effective, then amiodarone or sotalol can be tried with monitoring for adverse effects during administration.

6.3.2.2. Patients With Implantable Cardioverter-Defibrillators Who Have Recurrent Ventricular Tachycardia/Ventricular Fibrillation With Frequent Appropriate Implantable Cardioverter-Defibrillator Firing

This scenario, in its extreme, has been called defibrillator (tachycardia) storm, and it requires the addition of antiarrhythmic drugs and/or catheter ablation for control of the recurrent VT and associated ICD shocks. Sotalol is effective in suppressing atrial and ventricular arrhythmias (253); the combination of beta blockers and amiodarone is an alternative approach. Because many such patients have low EF and poor renal function, amiodarone and beta blockers rather than sotalol can be the first-line therapy for defibrillator storm. Sotalol should be avoided in patients with severely depressed LV function or significant HF. Animal studies (255,256) and a case report showed the benefits of neural modulation via spinal cord approaches (257). Intravenous amiodarone has been useful.

6.3.2.3. Patients With Implantable Cardioverter-Defibrillators Who Have Paroxysmal or Chronic Atrial Fibrillation With Rapid Rates and Inappropriate Implantable Cardioverter-Defibrillator Firing

Control of the rapid ventricular response to atrial tachyarrhythmias is essential, and combination therapy with a beta blocker and/or a calcium channel blocker is useful. Amiodarone has been used off-label for rate control if other therapies are contraindicated, not tolerated, or ineffective. Ablation of the AV node may be required when pharmacological therapy is not effective.

6.4. Nonantiarrhythmic Drugs

Use of nonantiarrhythmic drugs in the acute setting is further discussed in Section 7.

6.4.1. Electrolytes

Administration of potassium and magnesium, either as intravenously in the acute setting or orally for chronic augmentation in the blood levels of these electrolytes, can favorably influence the EP substrate involved in ventricular arrhythmias. These drugs are especially useful in the presence of hypokalemia and hypomagnesemia and should be considered as adjunctive therapies in the absence of low-level electrolytes. Adverse remodeling occurs in the ventricle following MI or in association with nonischemic cardiomyopathy; these structural changes with secondary ion channel alterations can exacerbate the potential for ventricular arrhythmias. Several drugs, such as ACE inhibitors, angiotensin II receptor antagonists, and aldosterone blockade with spironolactone or eplerenone, improve the myocardial substrate through reverse remodeling, and these therapies have been associated with a reduction in SCD as well as non-SCD (110,258). It is important to remember that electrolyte disturbances are common in patients with HF, particularly those using high doses of loop diuretics.

6.4.2. Antithrombins/Antiplatelets

In a retrospective analysis of more than 6700 patients participating in the Studies Of Left Ventricular Dysfunction (SOLVD) prevention and treatment trials, antithrombin therapy was associated with reduction in SCD (259). Antiplatelet therapy that included aspirin and anticoagulant therapy contributed to this reduction in SCD, possibly as a result of reducing the frequency of coronary thrombotic occlusions in this high-risk group of patients.

6.4.3. n-3 Fatty Acids and Lipids

Increasing experimental and clinical evidence suggests that n-3 fatty acids are antiarrhythmic (260) and may prevent SCD in humans (261). However, data are conflicting. In a randomized trial in patients with a recent episode of sustained ventricular arrhythmia and an ICD, fish oil supplementation did not reduce the risk of VT/VF and perhaps was proarrhythmic in some patients (262). However, a second similar study found a trend toward prolongation of the first VT/VF event or death from any cause ($p = 0.057$) and significant risk reduction when all probable VT/VF events were included (262,263).

Findings indicate that statins reduce the occurrence of life-threatening ventricular arrhythmias in high-risk cardiac patients with electrical instability (264). Both of these therapies suggest that the mechanism of the antiarrhythmic effects may be related to EP stabilization of the bilipid myocyte membrane involved in maintaining electrolyte gradients.

6.5. Implantable and External Cardioverter Devices

6.5.1. Implantable Cardioverter-Defibrillator

Several prospective multicenter clinical trials have documented improved survival with ICD therapy in high-risk patients with LV dysfunction due to prior MI and nonischemic cardiomyopathy (8,192,265–270) (Fig. 2). ICD therapy, compared with conventional or traditional antiarrhythmic drug therapy, has been associated with mortality reductions from 23% to 55% depending on the risk group participating in the trial, with the improvement in survival due almost exclusively to a reduction in SCD. The trials may be subcategorized into 2 types: primary prevention (prophylactic) trials in which the subjects have not experienced a life-threatening ventricular arrhythmia or a symptomatic equivalent and secondary prevention trials involving subjects who have had an abortive cardiac arrest, a life-threatening VT, or unexplained syncope with work-up suggesting a high probability that a ventricular tachyarrhythmia was the cause of the syncope.

Important ICD advancements continue to occur in the transvenous implantation procedure, generator size reduction, system longevity, arrhythmia detection, and multiprogrammable features. However, it is important to remember that device failure, although rare, can occur. Current ICDs include options for single-chamber, dual-chamber, and biventricular cardiac resynchronization pacing for nonshock termination of ventricular arrhythmia in addition to multilevel shock discharge for VT or VF. Problems associated with ICD therapy include inappropriate shock discharge

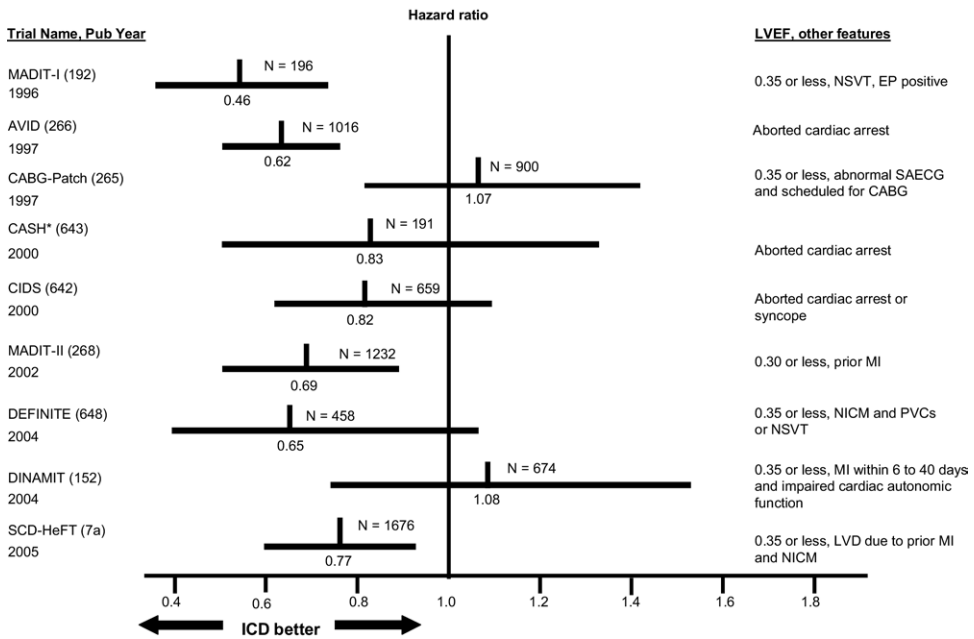

Figure 2. Major implantable cardioverter-defibrillator (ICD) trials. Hazard ratios (vertical line) and 95% confidence intervals (horizontal lines) for death from any cause in the ICD group compared with the non-ICD group. *Includes only ICD and amiodarone patients from CASH. For expansion of trial names, see Appendix 3. CABG = coronary artery bypass graft surgery; EP = electrophysiological study; LVD = left ventricular dysfunction; LVEF = left ventricular ejection fraction; MI = myocardial infarction; N = number of patients; NICM = nonischemic cardiomyopathy; NSVT = nonsustained ventricular tachycardia; PVCs = premature ventricular complexes; SAECG = signal-averaged electrocardiogram.

mostly for AF with rapid ventricular response, defibrillator storm with appropriate recurrent ICD discharge for recurrent ventricular tachyarrhythmias or inappropriate discharge for a multiplicity of reasons, infections related to device implantation, and exacerbation of HF when a high percentage of the heartbeats are paced from the RV apex, especially when ventricular function is already compromised. It is probably advisable to limit RV pacing to a minimum for any given patient. Possible solutions include the selection of an appropriately low minimum rate and an appropriately long AV interval. Avoidance of overly aggressive rate acceleration in rate-modulated modes and, in some recent pacemaker models, the use of an automatic pacing mode selecting algorithms that strongly favor atrial over ventricular pacing (271). The HF is likely to occur in the setting of advanced LV dysfunction with the ICD unit programmed to dual-chamber (DDD) pacing at heart rates that dominate the rhythm, thus contributing to paced ventricular desynchronization.

The ACC/AHA/NASPE 2002 Guidelines Update for Implantation of Cardiac Pacemakers and Antiarrhythmia Devices, the ACC/AHA 2004 Guidelines for Management of Patients With ST-Elevation Myocardial Infarction, the ESC 2001 and 2003 Guidelines on Prevention of SCD, the ESC Guidelines for the Diagnosis and Treatment of Chronic Heart Failure, and the ACC/AHA 2005 Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult include a large number of recommendations on ICD therapy which merit attention (1–6). Details and background references are provided in the full-text guidelines, which are on the ACC, AHA, HRS (formerly known as NASPE), and ESC Websites. The findings from the SCD-HeFT trial provide additional evidence that the ICD is effective in high-risk cardiac patients with ischemic and nonischemic cardiomyopathy (8). Differences in the recommendations in these guidelines from those previously published reflect primarily data from new studies. Detailed discussion on the considerations for therapy recommendations is found in the Introduction. However, there are inconsistencies among guidelines regarding the EF cutoff used in the recommendations.

6.5.2. Automated External Defibrillator

The automated external defibrillator (AED) saves lives when external defibrillation can be rendered within minutes of onset of VF. The AED represents an efficient method of delivering defibrillation to persons experiencing out-of-hospital cardiac arrest, and its use by both traditional and nontraditional first responders appears to be safe and effective (272,273). Appropriate device location to reduce time delay after onset of cardiac arrest is critical. Federal, state, and community efforts have been effective in placing AEDs in schools, sporting events, high-density residential sites, and airports as well as on airplanes and in police and fire department vehicles (274–277). Approximately 80% of cardiac arrests occur in the home, and placement of AEDs in the home appears to be reasonable and appropriate for patients at high risk for life-threatening arrhythmias. Federal regulatory authorities in the United States have approved the AED for home use in families with high-risk inherited arrhythmias such as the LQTS and HCM. The FDA has now approved over-the-counter sales of AEDs.

6.5.3. Wearable Automatic Defibrillator

The wearable automatic defibrillator is a vestlike device worn under the clothing that continuously monitors heart rhythm and automatically delivers an electric shock when VF is detected. This device is worn continuously on a 24-h-a-day basis, except when the wearer is bathing or showering. The wearable automatic defibrillator has been approved in the United States by the FDA for cardiac patients with a transient high risk for VF such as those awaiting cardiac transplantation, those at very high risk after a recent MI or an invasive cardiac procedure, or those requiring temporary removal of an infected implanted defibrillator for antibiotic therapy.

6.6. Ablation

Recommendations

Class I

1. **Ablation is indicated in patients who are otherwise at low risk for SCD and have sustained predominantly monomorphic VT that is drug resistant, who are drug intolerant, or who do not wish long-term drug therapy. *(Level of Evidence: C)***
2. **Ablation is indicated in patients with bundle-branch reentrant VT. *(Level of Evidence: C)***
3. **Ablation is indicated as adjunctive therapy in patients with an ICD who are receiving multiple shocks as a result of sustained VT that is not manageable by reprogramming or changing drug therapy or who do not wish long-term drug therapy (206,278). *(Level of Evidence: C)***
4. **Ablation is indicated in patients with WPW syndrome resuscitated from sudden cardiac arrest due to AF and rapid conduction over the accessory pathway causing VF (279). *(Level of Evidence: B)***

Class IIa

1. **Ablation can be useful therapy in patients who are otherwise at low risk for SCD and have symptomatic nonsustained monomorphic VT that is drug resistant, who are drug intolerant or who do not wish long-term drug therapy. *(Level of Evidence: C)***
2. **Ablation can be useful therapy in patients who are otherwise at low risk for SCD and have frequent symptomatic predominantly monomorphic PVCs that are drug resistant or who are drug intolerant or who do not wish long-term drug therapy. *(Level of Evidence: C)***

3. **Ablation can be useful in symptomatic patients with WPW syndrome who have accessory pathways with refractory periods less than 240 ms in duration (279).** ***(Level of Evidence: B)***

Class IIb

1. **Ablation of Purkinje fiber potentials may be considered in patients with ventricular arrhythmia storm consistently provoked by PVCs of similar morphology (280).** ***(Level of Evidence: C)***
2. **Ablation of asymptomatic PVCs may be considered when the PVCs are very frequent to avoid or treat tachycardia-induced cardiomyopathy (281).** ***(Level of Evidence: C)***

Class III

Ablation of asymptomatic relatively infrequent PVCs is not indicated. ***(Level of Evidence: C)***

6.6.1. Catheter Ablation—Background

The specific application of radiofrequency (RF) ablation to VT has evolved as the technology has developed. RF ablation can be applied in the treatment of VT in patients with LV dysfunction due to prior MI, cardiomyopathy, bundle-branch reentry, and various forms of idiopathic VT (282–294).

6.6.2. No Apparent Structural Heart Disease

Specific mapping and ablation techniques that are used differ depending on the type of VT. While patients with no overt structural heart disease account for a small percentage of patients with VT, they are of particular interest for ablation therapy as this technique may be curative (295,296). These typically present as a single VT arising from the RV with an LBBB inferior axis morphology or from the LV with a right bundle-branch block (RBBB) morphology and, in general, are associated with a good prognosis (289,297–300).

6.6.3. Bundle-Branch Reentrant VT

Bundle-branch reentrant VT is often associated with cardiomyopathy (279). RF catheter ablation of the bundle branches is curative of the arrhythmia but not of the underlying structural abnormality (301). Because of the severity of underlying heart disease and the high prevalence of conduction abnormalities, adjunct device therapy should be strongly considered in these patients (301).

6.6.4. Structural Heart Disease

VT is a common complication of structural heart disease and carries significant risk for mortality in CHD patients with low EF. In those with extensive structural abnormalities, especially those with prior MI, multiple morphologies of VT are often present. As a result, ablation of a single VT morphology can provide palliation but not eliminate the need for device or antiarrhythmic therapy. In these patients, VT can originate in, or involve, extensive areas of the myocardium and standard RF delivery carries a relatively low success rate (302–304). Given the inhomogeneous scarring present in ischemic VT, mapping techniques have evolved that take into account the complex nature of the circuits, including bystander regions of abnormal conduction. The newer 3-dimensional mapping systems permit anatomical reconstructions and correlation of EP characteristics with anatomy (190,305–308). These systems have led to an approach whereby circuits can be mapped during sinus rhythm and can facilitate ablation in the ischemic patient who often does not tolerate VT well (303,309–312). Use of these techniques may result in better long-term success rates (313).

6.6.5. Additional Ablation Tools

Depending on the arrhythmic substrate, VT circuits can be close to the endocardium or exist deeper within the myocardium. The focal lesion of traditional RF delivery systems may not create lesions deep enough to penetrate intramyocardial circuits. As a result, saline-irrigated cooled-tip catheters have been developed and used in VT ablation. Cooling the tip of the catheter permits deeper tissue heating. Preliminary results are promising, but further data are needed (314). Another novel technique involves transthoracic pericardial access for mapping and ablation. This technique was developed to address VTs that are extremely deep within the myocardium or actually epicardial. It involves inserting a sheath into the pericardial space and performing mapping from the epicardium (206,315,316). Few centers have taken on this approach. This technique must be performed with surgical support available if needed, and caution must be taken to avoid the epicardial coronary arteries (317,318). Another novel technique, not used recently, is transcoronary chemical ablation of incessant VT and VF (319,320). A more recent technique involves spinal cord modulation to suppress ventricular arrhythmias (255–257). Additional studies have suggested that catheter ablation of VF in structurally normal hearts may be feasible by targeting dominant triggers from the distal Purkinje system. These techniques are still considered highly experimental (280,317,318,321).

6.7. Surgery and Revascularization Procedures

Surgical therapy for the management of ventricular arrhythmias may involve ablation or surgical resection of an arrhythmogenic focus, cardiac sympathectomy, or aneurysm resection. Surgical or percutaneous coronary revascularization with improved coronary blood flow and reduction in myocardial ischemia has favorable antiarrhythmic effects. (See the ACC/AHA 2004 Guideline Update for Coronary Artery Bypass Graft Surgery [322]).

6.7.1. Antiarrhythmic Surgery

In patients with recurrent VT refractory to drugs, implanted defibrillators, and RF catheter ablation, direct surgical ablation or resection of the arrhythmogenic focus is an approach that continues to be used in experienced centers. Surgery requires accurate preoperative and intraoperative mapping to determine the site or sites of the tachycardia. Some centers use a scar-based approach to resecting arrhythmogenic sites. The short- and long-term success rates of map-guided surgical therapy for recurrent-refractory VT are based mostly on the older literature, and few reports are available to evaluate risk-to-benefit considerations in the current era in patients refractory to catheter ablation and implanted defibrillators (323).

Left cervicothoracic sympathetic ganglionectomy was introduced in 1971 for the treatment of adrenergically triggered life-threatening ventricular arrhythmias associated with the LQTS (324). This procedure, performed through a limited supraclavicular approach, involves resection of the lower half of the left stellate ganglion and removal of at least the second and third thoracic sympathetic ganglia on the left side (325). This surgical therapy is associated with reduction in the frequency of arrhythmogenic syncope in this syndrome and may be useful as adjunctive therapy in high-risk LQTS patients who have recurrent syncope and/or aborted cardiac arrest despite combined ICD and beta-blocker therapy or in LQTS patients who cannot tolerate beta blockers (326).

Large myocardial aneurysms secondary to MI are associated with hemodynamic compromise and are frequently accompanied by major ventricular arrhythmias. In selected patients, aneurysm resection can improve cardiac function and, along with map-guided EP mapping and resection of arrhythmogenic ventricular myocardium, may reduce or eliminate the accompanying ventricular arrhythmias (327).

6.7.2. Revascularization for Arrhythmia Management

In patients with ventricular arrhythmias, assessment for the presence of obstructive coronary disease and active ischemia is essential. Coronary revascularization involving either percutaneous balloon/stent angioplasty or bypass surgery is effective anti-ischemic therapy. A review of coronary revascularization studies reveals improved survival and reduction in SCD during long-term follow-up (328,329). If obstructive CHD is complicated by ventricular arrhythmias, especially in patients with left main and proximal left anterior descending coronary artery disease, there is a reasonable likelihood that revascularization will reduce the frequency and complexity of the arrhythmias and, in some patients, will eliminate such arrhythmias. No controlled trials have evaluated the effects of myocardial revascularization on VT or VF. However, observational studies suggest that:

- Sustained monomorphic VT in patients with prior MI is unlikely to be affected by revascularization (330).
- Myocardial revascularization is unlikely to prevent recurrent cardiac arrest in patients with markedly abnormal LV function, even if the original arrhythmia appeared to result from transient ischemia (331).

Further discussion can be found in Section 8.7.

Because ventricular arrhythmias are not always reduced by revascularization (332,333) and may in fact be exacerbated by unrecognized procedure-related MI, careful post-procedure monitoring for arrhythmia suppression is indicated. Suppression of ischemia-mediated ventricular arrhythmias and improvement in survival associated with coronary revascularization may have contributed to the lack of ICD efficacy in the Coronary Artery Bypass Graft (CABG) Patch Trial (265). In patients undergoing revascularization surgery following aborted cardiac arrest unrelated to an AMI, it is reasonable to implant a defibrillator after revascularization surgery in view of the assumed high-risk state. However, it is reasonable not to implant an ICD if there was direct, clear evidence of myocardial ischemia immediately preceding the onset of VF and there was no evidence for prior MI (see also Sections 8.1 and 8.3).

7. ACUTE MANAGEMENT OF SPECIFIC ARRHYTHMIAS

7.1. Management of Cardiac Arrest

Cardiac arrest is characterized by an abrupt loss of effective blood flow, sufficient to cause immediate loss of consciousness, leading immediately to death if untreated. The most common electrical mechanisms for cardiac arrest are VF and pulseless VT (see Section 3), but substantial numbers of cardiac arrests begin as severe bradyarrhythmias, asystole, or pulseless electrical activity. Survival probabilities are better for victims presenting with VT/VF than for those with bradyarrhythmic or asystolic mechanisms. A rapid response time is the major determinant of survival.

Recommendations

Class I

1. **After establishing the presence of definite, suspected, or impending cardiac arrest, the first priority should be activation of a response team capable of identifying the specific mechanism and carrying out prompt intervention.** ***(Level of Evidence: B)***
2. **Cardiopulmonary resuscitation (CPR) should be implemented immediately after contacting a response team.** ***(Level of Evidence: A)***
3. **In an out-of-hospital setting, if an AED is available, it should be applied immediately and shock therapy administered according to the algorithms contained in the documents on CPR (334,335) developed by the AHA in association with the International Liaison Committee on Resuscitation (ILCOR) and/or the European Resuscitation Council (ERC).** ***(Level of Evidence: C)***

4. **For victims with ventricular tachyarrhythmic mechanisms of cardiac arrest, when recurrences occur after a maximally defibrillating shock (generally 360 J for monophasic defibrillators), intravenous amiodarone should be the preferred antiarrhythmic drug for attempting a stable rhythm after further defibrillations.** ***(Level of Evidence: B)***
5. **For recurrent ventricular tachyarrhythmias or nontachyarrhythmic mechanisms of cardiac arrest, it is recommended to follow the algorithms contained in the documents on CPR (334,335) developed by the AHA in association with ILCOR and/or the ERC.** ***(Level of Evidence: C)***
6. **Reversible causes and factors contributing to cardiac arrest should be managed during advanced life support, including management of hypoxia, electrolyte disturbances, mechanical factors, and volume depletion.** ***(Level of Evidence: C)***

Class IIa

For response times greater than or equal to 5 min, a brief (less than 90 to 180 s) period of CPR is reasonable prior to attempting defibrillation. ***(Level of Evidence: B)***

Class IIb

A single precordial thump may be considered by health care professional providers when responding to a witnessed cardiac arrest. ***(Level of Evidence: C)***

A number of strategies for responding to unexpected cardiac arrest have resulted in improved survival probabilities for cardiac arrest victims (336). Nonetheless, the absolute number and proportion of survivors remain low (337), except in unique circumstances where there is an extraordinarily rapid response time to victims in VF or VT. A decrease in cardiac arrest survival occurs at about 7% to 10% per minute if no CPR is initiated and at 3% to 4% per minute with bystander CPR. In contrast, when immediate defibrillation in highly protected environments is available, such as in monitored intensive care units and EP laboratories, where response times of less than 30 s are usually achievable, survival from VF is greater than 90%, the exception being patients with pathophysiological conditions that favor the persistence of this potentially fatal arrhythmia. Survivability falls off rapidly after the initial 2 min from the onset of cardiac arrest, so that by 4 to 5 min survivability may be 25% or less, and by 10 min it is less than 10%. Studies have suggested that while immediate defibrillation is the preferred method within 1 to 2 min after the onset of cardiac arrest, a brief period of CPR to provide oxygenation of the victim improves survivability when time to defibrillation is longer (338–340).

Advanced life support activities, other than those directly related to electrical methods for control of tachyarrhythmias, led to the generation of complex protocols to guide responders. These documents, published by the AHA (334) and the ERC (335), cover the broad expanse of clinical circumstances and considerations of mechanisms. They provide management information, stratified for special circumstances such as age of the victim (from infancy to the elderly), pathophysiological status, and survival probabilities. The response algorithms to these various circumstances are complex and the reader is referred to the source documents for details (334,335). As management guidelines, these documents are classified as Level of Evidence: C, but they are derived from a combination of varied studies and opinion that range from Level of Evidence: A, B, or C. Abbreviated versions for tachyarrhythmias and nontachyarrhythmic mechanisms are shown in Figure 3.

Consistent with the AHA/ERC 2005 guidelines, the amount of energy and timing of shocks for treatment of VT in patients with pulses are determined by the patient's condition and the morphological characteristics of the VT. Unstable monomorphic VT is treated with synchronized cardioversion, while unstable polymorphic VT is treated as VF using high-energy unsynchronized shocks at defibrillation doses. Monomorphic VT in patients with pulses generally responds well to monophasic waveform cardioversion synchronized shocks at initial energies of 100 J or higher. More data are needed before specific comparative recommendations can be made for energy doses of biphasic devices. Synchronized cardioversion is generally not recommended to treat unstable polymorphic VT because of unreliable synchronization to a QRS complex and high-energy unsynchronized shock at defibrillation doses is recommended. If there is any doubt whether monomorphic or polymorphic VT is present in the unstable patient, shock delivery should not be delayed for detailed rhythm analysis. The initial recommended shock energy with a biphasic defibrillator is 150 to 200 J (use recommended device-specific dose; in absence of a recommended dose, 200 J should be used) and an equal or higher dose is recommended for second and subsequent shocks. If a monophasic defibrillator is used, 360 J is used for all shocks. Lower energy levels should not be used for unsynchronized shocks because they can provoke VF when given in an unsynchronized mode. After shock delivery, the health care provider should be prepared to provide immediate CPR and follow the advanced cardiac life support (ACLS) pulseless arrest algorithm if pulseless arrest develops (Fig. 3).

The general goals of advanced life support are to establish hemodynamically effective cardiac rhythm, to optimize ventilation, and to maintain and support the restored circulation. While 3 successive ("stacked") shocks were recommended in the previous version of the ECC guidelines (341), a 1-shock strategy is now recommended to minimize time between chest compressions and shock delivery and resumption of chest compressions (6,334,335) (see Fig. 3). Epinephrine, 1 mg intravenously, is administered and followed by repeated defibrillation attempts at 360 J. Epineph-

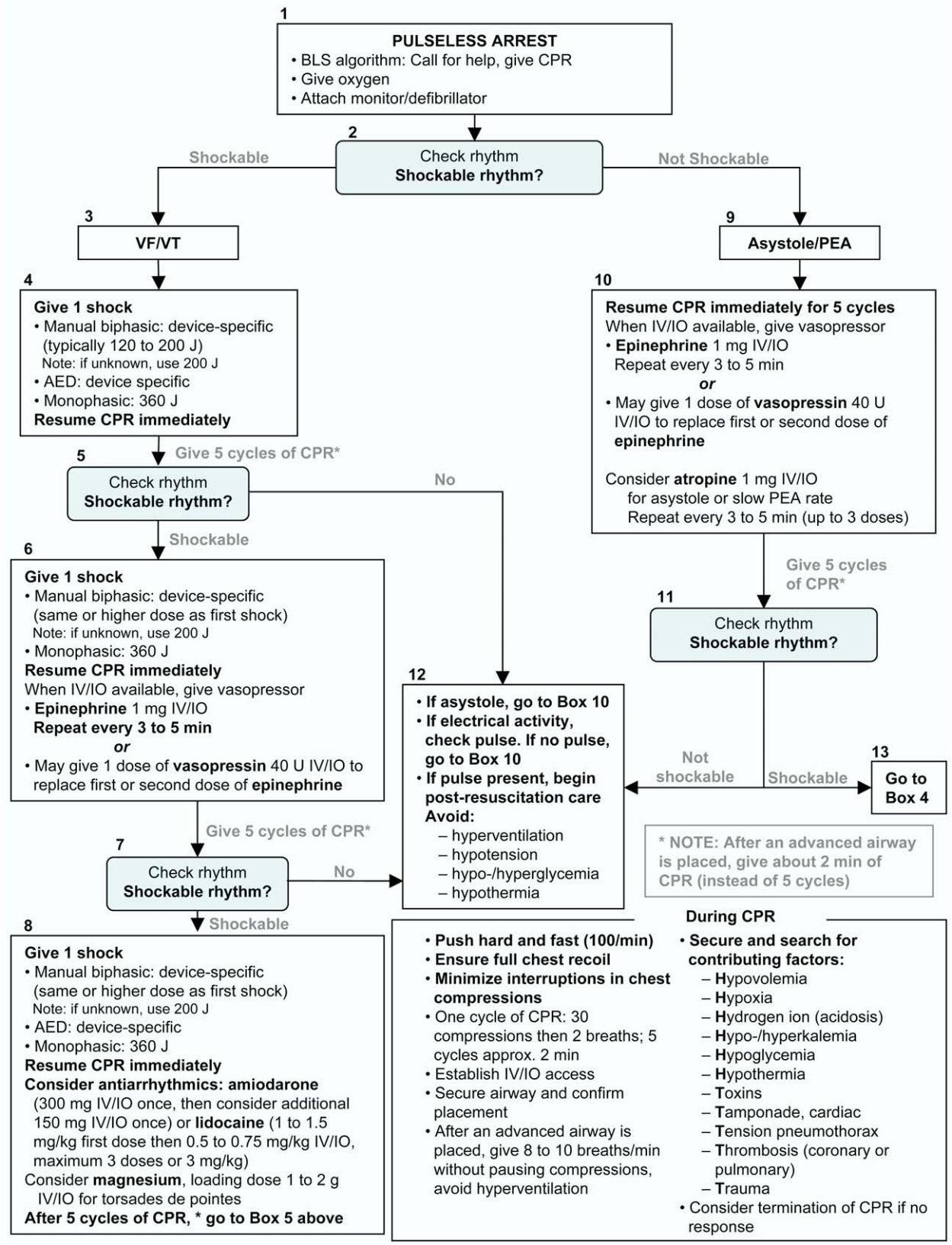

Figure 3. Advanced cardiac life support pulseless arrest algorithm. Reprinted with permission from Circulation 2005;112:IV57–66. AED = automated external defibrillator; BLS = basic life support; CPR = cardiopulmonary resuscitation; IV/IO = intravenous/intraosseous; PEA = pulseless electrical activity; VF = ventricular fibrillation; VT = ventricular tachycardia.

rine may be repeated at 3- to 5-min intervals with defibrillator shocks in-between doses (334), but high-dose epinephrine does not appear to provide added benefit (342).

Intravenous amiodarone has replaced intravenous lidocaine and other antiarrhythmic medications for the management of resistant ventricular tachyarrhythmias causing repeated episodes of ventricular tachyarrhythmias (343). Amiodarone need not be given routinely to the individual who responds to initial defibrillation with a stable rhythm. If there is sufficient clinical evidence that a cardiac arrest was heralded by the onset of an ACS, intravenous lidocaine may still be used for resistant arrhythmias. Beta blockers may be preferred for ACSs if not already being taken. For pharmacological hemodynamic support during cardiac arrest management, vasopressin has been suggested as an alternative to epinephrine (344), but the evidence for superiority is not clearly established. Responses to nontachyarrhythmic cardiac arrest largely focus on control of metabolic and transient factors that may precipitate bradyarrhythmic events or pulseless electrical activity (Fig. 3).

Simultaneously, the rescuer should focus on ventilation to correct the chemistry of the blood, efforts that render the heart more likely to reestablish a stable rhythm (i.e., improved oxygenation, reversal of acidosis, and improvement of the underlying EP condition). Although adequate oxygenation of the blood is crucial in the immediate management of the metabolic acidosis of cardiac arrest, additional correction can be achieved if necessary by intravenous administration of sodium bicarbonate. This is recommended for circumstances of known or suspected preexisting bicarbonate-responsive causes of acidosis, certain drug overdoses, and prolonged resuscitation runs (334). The more general role for bicarbonate during cardiac arrest has been questioned; but in any circumstance, much less sodium bicarbonate than was previously recommended is adequate for treatment of acidosis in this setting. Excessive quantities can be deleterious.

In patients in whom acute hyperkalemia is the triggering event for resistant VF, or who have hypocalcemia or are toxic from Ca^{2+} entry–blocking drugs, 10% calcium gluconate, 5 mL to 20 mL infused at a rate of 2 to 4 mL/min, may be helpful (334). Calcium should not be used routinely during resuscitation, even though ionized Ca^{2+} levels may be low during resuscitation from cardiac arrest. Some resistant forms of polymorphic VT or torsades de pointes, rapid monomorphic VT or ventricular flutter (rate greater than or equal to 260/min), or resistant VF may respond to intravenous beta-blocker therapy (propranolol, 1-mg intravenous boluses to a total dose of up to 15 to 20 mg; metoprolol, 5 mg intravenously, up to 20 mg) or intravenous $MgSO_4$ (1 to 2 g intravenously given over 1 to 2 min).

The approach to the patient with bradyarrhythmic or asystolic arrest or pulseless electrical activity differs from the approach to patients with tachyarrhythmic events of VT/VF (334). Once this form of cardiac arrest is recognized, efforts should focus first on establishing control of the cardiorespiratory status (i.e., continue CPR, intubate, and establish intravenous access), then on reconfirming the rhythm (in 2 leads if possible), and finally on taking actions that favor the emergence of a stable spontaneous rhythm or attempt to pace the heart. Possible reversible causes, particularly for bradyarrhythmia and asystole, should be considered and excluded (or treated) promptly. These include pulmonary embolus, AMI, hypovolemia, hypoxia, cardiac tamponade, tension pneumothorax, preexisting acidosis, drug overdose, hypothermia, and hyperkalemia. Cardiac pacing for bradyarrhythmic or asystolic arrests is usually ineffective (345), but reversal of hypoxemia, acidosis, or electrolyte imbalances may help in some instances. Epinephrine (1.0 mg intravenously every 3 to 5 min) is commonly used in an attempt to elicit spontaneous electrical activity or increase the rate of a bradycardia. For asystole and pulseless electrical activity, atropine as 1.0 mg intravenously/intraosseously, repeated every 3 to 5 min up to a total of 3 doses or 0.03 to 0.04 mg/kg is recommended. For bradycardia, atropine 0.5 mg intravenously/intraosseously, repeated every 3 to 5 min up to a total dose of 0.04 mg/kg, is recommended. Sodium bicarbonate, 1 mEq/kg, may be tried for known or suspected preexisting hyperkalemia or bicarbonate-responsive acidosis.

7.1.1. Arrhythmias Associated With Acute Coronary Syndromes

For recommendations, see Section 7.1 in these guidelines and refer to the current guidelines on ACLS (334,335).

ACS can give rise to a life-threatening arrhythmia that may be the first manifestation of ischemia. The mechanisms of these arrhythmias may be different from those seen in chronic stable ischemic heart disease. Arrhythmias during acute ischemia may be related to re-entry, abnormal automaticity, or triggered activity and are affected by a variety of endogenous factors such as potassium levels and autonomic states. These arrhythmias may cause many of the reported sudden deaths in patients with ischemic syndromes. VF or sustained VT has been reported in up to 20% of AMIs (346,347).

The incidence of VF (occurring within 48 h of the onset of the ACS) may be decreasing owing to aggressive revascularization limiting infarct size and to increased beta-blocker use (348). VF occurring early in the ACS has been associated with an increase in hospital mortality but not with increased long-term mortality (346). Prophylaxis with lidocaine may reduce the incidence of VF in the ACS but appears to be associated with increased mortality likely owing to bradycardia and this treatment has largely been abandoned (349). Use of prophylactic beta blockers in the setting of AMI reduces the incidence of VF, and this practice is encouraged when appropriate. Similarly, correction of hypomagnesemia and hypokalemia is encouraged because of the potential contribution of electrolyte disturbances to VF (350).

More recent data showed the benefit of the eplerenone, an aldosterone antagonist, in reducing the risk of SCD mortality by 37% ($p = 0.051$) 30 d after randomization in patients after AMI (when initiated at a mean of 7.3 d after AMI) in addition to conventional therapy in patients with an LVEF less than or equal to 40% and signs of HF (351).

7.1.1.1. Pulseless Ventricular Tachycardia/Ventricular Fibrillation

In the event of pulseless VT or VF in ACS, the standard ACLS protocol is initiated including unsynchronized electric shock following basic assessment of airway and initiation of CPR. Energy delivery consists of 1 or more monophasic shocks at 360 J or biphasic shocks at a dose range demonstrated by manufacturer to be effective. If not available, a dose of 200 J is recommended for the first shock and an equal or higher dose for subsequent shocks. The optimal dose for biphasic shocks has not been determined, and no waveform or escalating energy levels recommendations can be made for biphasic defibrillators at this time. If return to normal rhythm is not accomplished by defibrillation, the ACLS protocol for pulseless VT or VF is followed. This includes epinephrine (1 mg intravenously every 3 to 5 min) or vasopressin (40 U intravenously once only; 1 dose of vasopressin intravenously/intraosseously may replace either the first or second dose of epinephrine), and amiodarone (300-mg or 5-mg/kg intravenous push, with a possible repeat 150-mg intravenous push once only), or as a second tier, lidocaine (1.0 to 1.5 mg/kg with repeat dose of 0.5 to 0.75 mg intravenously/intraosseously up to a total dose of 3 mg/kg). Additional second-tier therapy includes intravenous magnesium (1 to 2 g) or procainamide (30 mg/min up to 17 mg/kg). The latter is considered acceptable but is no longer recommended (334).

Following resuscitated VF, prophylactic drug infusion, typically with amiodarone plus a beta blocker, may be continued. The antiarrhythmic should be withdrawn as appropriate to assess the presence of ongoing arrhythmias.

7.1.1.2. Idioventricular Rhythm and Nonsustained Ventricular Tachycardia

Neither idioventricular rhythm nor NSVT (lasting less than 30 s) occurring in the setting of ACS serves as a reliably predictive marker for early VF. In fact, accelerated idioventricular rhythm has been associated with reperfusion (352). As such, these arrhythmias do not warrant prophylactic antiarrhythmic therapy. However, sustained and/or hemodynamically compromising VT in ACS requires suppressive therapy (2). Management of pulseless VT follows the ACLS guidelines for pulseless VT/VF.

7.1.1.3. Unstable Sustained Ventricular Tachycardia

For recurrent VT, if VT is monomorphic and the EF is normal, either procainamide, sotalol, amiodarone, or lidocaine can be used. Alternately, if the EF is low, amiodarone or lidocaine is recommended (amiodarone 150 mg intravenously over 10 min or lidocaine 0.5 to 0.75 mg/kg intravenous push). If the VT is polymorphic and the baseline QT is normal, correction of underlying ischemia and electrolyte abnormalities is emphasized. This may be followed by, or performed concurrently with, administration of a beta blocker or lidocaine or amiodarone or procainamide or sotalol. If the VT is polymorphic and the EF is low, treatment with amiodarone 150 mg intravenously over 10 min or lidocaine 0.5 to 0.75 mg/kg intravenous push is recommended. In polymorphic VT, if the baseline QT is prolonged, correction of electrolytes is emphasized and other treatments may include magnesium, overdrive pacing, isoproterenol, phenytoin, or lidocaine.

7.1.1.4. Bradycardia and Heart Block

Bradycardia and heart block can occur as a result of MI. The likelihood of developing complete heart block complicating MI increases in the presence of underlying conduction system disease. Occurrence of heart block as a result of MI has been associated with an increase in hospital mortality but does not predict long-term mortality in those surviving to discharge (353). The increase in hospital mortality is related to the extensive amount of myocardial damage required to develop heart block rather than to the heart block itself. While pacing has not been shown to increase long-term survival post-MI, it is still indicated in symptomatic bradyarrhythmias associated with AMI, and pacing guidelines are as stated in the 2004 ACC/AHA Guidelines for the Management of Patients With ST-Elevation Myocardial Infarction (2) and the ACC/AHA/NASPE 2002 Guidelines Update for Implantation of Cardiac Pacemakers and Antiarrhythmia Devices (1).

7.1.2. Ventricular Tachycardia Associated With Low Troponin Myocardial Infarction

Recommendations

Class I

Patients presenting with sustained VT in whom low-level elevations in cardiac biomarkers of myocyte injury/necrosis are documented should be treated similarly to patients who have sustained VT and in whom no biomarker rise is documented. *(Level of Evidence: C)*

Prolonged episodes of sustained monomorphic VT may be associated with rise in cardiac biomarkers due to myocardial metabolic demands exceeding supply, especially in patients with CHD. Such patients usually have a history of MI. It is reasonable to evaluate for myocardial ischemia in patients exhibiting these findings. When sustained VT is accompanied by a modest elevation in cardiac enzymes, it should not be assumed that a new MI occurred to cause the tachycardia. In the absence of other data, it should be assumed that patients experiencing sustained monomorphic VT are at risk for recurrent VT and should be treated for this arrhythmia in the same manner as are patients without biomarker release accompanying VT.

7.2. Sustained Monomorphic Ventricular Tachycardia

Recommendations

Class I

1. **Wide-QRS tachycardia should be presumed to be VT if the diagnosis is unclear.** ***(Level of Evidence: C)***
2. **Direct current cardioversion with appropriate sedation is recommended at any point in the treatment cascade in patients with suspected sustained monomorphic VT with hemodynamic compromise.** ***(Level of Evidence: C)***

Class IIa

1. **Intravenous procainamide (or ajmaline in some European countries) is reasonable for initial treatment of patients with stable sustained monomorphic VT.** ***(Level of Evidence: B)***
2. **Intravenous amiodarone is reasonable in patients with sustained monomorphic VT that is hemodynamically unstable, refractory to conversion with countershock, or recurrent despite procainamide or other agents.** ***(Level of Evidence: C)***
3. **Transvenous catheter pace termination can be useful to treat patients with sustained monomorphic VT that is refractory to cardioversion or is frequently recurrent despite antiarrhythmic medication.** ***(Level of Evidence: C)***

Class IIb

Intravenous lidocaine might be reasonable for the initial treatment of patients with stable sustained monomorphic VT specifically associated with acute myocardial ischemia or infarction. ***(Level of Evidence: C)***

Class III

Calcium channel blockers such as verapamil and diltiazem should not be used in patients to terminate wide-QRS-complex tachycardia of unknown origin, especially in patients with a history of myocardial dysfunction. ***(Level of Evidence: C)***

Electrical cardioversion is always indicated for hemodynamically unstable tachycardia. Managing the patient presenting with well-tolerated, wide-QRS tachycardia is facilitated by differentiating between VT, SVT with aberrant conduction, and preexcited tachycardia (354). This can usually be accomplished by consideration of the history and examination of the 12-lead ECG during tachycardia. *The hemodynamic status of the patient is not helpful in distinguishing these mechanisms.* A working diagnosis of VT is appropriate when the diagnosis is unclear because VT is more prevalent, especially in the patient with structural heart disease, and therapy directed inappropriately at SVT may have adverse consequences (355,356). Monomorphic VT is usually related to a structural abnormality such as MI scarring but is mechanistically heterogeneous. Some "idiopathic" VTs respond well and terminate with intravenous verapamil or adenosine, and those expert in arrhythmia management may choose to treat the acute episode with these agents (357,358). If these unique VT entities cannot be recognized with confidence, it is prudent to assume that one is dealing with VT related to structural heart disease.

Correction of potentially causative or aggravating conditions such as hypokalemia and ischemia is an early priority. Timely termination is usually desirable even if VT is well tolerated. This can be achieved with cardioversion, antiarrhythmic medications, or pacing techniques. DC cardioversion even at early stage or as "first line" is reasonable (359,360). Advantages include the absence of proarrhythmia and high efficacy in a timely fashion. Cardioversion does not prevent recurrence, and a major disadvantage is the need for deep sedation or anesthesia. Caution needs to be exercised if the patient also has concurrent AF (e.g., double tachycardia). If such is the case, the ACC/AHA/ESC 2006 Guidelines for the Management of Patients With Atrial Fibrillation need to be followed when feasible (361).

Initial treatment often includes the administration of intravenous antiarrhythmic medication. The advantages include the lack of necessity for anesthesia and ready availability. Disadvantages include delay in termination, failure to terminate in some patients, and adverse effects including hypotension and proarrhythmia. Although drugs such as flecainide, propafenone, and sotalol are available in intravenous preparations in some countries, only intravenous procainamide, lidocaine, and amiodarone are widely available. Intravenous ajmaline is used frequently in some European countries. Intravenous amiodarone loading has proved useful in unstable and recurrent VT, especially when VT is recurrent after countershock and other antiarrhythmic measures (362–366). It is also reasonable in patients in whom oral amiodarone is required after the intravenous phase. It has proved superior to lidocaine in improving survival to hospital in patients with cardiac arrest and shock-resistant VF (343). Although intravenous amiodarone has an early effect on AV nodal conduction and early antiadrenergic effects, the effects on myocardial conduction and refractoriness are gradual in onset and maximum effect may not be seen for weeks or months (367–369). Intravenous amiodarone is not ideal for early conversion of stable monomorphic VT. Intravenous procainamide is more appropriate when early slowing of the VT rate and termination of monomorphic VT are desired (370,371). Close monitoring of blood pressure and cardiovascular status is recommended in the presence of congestive HF or severe LV dysfunction as intravenous procainamide can cause transient hypotension (372). Lidocaine is effective when VT is thought to be related to myocardial ischemia (373,374).

7.3. Repetitive Monomorphic Ventricular Tachycardia

Recommendations

Class IIa

Intravenous amiodarone, beta blockers, and intravenous procainamide (or sotalol or ajmaline in Europe) can be useful for treating repetitive monomorphic VT in the context of coronary disease (375) and idiopathic VT. ***(Level of Evidence: C)***

Repetitive monomorphic VT is characterized electrocardiographically by frequent ventricular ectopy and salvos of NSVT with intervening sinus rhythm. It typically occurs at rest and is self-terminating although the arrhythmia can be present for much of the time (376). Although this terminology can refer to mechanistically diverse arrhythmias, it generally refers to idiopathic VT, most frequently the RV outflow type (377–379). This tachycardia can cause palpitations or, rarely, tachycardia-related cardiomyopathy (380). Many patients have no symptoms related to the arrhythmia. In some patients, tachycardia is provoked by exercise (297). An electrocardiographically similar presentation is less frequent in patients with structural heart disease and, specifically, previous MI (375).

Treatment is rarely required on an urgent basis, and chronic management should be based on symptoms and frequency of tachycardia. Tachycardia-induced cardiomyopathy is unusual in this entity, and there is usually no need to treat asymptomatic patients with preserved LV function. For patients with mild symptoms, reassurance may be the only treatment necessary. Repetitive monomorphic VT is usually an issue of chronic management (pharmacologically or by ablation), and the strategy will vary considerably dependent on the clinical situation and etiology of the VT. Beta-blocking agents or calcium channel blockers are often effective. Ablation is generally successful in problematic RV outflow tachycardia (381). When acute therapy is required, antiarrhythmic drug selection will depend on etiology and underlying ventricular function, with drug selection considerations similar to that described for sustained monomorphic VT (see Section 7.2 for further discussion).

7.4. Polymorphic VT

Recommendations

Class I

1. **Direct current cardioversion with appropriate sedation as necessary is recommended for patients with sustained polymorphic VT with hemodynamic compromise and is reasonable at any point in the treatment cascade.** ***(Level of Evidence: B)***
2. **Intravenous beta blockers are useful for patients with recurrent polymorphic VT, especially if ischemia is suspected or cannot be excluded.** ***(Level of Evidence: B)***
3. **Intravenous loading with amiodarone is useful for patients with recurrent polymorphic VT in the absence of abnormal repolarization related to congenital or acquired LQTS.** ***(Level of Evidence: C)***
4. **Urgent angiography with a view to revascularization should be considered for patients with polymorphic VT when myocardial ischemia cannot be excluded.** ***(Level of Evidence: C)***

Class IIb

Intravenous lidocaine may be reasonable for treatment of polymorphic VT specifically associated with acute myocardial ischemia or infarction. ***(Level of Evidence: C)***

Polymorphic VT may be sustained, generally requiring urgent electrical cardioversion, or self-terminating with interludes of sinus rhythm. It is useful to distinguish polymorphic tachycardia associated with normal repolarization from that associated with abnormal repolarization (e.g., prolonged QT interval). Both VTs may be similar with gross irregularity of rate and QRS morphology with phasic increase and decrease of QRS amplitude often described as "torsades de pointes" (see Section 7.5. for further discussion).

Polymorphic VT with a normal QT interval during intervening sinus rhythm is most frequently seen in the context of acute ischemia or MI, but the QRS pattern during VT is not specific and may be seen with other cardiac disease states such as cardiomyopathy or HF or in the absence of overt cardiac disease (e.g., idiopathic polymorphic VT, catecholaminergic VT) (15,382,383). Intravenous beta blockers are useful in this context and improve mortality in the setting of recurrent polymorphic VT with AMI (384). Intravenous loading with amiodarone is also useful (341,385,386). Urgent coronary angiography should be considered in the setting or recurrent polymorphic VT when ischemia is suspected or cannot be excluded (387). In all instances, treatment of HF and associated correctable conditions and repletion of potassium and magnesium should be done concurrently with the above.

7.5. Torsades de Pointes

Recommendations

Class I

1. **Withdrawal of any offending drugs and correction of electrolyte abnormalities are recommended in patients presenting with torsades de pointes.** ***(Level of Evidence: A)***
2. **Acute and long-term pacing is recommended for patients presenting with torsades de pointes due to heart block and symptomatic bradycardia.** ***(Level of Evidence: A)***

Class IIa

1. **Management with intravenous magnesium sulfate is reasonable for patients who present with LQTS and few episodes of torsades de pointes. Magnesium is not likely to be effective in patients with a normal QT interval.** ***(Level of Evidence: B)***

2. **Acute and long-term pacing is reasonable for patients who present with recurrent pause-dependent torsades de pointes.** ***(Level of Evidence: B)***
3. **Beta blockade combined with pacing is reasonable acute therapy for patients who present with torsades de pointes and sinus bradycardia.** ***(Level of Evidence: C)***
4. **Isoproterenol is reasonable as temporary treatment in acute patients who present with recurrent pause-dependent torsades de pointes who do not have congenital LQTS.** ***(Level of Evidence: B)***

Class IIb

1. **Potassium repletion to 4.5 to 5 mmol/L may be considered for patients who present with torsades de pointes.** ***(Level of Evidence: B)***
2. **Intravenous lidocaine or oral mexiletine may be considered in patients who present with LQT3 and torsades de pointes.** ***(Level of Evidence: C)***

Marked QT interval prolongation and the morphologically distinctive polymorphic VT torsades de pointes occur in 3 common settings: in congenital LQTS, in a drug-associated form, and in patients with advanced conduction system disease that has progressed to heart block (see Section 11.1.1 for further discussion). Torsades de pointes complicating heart block is managed with temporary pacing followed by permanent pacing. Other causes, such as severe electrolyte abnormalities alone or central nervous system injury, are less common. Presentation with frequently recurring torsades de pointes in the congenital syndrome is unusual. In this setting, catecholamines should be avoided. However, other maneuvers useful in the drug-associated form (magnesium, potassium, pacing) can be used, and pacing along with beta blockade or lidocaine may be considered (388).

7.6. Incessant Ventricular Tachycardia

Recommendations

Class I

Revascularization and beta blockade followed by intravenous antiarrythmic drugs such as procainamide or amiodarone are recommended for patients with recurrent or incessant polymorphic VT due to acute myocardial ischemia. ***(Level of Evidence: C)***

Class IIa

Intravenous amiodarone or procainamide followed by VT ablation can be effective in the management of patients with frequently recurring or incessant monomorphic VT. ***(Level of Evidence: B)***

Class IIb

1. **Intravenous amiodarone and intravenous beta blockers separately or together may be reasonable in patients with VT storm.** ***(Level of Evidence: C)***
2. **Overdrive pacing or general anesthesia may be considered for patients with frequently recurring or incessant VT.** ***(Level of Evidence: C)***
3. **Spinal cord modulation may be considered for some patients with frequently recurring or incessant VT.** ***(Level of Evidence: C)***

7.6.1. Clinical Features

The syndrome of very frequent episodes of VT requiring cardioversion has been termed "VT storm" (see Section 13.5 for further discussion). Frequent appropriate ICD shocks represent another variant. While a definition of greater than 2 episodes in 24 h has been used (389,390), much more frequent episodes can also occur. Hemodynamically stable VT lasting hours has been termed "incessant." Management guidelines for these syndromes rely on anecdotal evidence because they are rare, there are multiple potential underlying mechanisms, and no randomized trials have been conducted.

Severe underlying heart disease is frequently present. More rarely, VT storm can occur (e.g., in Brugada syndrome, LQTS, catecholaminergic VT, or in drug overdose) in patients who have a structurally normal heart. "VT storm" can be monomorphic or polymorphic. Polymorphic VT storm in a patient with coronary disease is strongly suggestive of acute myocardial ischemia; pauses may occur prior to polymorphic VT even in the absence of QT prolongation. Pause-dependent VT with marked QT prolongation should be managed as torsades de pointes (see Section 7.5), although acute ischemia can also present in this fashion (391). Frequent appropriate ICD shocks may represent part of the natural history of advanced heart disease and may or may not portend a serious deterioration in underlying prognosis (392).

7.6.2. Management

The first step in VT storm is to identify and correct inciting factors, commonly including drugs, electrolyte disturbances, and acute myocardial ischemia (see Sections 13.5 and 13.6 for further discussion). With frequent ICD shocks, electrograms and programming should be reviewed to determine if device reprogramming is desirable (393,394).

Intravenous beta blockade should be considered for a polymorphic VT storm as it is the single most effective therapy. Revascularization procedures may be urgently needed. It is of utmost importance to try and understand the substrate of incessant arrhythmias, because if a diagnosis is established, a targeted treatment may be possible. For example, in Brugada syndrome, quinidine or isoproterenol may terminate incessant arrhythmias (139,395). In acute ischemia, intravenous amiodarone seems more effective than other antiarrhythmic drugs (396). Intra-aortic balloon counterpulsation can be tried. Pacing may be useful especially if the tachycardia onset is pause dependent. Other potential therapies include ablation (397) or general anesthesia (398). Autonomic alternative via spinal cord modulation may be tried.

Monomorphic VT storm can be managed by intravenous antiarrhythmics (e.g., amiodarone, procainamide) to slow the rate but may aggravate the tachycardia by promoting frequent or incessant episodes. Ablation can also be effective. ICD therapy may eventually be needed.

8. VENTRICULAR ARRHYTHMIA AND SUDDEN CARDIAC DEATH RELATED TO SPECIFIC PATHOLOGY

8.1. Left Ventricular Dysfunction Due to Prior Myocardial Infarction

Recommendations

Class I

1. **Aggressive attempts should be made to treat HF that may be present in some patients with LV dysfunction due to prior MI and ventricular tachyarrhythmias. *(Level of Evidence: C)***
2. **Aggressive attempts should be made to treat myocardial ischemia that may be present in some patients with ventricular tachyarrhythmias. *(Level of Evidence: C)***
3. **Coronary revascularization is indicated to reduce the risk of SCD in patients with VF when direct, clear evidence of acute myocardial ischemia is documented to immediately precede the onset of VF. *(Level of Evidence: B)***
4. **If coronary revascularization cannot be carried out and there is evidence of prior MI and significant LV dysfunction, the primary therapy of patients resuscitated from VF should be the ICD in patients who are receiving chronic optimal medical therapy and those who have reasonable expectation of survival with a good functional status for more than 1 y. *(Level of Evidence: A)***
5. **ICD therapy is recommended for primary prevention to reduce total mortality by a reduction in SCD in patients with LV dysfunction due to prior MI who are at least 40 d post-MI, have an LVEF less than or equal to 30% to 40%, are NYHA functional class II or III, are receiving chronic optimal medical therapy, and who have reasonable expectation of survival with a good functional status for more than 1 y. *(Level of Evidence: A)* (See Section 1.2.)**
6. **The ICD is effective therapy to reduce mortality by a reduction in SCD in patients with LV dysfunction due to prior MI who present with hemodynamically unstable sustained VT, are receiving chronic optimal medical therapy, and who have reasonable expectation of survival with a good functional status for more than 1 y. *(Level of Evidence: A)***

Class IIa

1. **Implantation of an ICD is reasonable in patients with LV dysfunction due to prior MI who are at least 40 d post-MI, have an LVEF of less than or equal to 30% to 35%, are NYHA functional class I on chronic optimal medical therapy, and who have reasonable expectation of survival with a good functional status for more than 1 y. *(Level of Evidence: B)* (See Section 1.2.)**
2. **Amiodarone, often in combination with beta blockers, can be useful for patients with LV dysfunction due to prior MI and symptoms due to VT unresponsive to beta-adrenergic–blocking agents. *(Level of Evidence: B)***
3. **Sotalol is reasonable therapy to reduce symptoms resulting from VT for patients with LV dysfunction due to prior MI unresponsive to beta-blocking agents. *(Level of Evidence: C)***
4. **Adjunctive therapies to the ICD, including catheter ablation or surgical resection, and pharmacological therapy with agents such as amiodarone or sotalol are reasonable to improve symptoms due to frequent episodes of sustained VT or VF in patients with LV dysfunction due to prior MI. *(Level of Evidence: C)***
5. **Amiodarone is reasonable therapy to reduce symptoms due to recurrent hemodynamically stable VT for patients with LV dysfunction due to prior MI who cannot or refuse to have an ICD implanted. *(Level of Evidence: C)***
6. **Implantation is reasonable for treatment of recurrent ventricular tachycardia in patients post-MI with normal or near normal ventricular function who are receiving chronic optimal medical therapy and who have reasonable expectation of survival with a good functional status for more than 1 y. *(Level of Evidence: C)***

Class IIb

1. **Curative catheter ablation or amiodarone may be considered in lieu of ICD therapy to improve symptoms in patients with LV dysfunction due to prior MI and recurrent hemodynamically stable VT whose LVEF is greater than 40%. *(Level of Evidence: B)***
2. **Amiodarone may be reasonable therapy for patients with LV dysfunction due to prior MI with an ICD indication, as defined above, in patients who cannot or refuse to have an ICD implanted. *(Level of Evidence: C)***

Class III

1. **Prophylactic antiarrhythmic drug therapy is not indicated to reduce mortality in patients with asymptomatic nonsustained ventricular arrhythmias. *(Level of Evidence: B)***
2. **Class IC antiarrhythmic drugs in patients with a past history of MI should not be used. *(Level of Evidence: A)***

Considerations taken by the Writing Committee in formulating recommendations for this section are discussed in detail in the Introduction.

Patients with chronic CHD manifest 3 general types of ventricular tachyarrhythmias: NSVT (defined as 3 or more repetitive ventricular beats in a row lasting up to 30 s in

duration at a rate greater than 100 beats per minute), sustained VT, and cardiac arrest resulting from VT or VF. The cardiac mortality of patients with all types of ventricular tachyarrhythmias is high. The high mortality results from nonsudden, as well as sudden, cardiac death. These arrhythmias may result from myocardial ischemia, or effects of HF, in addition to primary electrical abnormalities. Aggressive attempts should be made to treat HF and to search for and correct myocardial ischemia in patients with ventricular tachyarrhythmias. In some cases, appropriate treatment of ischemia and HF will abolish the arrhythmia (primarily polymorphic VT, VF, and NSVT). Even if specific antiarrhythmic therapy is necessary, the frequency and tolerance of arrhythmias may be improved with appropriate therapy for ischemia and HF.

8.1.1. Nonsustained Ventricular Tachycardia

Most NSVT in patients with chronic CHD is brief and does not cause symptoms. There is no evidence that suppression of asymptomatic NSVT prolongs life. Thus, there is no indication to treat NSVT, except in the relatively uncommon circumstances where frequent (incessant) or very rapid episodes compromise hemodynamic stability. In such cases, NSVT may be treated with pharmacological antiarrhythmic therapy, catheter ablation, or surgical resection. When NSVT causes symptoms that require therapy, attempts should be made to characterize the NSVT electrocardiographically, in order to determine whether the NSVT is related to prior MI or arises by a distinct mechanism that may be especially amenable to RF catheter ablation, such as tachycardia arising from the ventricular outflow tract. Initial pharmacological therapy of symptomatic NSVT should consist of beta adrenergic–blocking agents, if they are not already being used at an adequate dosage. Pharmacological therapy in patients with symptomatic NSVT unresponsive to beta adrenergic–blocking agents would most appropriately be amiodarone or sotalol.

8.1.2. Sustained Ventricular Tachycardia

The treatment of sustained VT in patients with chronic CHD should be tempered by the clinical manifestations produced by the tachycardia, as well as the frequency of episodes. Patients who present with sustained monomorphic VT that does not precipitate cardiac arrest or cause severe hemodynamic instability are usually, but not always, at relatively low risk for SCD (2% yearly) (399,400). Twelve-lead ECGs should be obtained during episodes of sustained VT, and the morphology assessed to be certain that it is consistent with location of prior MI(s). The possibility should be considered that patients with prior MI may develop sustained VT unrelated to the infarction, due to other mechanisms such as bundle-branch reentry or idiopathic VT. If episodes are relatively infrequent, the ICD alone may be the most appropriate initial therapy, because antitachycardia pacing therapies or high-energy shock therapy may reduce the need for hospitalization and pharmacological antiarrhythmic therapy. Suitable adjunctive therapies include catheter ablation, surgical resection, and pharmacological therapy with agents such as sotalol or amiodarone.

Curative therapy of sustained VT using either surgical resection or catheter ablation should be considered in patients with frequent recurrences of VT unresponsive to antiarrhythmic drugs. Patients in whom the tachycardia is hemodynamically stable may be considered for curative catheter ablation. The major limitation to catheter ablation is the fact that most patients with sustained VT resulting from prior MI have multiple tachycardias, and it is often difficult to ablate all tachycardias completely, using currently available RF ablation technology. Some patients have only 1 or 2 tachycardia circuits and may be cured of their arrhythmia by catheter ablation. However, they may develop new VT in the future using a different circuit. Although all morphologically distinct tachycardias may not be cured by catheter ablation, the tachycardia substrate may be modified sufficiently to decrease the frequency of arrhythmia episodes. Ablation of the tachycardia using surgery to resect or modify the arrhythmia substrate is an alternative therapy that may be suitable for patients in whom catheter ablation is unsuccessful.

Following correction of ischemia, patients who present with sustained VT that causes severe hemodynamic compromise may benefit from EP testing. Such testing will occasionally reveal curable arrhythmias such as bundle-branch reentry. In addition, the results of testing often help in appropriate programming of implantable defibrillators. The ICD is the primary therapy for such patients.

8.1.3. Treatment of Ventricular Fibrillation and Cardiac Arrest Survivors

Patients experiencing cardiac arrest due to VF that does not occur within the first 24 to 48 h of AMI may be at risk for recurrent cardiac arrest. As is the case for patients presenting with sustained VT, such patients should be evaluated and treated for myocardial ischemia. If there is direct, clear evidence of acute myocardial ischemia immediately preceding the onset of VF and there is no evidence of prior MI, the primary therapy should be complete coronary revascularization. If coronary revascularization cannot be carried out and there is evidence of prior MI and significant LV dysfunction, the primary therapy of patients resuscitated from VF should be the ICD.

8.1.4. Primary Prevention of Sudden Cardiac Death

All patients with CHD are at risk for SCD, and most SCD occurs in patients without severe LV dysfunction. However, in the absence of symptomatic arrhythmias, patients without prior MI and even those with prior MI whose LVEF is greater than 40% are at such low risk that prophylactic therapy is not indicated. Nevertheless, the risk for SCD in patients who do not have symptomatic arrhythmias, without prior MI, and those with prior MI whose LVEF is greater than 40% is sufficiently low that prophylactic therapy is not indicated at the present time. In addition, when EF is greater than 40%, the risk of SCD is low enough that

prophylactic antiarrhythmic therapy is not indicated for patients with asymptomatic arrhythmias, such as NSVT.

Subpopulations of patients remain at risk for SCD for years after the AMI. Multiple factors in addition to reduced EF have been demonstrated to contribute to the risk for SCD after MI; these include the presence of NSVT, symptomatic HF, and sustained monomorphic VT inducible by EP testing. The only specific antiarrhythmic treatment proved consistently effective to reduce risk of both SCD and total mortality is the ICD. ICD therapy is indicated to reduce the risk of SCD in 2 patient groups: patients whose LVEF is less than or equal to 40% as a result of prior MI and who have spontaneous NSVT and sustained monomorphic VT inducible by EP testing (267), and patients whose LVEF is less than 30% as a result of an MI that occurred greater than or equal to 40 d earlier when HF (NYHA functional class II or III symptoms) is present (248,268). The rationale for recommending that an ICD be used in patients with symptomatic HF, in addition to reduced EF, is that the evidence for ICD benefit is strongest in such patients; most patients enrolled in primary prevention trials had symptomatic HF (8). Evaluation of the need for an ICD and implantation should be deferred until at least 3 mo after revascularization procedures (i.e., surgical bypass grafting or percutaneous angioplasty) to allow adequate time for recovery of ventricular function following revascularization. In general, ICD implantation should be deferred until at least 40 d after AMI in patients meeting the above criteria in order to allow time for recovery of ventricular function and because ICD therapy has not been demonstrated to improve survival when implanted within 40 d after MI (152,248,401–403). In cases of doubt, an EP study could be considered.

Amiodarone therapy has been thought to be relatively safe in patients with prior MI who had symptomatic arrhythmias that required suppression. Although randomized trials have not demonstrated a survival benefit when empiric amiodarone is initiated early after MI, mortality was not increased, and arrhythmic deaths showed a consistent trend toward reduction with amiodarone treatment (404,405). However, in patients with advanced HF (NYHA functional class III), amiodarone may not be beneficial (8,248). Thus, amiodarone should not be used routinely after MI but is probably the safest agent to use to suppress symptomatic arrhythmias.

8.1.5. Use of Implantable Cardioverter-Defibrillator for Ventricular Tachycardia in Patients With Normal or Near Normal Left Ventricular Ejection Fraction

Recurrent sustained VT is usually treated by management of the underlying condition, prevention of predisposing and trigger factors, and the use of antiarrhythmic therapies such as class I and class III antiarrhythmic drugs. The use of antiarrhythmic agents may predispose the patient to proarrhythmic complications that might pose significant threats to life. Increasingly, the ICD is being used effectively to treat these arrhythmias, which in themselves may not be life-threatening, in order to avoid the relative ineffectiveness and adverse complications of pharmaceutical therapy. In the case of monomorphic VT, antitachycardia pacing is often applied successfully without provocation of untoward symptoms. On the other hand, polymorphic VT or VF, whether or not related to antiarrhythmic drug treatment, may require shock therapy. In any event, the strategy of using devices to manage such arrhythmias appears to be clinically successful, although expensive.

8.2. Valvular Heart Disease

Recommendations

Class I

Patients with valvular heart disease and ventricular arrhythmias should be evaluated and treated following current recommendations for each disorder. ***(Level of Evidence: C)***

Class IIb

The effectiveness of mitral valve repair or replacement to reduce the risk of SCD in patients with mitral valve prolapse, severe mitral regurgitation, and serious ventricular arrhythmias is not well established. ***(Level of Evidence: C)***

Ventricular arrhythmias occurring in patients with valvular heart disease can be caused by any of the mechanisms responsible for ventricular arrhythmias in other cardiac diseases. These patients can have associated CHD, myocardial dysfunction, severe LVH, adrenergic-dependent rhythm disturbances, or an inherited molecular abnormality. Valve abnormalities are not likely to cause ventricular arrhythmias but may contribute by virtue of their effect on the myocardium. Although SCD in patients with significant valvular lesions is frequently caused by a serious ventricular arrhythmia, it is uncertain whether the event is triggered by preexisting ventricular arrhythmias. In general, there is more knowledge on the risk for SCD in patients with aortic valve disease compared with other valvular lesions. Although the overall risk is small, sudden arrhythmic death appears to be more frequent in aortic stenosis than in other lesions: approximately 0.4% per year for aortic stenosis, less than 0.2% per year for regurgitation, and less than 0.2% per year for mitral valve disease (406,407).

Most patients who die suddenly have been symptomatic from their valvular disease (406). Although recurrent NSVT may place a patient with severe aortic stenosis at risk for syncope, the management of such a patient is usually guided by the severity of the valvular lesion. To date, there are insufficient data demonstrating reduction in ventricular arrhythmias as a result of valve repair or replacement in most patients with valvular disease. For these reasons, patients with valvular heart disease and ventricular arrhythmias should be evaluated and treated following current

recommendations for each disorder (406). The presence of a ventricular arrhythmia alone does not constitute an indication for valve repair or replacement. An exception to this general guideline has been suggested for patients with myxomatous mitral valve prolapse (MVP) and serious ventricular arrhythmias, in whom there may be an increased risk for SCD, particularly in the subgroup that also has a flail leaflet (408,409). For this reason, the frequent occurrence of ventricular arrhythmias in patients with severe myxomatous mitral regurgitation has been considered a class IIb indication for surgery (406), although its effectiveness in reducing SCD has not been established. The role of QT prolongation in subgroups of patients with MVP remains unclear (3,410).

Patients with mild valvular lesions who have no LV enlargement, LVH or depressed function should be managed as if they had no structural heart disease.

8.3. Congenital Heart Disease

Recommendations

Class I

1. **ICD implantation is indicated in patients with congenital heart disease who are survivors of cardiac arrest after evaluation to define the cause of the event and exclude any reversible causes. ICD implantation is indicated in patients who are receiving chronic optimal medical therapy and who have reasonable expectation of survival with a good functional status for more than 1 y.** ***(Level of Evidence: B)***
2. **Patients with congenital heart disease and spontaneous sustained VT should undergo invasive hemodynamic and EP evaluation. Recommended therapy includes catheter ablation or surgical resection to eliminate VT. If that is not successful, ICD implantation is recommended.** ***(Level of Evidence: C)***

Class IIa

Invasive hemodynamic and EP evaluation is reasonable in patients with congenital heart disease and unexplained syncope and impaired ventricular function. In the absence of a defined and reversible cause, ICD implantation is reasonable in patients who are receiving chronic optimal medical therapy and who have reasonable expectation of survival with a good functional status for more than 1 y. ***(Level of Evidence: B)***

Class IIb

EP testing may be considered for patients with congenital heart disease and ventricular couplets or NSVT to determine the risk of a sustained ventricular arrhythmia. ***(Level of Evidence: C)***

Class III

Prophylactic antiarrhythmic therapy is not indicated for asymptomatic patients with congenital heart disease and isolated PVCs. ***(Level of Evidence: C)***

Congenital heart disease represents a diverse spectrum of anatomical and physiological defects with significant differences in respect to natural history, preoperative and postoperative physiology, and the risk of arrhythmias and late SCD. Overall, congenital heart defects are the leading cause of infant mortality (less than 1 y of age) in the industrialized world. However, with advances in cardiovascular medicine, this mortality rate has been reduced from 105 to 59 deaths per 100 000 live births between 1980 and 1995 (411). Nearly all defects can now be repaired or palliated, with estimates of greater than 1 million worldwide long-term survivors of surgery for congenital heart disease (412). Although the short- and long-term survival of these patients is a matter of ongoing study, it is apparent that patients with certain defects have an increased risk of late sudden and total cardiac mortality (413). Given the overall low incidence of late SCD in postoperative congenital heart disease patients, no prospective randomized clinical trials have been performed to define either risk factors for SCD or the role of primary prevention therapies. Therefore, the level of evidence for most recommendations is class C.

During infancy and childhood, greater than 75% of deaths in patients with congenital heart disease are in-hospital events, most occurring during the perioperative period (414). The remaining deaths occur as out-of-hospital or emergency department events, often in patients with other congenital anomalies or sepsis. Therefore, the number of very young patients with congenital heart disease who are victims of arrhythmic SCD is quite small.

Beyond 20 y of age, there is a progressive increase in the incidence of sudden and total cardiac mortality in postoperative congenital heart disease patients (413). Hence, most studies of sudden death in congenital heart disease have evaluated adolescents and young adults (415). Five congenital heart defects have been associated with the greatest risks of late SCD: tetralogy of Fallot, D- and L-transposition of the great arteries, aortic stenosis, and functional single ventricle (413,416,417).

The largest number of late SCD studies in postoperative patients with congenital heart disease have been for tetralogy of Fallot. A meta-analysis of 39 studies including 4627 patients showed that the combination of ventricular dysfunction and complex ventricular ectopy was the primary correlate of late SCD (418). Although more than 20 risk factors for SCD have been proposed (419), volume overload due to pulmonary insufficiency and QRS duration greater than 160 ms appear to be the additional factors most likely to be associated with an increased risk of SCD due to ventricular arrhythmias (420,421). The results of EP testing for risk stratification in these patients have been inconsistent, in part due to variable study protocols and definitions of response to such testing (422–424).

Postoperative patients with D-transposition of the great arteries appear to have a differing risks for late SCD, based on whether they have undergone an atrial (Mustard or Senning) or arterial switch procedure. A very high incidence of late atrial arrhythmias has been noted in patients following atrial switch procedures, complicated by profound sinus bradycardia (425,426). The mechanism of SCD appears to be atrial flutter with 1:1 AV conduction, followed by myocardial ischemia resulting in polymorphic VT or VF (427). In both D- and L-transposition, progressive ventricular dysfunction may also result in ventricular arrhythmias as the cause of SCD (416,428).

In general, postoperative patients with unexplained syncope should undergo both hemodynamic and EP evaluation. A high incidence of inducible sustained ventricular arrhythmias has been reported in syncopal postoperative patients who have complex ventricular ectopy (429,430). Furthermore, a positive response to EP testing, independent of the clinical indication, may identify patients with a high-risk of late SCD (423). Conversely, isolated ventricular ectopy is common in older postoperative congenital heart disease patients. In the absence of ventricular dysfunction or symptoms, isolated ventricular ectopy has minimal prognostic significance, and the risks of antiarrhythmic drug treatment can exceed any potential benefit (431). There remain many patients with simple or complex ventricular ectopy, with vague symptoms, or modest impairment of ventricular function who require individual judgment regarding the need for evaluation and treatment (432). Also, there are nonarrhythmic causes of late sudden death in postoperative patients, including cerebral or pulmonary embolism, endocarditis, and aneurysm rupture (413,416).

Another class of congenital anomalies that may result in SCD is coronary artery abnormalities. The most common congenital coronary artery anomaly causing SCD in the young is anomalous origin of the left coronary artery from the right sinus of Valsalva. The proposed mechanism of SCD is that either acute angulation of the coronary ostium or compression of the left coronary artery as it traverses the region between the aortic wall and RVOT results in acute myocardial ischemia and the development of VT or VF. The risk of SCD appears greatest during the first 3 decades of life. Diagnosis may be difficult as only one third of patients have a prior history or exertional syncope or angina. Definitive diagnosis by coronary angiography is an indication for surgical revascularization. Similar risks for SCD have also been reported for anomalous origin of the right coronary artery from the left sinus of Valsalva (433).

Anomalous origin of the left coronary artery from the pulmonary artery generally presents during the first month of life. With the normal decline in pulmonary vascular resistance, myocardial ischemia and dysfunction develop as coronary perfusion is shunted to the pulmonary circulation. When the diagnosis is established by echocardiography during infancy, surgical reimplantation of the left coronary ostium is generally associated with recovery of ventricular function. However, a small percentage of these patients may survive an early MI and subsequently develop extensive right to left coronary artery collateral circulation. These patients may present years or decades later with angina, HF, or ventricular arrhythmias (434).

8.4. Metabolic and Inflammatory Conditions

Although disorders in this category are important causes of life-threatening ventricular arrhythmias, the occurrence of VT/SCD is relatively rare and hence, in most cases, there are few trial data as to how the arrhythmias should best be managed. Data relating to the prevention of life-threatening ventricular arrhythmias are even more sparse. All recommendations in this section therefore have Level of Evidence B or C.

Acute emergencies, as a consequence of any underlying ailment in this section, should be managed conventionally.

8.4.1. Myocarditis, Rheumatic Disease, and Endocarditis

Recommendations

Class I

1. **Temporary pacemaker insertion is indicated in patients with symptomatic bradycardia and/or heart block during the acute phase of myocarditis.** ***(Level of Evidence: C)***
2. **Acute aortic regurgitation associated with VT should be treated surgically unless otherwise contraindicated.** ***(Level of Evidence: C)***
3. **Acute endocarditis complicated by aortic or annular abscess and AV block should be treated surgically unless otherwise contraindicated.** ***(Level of Evidence: C)***

Class IIa

1. **ICD implantation can be beneficial in patients with life-threatening ventricular arrhythmias who are not in the acute phase of myocarditis, as indicated in the ACC/AHA/NASPE 2002 Guideline Update for Implantation of Cardiac Pacemakers and Antiarrhythmia Devices (1), who are receiving chronic optimal medical therapy, and who have reasonable expectation of survival with a good functional status for more than 1 y.** ***(Level of Evidence: C)***
2. **Antiarrhythmic therapy can be useful in patients with symptomatic NSVT or sustained VT during the acute phase of myocarditis.** ***(Level of Evidence: C)***

Class III

ICD implantation is not indicated during the acute phase of myocarditis. ***(Level of Evidence: C)***

8.4.1.1. Myocarditis

Myocarditis is an inflammatory process affecting the cardiac myocardium and is most often related to infection.

However, other toxic exposures, such as exposure to radiation, chemicals, and other physical agents, can lead to cardiac inflammation. The most common infectious agents leading to myocarditis are viruses (435,436). Other infective agents causing myocarditis include bacteria, fungi, protozoa, metazoa, spirochete, and rickettsia (435,437–453). Immunosuppression does not appear to reliably influence prognosis significantly and is not recommended at this time (453).

The acute course of myocarditis varies, as does its presentation (454). Presentation ranges from an asymptomatic finding detected because of transient ST-T changes noted on an ECG to a fulminant and life-threatening condition with symptoms that mimic ischemia. Acute management is largely supportive but may be quite aggressive depending on the presentation (455). Cardiac arrhythmias associated with acute myocarditis can range from conduction abnormalities to difficult to suppress life-threatening ventricular arrhythmias. Death can occur related to HF and arrhythmias including heart block (444,445,455–460). Patients with arrhythmias or syncope may require antiarrhythmic drugs and/or device therapy (461). Temporary pacemaker insertion is indicated in patients with acute myocarditis who present with symptomatic heart block as it would be in other causes of acute symptomatic heart block. Pacing is indicated in patients with symptomatic sinus node dysfunction or AV block as a sequela of myocarditis as it would be in other causes of sinus or AV node dysfunction.

Acute myocarditis can lead to chronic cardiomyopathy through a variety of mechanisms (455). In patients with residual severe cardiomyopathy and ventricular arrhythmias, defibrillators and/or biventricular devices are implanted for the same indications as recommended in the sections on HF and cardiomyopathy.

Idiopathic giant cell myocarditis is fairly uncommon but is of particular note as it typically affects young individuals and is usually fatal if untreated (462–467). The diagnosis is confirmed by endomyocardial biopsy. Patients may develop heart block, requiring temporary or permanent pacemakers. An ICD and antiarrhythmic drugs such as amiodarone may be needed for VT (462).

Lyme carditis is a complication of Lyme disease affecting between 0.3% and 8% of those infected with *Borrelia burgdorferi* (468–471). Patients can develop varying degrees of AV conduction abnormalities. Junctional rhythm and asystolic pauses can occur. LV dysfunction is generally mild, and the process is usually self-limiting when treated with antibiotics (468). Persistent heart block is rare, but in such cases permanent pacing may be needed (469,472). VT, usually nonsustained, has been reported infrequently (473–475).

Cardiac involvement has been frequently reported in patients with acquired immunodeficiency syndrome (AIDS) and is also seen in patients with human immunodeficiency virus (HIV) infection without AIDS (476–479). SCD has been reported with primary myocardial HIV involvement (480,481). QT prolongation and arrhythmias have been attributed to drug therapy (482–484).

Chagas disease is caused by the protozoan *Trypanosoma cruzi*; it is transmitted by an insect vector and is common in Central and South America. Acute myocarditis is rare but over one third develop late myocardial damage with progressive HF and have poor survival. Conduction defects with progression to complete heart block are common. Life-threatening ventricular arrhythmias are common. Amiodarone appears to be effective in treating ventricular tachyarrhythmias, and death occurs as a result of either refractory HF or arrhythmias (485). Device therapy including the ICD is frequently used in the late phase (486). In those with good functional status (e.g., NYHA functional class I and II), SCD is a rare event when patients are treated with amiodarone. However, VT recurrence rate is high at 30% per year. RF ablation from the epicardial surface has been reported to be useful therapy in this indication. In those with advanced HF, drug therapy is of little benefit and arrhythmia recurrence rates approach 100%. Mortality is high in these patients, on average 40% mortality in 1 y (487).

8.4.1.2. Rheumatic Disease

Acute rheumatic fever causes a pancarditis involving the pericardium, myocardium, and endocardium. Sinus tachycardia and PR prolongation are common. Bundle-branch block, nonspecific ST-T wave changes, and atrial and ventricular premature complexes may occur. Complete heart block and ventricular arrhythmias are rare (488–490). It has been associated with prolonged QT interval and torsades de pointes (489).

8.4.1.3. Endocarditis

Infective endocarditis can occur as subacute bacterial endocarditis or acute bacterial endocarditis. Subacute bacterial endocarditis is most often related to infections with streptococcal species and less commonly with *Staphylococcus aureus*, *S. epidermidis*, and fastidious *Haemophilus* sp. Typically, it will develop on abnormal valves after asymptomatic bacteremias from infected gums or the genitourinary or gastrointestinal tract. Acute endocarditis more often is related to infections with *S. aureus*, group A hemolytic streptococci, pneumococci, or gonococci and with less virulent microorganisms. It can develop on normal valves (491). Untreated endocarditis is almost always fatal. Prosthetic valve endocarditis comprises a substantial proportion of all cases of infective endocarditis. Although the overall incidence of infective endocarditis has not changed over the past 3 decades, the age of presentation has increased. Where right-sided endocarditis occurs, it is often related to intravenous drug abuse.

Endocarditis of the aortic and mitral valves has been associated with rapid death owing to acute valvular disruption, emboli to the coronary arteries, or abscesses in the valvular rings or the septum (492,493). While these deaths are often rapid, they typically are not classified as

sudden deaths. Uncommonly, endocarditis has been associated with SCD related to tamponade secondary to rupture (494,495). The development of cardiac rhythm disturbances portends poorly in infective endocarditis (496). Abscess formation in the valve annulus can result in first- or second-degree heart block. This occurs more often in aortic than mitral valve endocarditis (497). More advanced heart block can occur if the abscess erodes into the septum and disrupts the conduction system. New-onset heart block in a patient with endocarditis is highly specific for abscess (498). Patients with perivalvular abscess are at higher risk for other complications such as embolization and death (499).

Antimicrobial therapy will be given as appropriate to the specific causative organism (500). Surgery is recommended in those with recurrent emboli or refractory HF or those who do not respond to antimicrobial therapy. Most physicians believe that abscess formation or fungal endocarditis is an indication for surgery (501,502). The acute hemodynamic compromise related to acute aortic regurgitation secondary to endocarditis can result in VT and is an indication for early surgery (498,499,503). Drug treatment of arrhythmias does not differ from generally accepted clinical principles. Surgery may be indicated in the presence of documented myocardial involvement or abscess formation (504).

8.4.2. Infiltrative Cardiomyopathies

Recommendations

Class I

In addition to managing the underlying infiltrative cardiomyopathy, life-threatening arrhythmias should be treated in the same manner that such arrhythmias are treated in patients with other cardiomyopathies, including the use of ICD and pacemakers in patients who are receiving chronic optimal medical therapy and who have reasonable expectation of survival with a good functional status for more than 1 y. ***(Level of Evidence: C)***

The association between the infiltrative cardiomyopathies and VT/SCD is well documented. In all cases, where appropriate, treatment of the underlying condition must accompany management of cardiac manifestations.

8.4.2.1. Sarcoidosis

One quarter of patients with sarcoidosis have cardiac lesions, but there is a poor correlation between symptoms and myocardial involvement even in the most advanced cases, and hence SCD may be the first manifestation (505). In proven cases of cardiac sarcoidosis, supraventricular and ventricular arrhythmias occur frequently (73%) and bundle-branch block is present in about two thirds of patients.

Approximately one quarter of these patients develop complete heart block; a similar proportion has congestive cardiac failure. The ECG and Holter monitor are not sensitive or specific enough for detecting myocardial involvement but can be useful for the identification of rhythm disturbances once the diagnosis has been confirmed by other means (e.g., thallium-201 and gallium-67 SPECT or MRI). Myocardial biopsy, although insensitive, has a high specificity for the diagnosis of myocardial sarcoidosis. Corticosteroid therapy may reduce the number of premature ventricular complexes and episodes of tachycardia, rendering the arrhythmia easier to treat (506); the danger of SCD may also be diminished and an improvement may also be seen in conduction defects. The use of immunosuppression by no means eliminates the risk of further occurrence of arrhythmias. The resolution of granulomas may leave a substrate for arrhythmogenesis. Prospective trial data do not exist, but spontaneous VT, severe LV dysfunction, and severe intraventricular conduction disturbance warrant ICD and/or pacemaker therapy as appropriate (507).

8.4.2.2. Amyloidosis

Cardiac involvement in amyloidosis, irrespective of the subtype or chemotherapeutic intervention, carries a very poor prognosis. In the AL subtype, the median survival is 6 mo with a 6% 3-y survival rate (508,509). Progressive HF is usually the mode of death, but bradyarrhythmia and especially VT may be the terminal event. Complex ventricular arrhythmias are common, affecting 57% of patients; 29% have couplets and 18% have NSVT (510). Cardiac troponins, especially troponin T (511); the presence of couplets on Holter recordings (510); LV wall thickness, especially greater than 12 to 15 mm on 2-dimensional echocardiography (512); the presence of late potentials on SAECG (513); and prolonged infra-His (HV) conduction time on EP studies (514) may all be independent predictors of mortality. Elevated cardiac troponins may influence the final decision as median survival in patients with detectable values is 6 to 8 mo compared with 21 to 22 mo in those with undetectable levels (511). QTc is prolonged in patients with cardiac amyloid, but this does not seem to correlate with life-threatening arrhythmias (515). The use of permanent pacemakers and ICD devices may not influence long-term outcome but in familial cases may be used as a bridge to transplantation (516).

8.4.2.3. Fabry Disease

Fabry disease is an X-linked recessive lysosomal storage disorder caused by deficiency of lysosomal alpha-galactosidase. Fabry cardiomyopathy has a prevalence of 3% to 6% in male patients with unexplained LVH (517,518). Female carriers with low alpha-1 galactosidase activity may also exhibit cardiac manifestations (519). Although cardiac involvement causes a range of ECG abnormalities and conduction disturbances with AV block, ventricular arrhythmias and SCD appear to be very rare (520–525). Improvements of cardiac hypertrophy and conduction abnormalities have been obtained with enzyme replacement therapy (526).

8.4.2.4. Hemochromatosis

Up to one third of homozygotes with hemochromatosis have cardiac involvement. Although the natural course of untreated cardiac involvement is progressive HF, ventricular arrhythmias have been reported (527,528); their incidence and that of SCD are however, unknown. Early detection and appropriate management of hemochromatosis are essential for a favorable outcome as cardiac and liver involvement may be reversible in the early stages of the disease (529). Arrhythmias are managed conventionally.

8.4.3. Endocrine Disorders and Diabetes

Recommendations

Class I

1. **The management of ventricular arrhythmias secondary to endocrine disorders should address the electrolyte (potassium, magnesium, and calcium) imbalance and the treatment of the underlying endocrinopathy. *(Level of Evidence: C)***
2. **Persistent life-threatening ventricular arrhythmias that develop in patients with endocrine disorders should be treated in the same manner that such arrhythmias are treated in patients with other diseases, including use of ICD and pacemaker implantation as required in those who are receiving chronic optimal medical therapy and who have reasonable expectation of survival with a good functional status for more than 1 y. *(Level of Evidence: C)***
3. **Patients with diabetes with ventricular arrhythmias should generally be treated in the same manner as patients without diabetes. *(Level of Evidence: A)***

8.4.3.1. Introduction

Endocrine disorders can induce VT/SCD by excess or insufficient hormone activity on myocardial receptors (e.g., pheochromocytoma, hypothyroidism). The endocrinopathy can also cause myocardial changes (e.g., acromegaly) or electrolyte disturbances produced by hormone excess (e.g., hyperkalemia in Addison disease and hypokalemia in Conn syndrome), and certain endocrine disorders can accelerate the progression of conditions such as underlying structural heart disease secondary to dyslipidemia or hypertension, increasing the risk of serious arrhythmias.

8.4.3.2. Thyroid Disorders

Thyrotoxicosis commonly causes atrial arrhythmias; cases of VT/SCD are extremely uncommon but may occur with concomitant electrolyte disturbances (530). VT/SCD are more common in hypothyroidism, the basic underlying mechanism being possibly related to prolongation of the QT interval (531,532). Thyroxin replacement therapy usually corrects this abnormality and prevents any further arrhythmias, but antiarrhythmic drugs, such as procainamide, have been used successfully in an emergency (531).

8.4.3.3. Pheochromocytoma

Pheochromocytoma may present with VT/SCD, but there are no data to quantify its incidence, best mode of management, or response to treatment. The incidence is likely to be low and possibly exacerbated by reversible catecholamine-induced HCM/DCM (533). Not only will conventional antagonism of catecholamine excess with alpha receptor blockers followed by beta blockade help control hypertension and reverse or prevent any further structural deterioration (534), but there is anecdotal evidence that it prevents recurrence of ventricular arrhythmia (535). Early definite surgical treatment of the pheochromocytoma should be a priority, especially in cases with documented life-threatening arrhythmias. In some patients with VT associated with pheochromocytoma, a long QT interval has been identified (536,537).

8.4.3.4. Acromegaly

SCD is an established manifestation of acromegaly, and life-threatening arrhythmias are likely to be an important cause (538). Up to one half of all acromegalic patients have complex ventricular arrhythmias on 24-h Holter recordings, and of these, approximately two thirds are repetitive (539). There is a strong correlation between these ventricular arrhythmias and LV mass and duration of the disease but not hormone levels (539). Appropriate surgical management of the pituitary tumor is paramount for improved long-term outcome, as cardiac changes are reversible, especially in the young (540,541). Somatostatin analogues such as octreotide and lanreotide have both been shown to reduce LVH and improve the ventricular arrhythmia profile (542–544).

8.4.3.5 Primary Aldosteronism, Addison Disease, Hyperparathyroidism, and Hypoparathyroidism

Severe electrolyte disturbances form the basis of arrhythmogenesis and VT/SCD associated with the previously mentioned endocrinopathies. ECG changes including prolongation of QRS and QTc intervals can accompany the electrolyte disturbance. Electrolyte imbalance requires immediate attention before definitive treatment of the underlying cause (545–549).

8.4.3.6. Diabetes

Diabetes is a major risk factor for premature and accelerated atherosclerosis, resulting in an increased incidence of MI, stroke, and death compared with a similar age- and gender-matched population without diabetes (95). The management of atherosclerotic complications that predispose to ventricular arrhythmias and SCD in patients with diabetes is similar to that in patients with diabetes (550).

In addition to atherosclerosis and hyperglycemia that predispose the patient with diabetes to ventricular arrhythmias and SCD, autonomic neuropathy, transient hypoglycemic episodes that may occur with drug therapy, and target end-organ damage, such as renal failure, that results in hyperkalemia and occasionally hypokalemic episodes as a result of treatment, augment the risk of SCD (551–557).

Restrictive cardiomyopathy may be a late complication in some patients with diabetes.

Hypoglycemic episodes increase sympathetic tone. The likelihood of ventricular arrhythmias is enhanced, particularly when they occur in a patient with autonomic neuropathy. Severe hypoglycemia is associated with ventricular repolarization abnormalities, prolongation of the QT interval, and ventricular arrhythmias (551,552). Beta blockers have been shown to reduce the magnitude of these abnormalities during experimental hypoglycemia (558). Although they may mask symptoms of hypoglycemia, beta blockers significantly improve survival rates in patients with diabetes, and indications for their use are similar to those for patients with diabetes (559). In a prespecified diabetic subgroup of patients with diabetes and LVH enrolled in the Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) trial, losartan appeared to afford better protection against SCD than atenolol (560). ACE inhibitors or angiotensin-2 blockers are recommended in all patients with vascular complications of diabetes if no contraindications exist.

8.4.4. End-Stage Renal Failure

Recommendations

Class I

1. **The acute management of ventricular arrhythmias in end-stage renal failure should immediately address hemodynamic status and electrolyte (potassium, magnesium, and calcium) imbalance.** ***(Level of Evidence: C)***
2. **Life-threatening ventricular arrhythmias, especially in patients awaiting renal transplantation, should be treated conventionally, including the use of ICD and pacemaker as required, in patients who are receiving chronic optimal medical therapy and who have reasonable expectation of survival with a good functional status for more than 1 y.** ***(Level of Evidence: C)***

Cardiovascular causes account for at least 40% of deaths in patients with end-stage renal failure and 20% of these are sudden. Arrhythmias often occur during hemodialysis sessions and for at least 4 to 5 h afterward. During this period, hemodynamic status and fluctuations in electrolytes, especially potassium, magnesium, and calcium, are likely to play a crucial role in triggering events and should be monitored carefully. LQTS has been reported occasionally, sometimes related to therapy with sotalol (561). Risk factors predisposing to ventricular arrhythmias include LVH, hypertension, anemia, cardiac dysfunction, and underlying CHD (562). Of these, systolic blood pressure and myocardial dysfunction have been suggested to be the more important determinants of complex arrhythmia (563). Unfortunately, there are few data on how individuals at highest risk might be identified and treated. Restricted vascular access may influence the choice of therapy.

8.4.5. Obesity, Dieting, and Anorexia

Recommendations

Class I

Life-threatening ventricular arrhythmias in patients with obesity, anorexia, or when dieting should be treated in the same manner that such arrhythmias are treated in patients with other diseases, including ICD and pacemaker implantation as required. Patients receiving ICD implantation should be receiving chronic optimal medical therapy and have reasonable expectation of survival with a good functional status for more than 1 y. ***(Level of Evidence: C)***

Class IIa

Programmed weight reduction in obesity and carefully controlled re-feeding in anorexia can effectively reduce the risk of ventricular arrhythmias and SCD. ***(Level of Evidence: C)***

Class III

Prolonged, unbalanced, very low calorie, semistarvation diets are not recommended; they may be harmful and provoke life-threatening ventricular arrhythmias. ***(Level of Evidence: C)***

Extreme disorders of eating, and overzealous methods of rectifying them quickly, are all associated with SCD. In overweight individuals, this risk is particularly evident in the severely obese with a 40 to 60 times higher incidence compared with that in the aged-matched general population (564,565). This is most likely to be related to life-threatening ventricular arrhythmias, but changes in the conduction system of young obese victims of SCD have also been reported (566). Some obese individuals have prolonged QTc intervals (567,568) and studies have also documented an increased QT dispersion in these individuals (569). Cardiomyopathy of obesity (e.g., cardiomegaly, LV dilatation, and myocyte hypertrophy in the absence of interstitial fibrosis) is the most common association with SCD (92), and this can occur in normotensive individuals (570). Ventricular premature complexes are 30 times more common in obese patients with LVH compared with lean subjects. The complexity of the ventricular ectopy correlates with ventricular diastolic diameter and LV mass (571). Obstructive sleep apnea may play a role in the genesis of arrhythmias and HF in obese individuals (572).

The risk of SCD in obesity can be significantly reduced by weight loss. Cardiomyopathy of obesity is reversible, at least in the early stages of the disease (573,574), as are most ECG changes including prolonged QTc intervals (568,569,575). Weight reduction strategies must therefore be advocated in all obese patients at risk, but these must involve well-balanced low-calorie diets. Prolonged, unbal-

anced, very low calorie, semistarvation diets (especially liquid protein diets) have been reported to cause cardiac arrhythmias and SCD by a variety of mechanisms. Such diets must be avoided especially in those with underlying cardiac abnormalities (576–580).

Reported mortality rates in anorexia nervosa fluctuate from 5% to 20%, but the actual rate is likely to be around 6% (581). Up to one third of these deaths, including those occurring during re-feeding, are said to be due to cardiac causes but no precise data exist on SCD. Prolonged periods of starvation result in not only anatomical abnormalities such as cardiac muscle atrophy and pericardial effusions (582), but also ECG abnormalities, including sinus bradycardia and prolongation of the QTc interval, an effect that is likely to be compounded by the presence of concurrent electrolyte disturbances (582–584). SCD is therefore a frequent cause of mortality in this cohort. Low weight, low body mass index, and rapid weight loss immediately preceding assessment are the most important independent predictors of QTc interval prolongation (582). Most of the cardiac manifestations of anorexia nervosa are completely reversible by appropriate re-feeding (582). The "re-feeding syndrome" is characterized by cardiac, neurological, and hematological complications triggered by fluid and electrolyte disturbances during the re-feeding of chronically starved individuals (585). Cardiac complications of this syndrome usually occur within the first week of re-feeding and are typically associated with severe degrees of malnutrition (less than 70% ideal body weight) (586), hypophosphatemia (587), and total parenteral nutrition (588).

8.5. Pericardial Diseases

Recommendations

Class I

Ventricular arrhythmias that develop in patients with pericardial disease should be treated in the same manner that such arrhythmias are treated in patients with other diseases including ICD and pacemaker implantation as required. Patients receiving ICD implantation should be receiving chronic optimal medical therapy and have reasonable expectation of survival with a good functional status for more than 1 y. ***(Level of Evidence: C)***

SCD can occur in the course of pericardial disease resulting from a variety of pathological processes; these include both constrictive and restrictive processes, resulting from trauma, inflammation, neoplastic, and infectious etiologies. There is no evidence linking specific ventricular arrhythmias with these diseases. Reports of SCD in patients with pericardial diseases suggest that primary hemodynamic processes (i.e., acute tamponade, herniation of myocardium through pericardium) are responsible for the vast majority of SCD in such patients (589–592).

8.6. Pulmonary Arterial Hypertension

Recommendations

Class III

Prophylactic antiarrhythmic therapy generally is not indicated for primary prevention of SCD in patients with pulmonary arterial hypertension (PAH) or other pulmonary conditions. ***(Level of Evidence: C)***

SCD is responsible for 30% to 40% of mortality in patients with PAH. It appears more commonly in patients with primary PAH than in those with thromboembolic PAH (593). Patients experiencing SCD have lower partial pressure of oxygen than do those free of sudden death (594). SCD in patients with severe PAH appears to occur not only as a result of (presumed) ventricular arrhythmias but also as a result of pulmonary artery rupture or dissection (595,596). Cardiac arrhythmias may also result from ischemia. Marked dilatation of the main pulmonary artery has been reported to cause myocardial ischemia as a result of compression of the left main coronary artery (597). Cardiac catheterization is associated with increased risk of death, including documented VF in this population (598). In addition to patients with PAH, ventricular arrhythmias occur in persons with sleep disordered breathing and may be responsible for SCD in patients with sleep apnea (599).

No trials of prophylactic antiarrhythmic therapy have been conducted in patients with PAH or other pulmonary conditions. Antiarrhythmic therapy is not indicated for prevention of SCD in patients with PAH or other pulmonary conditions (600,601). Good clinical judgment should be used in the management of asymptomatic arrhythmias in such patients, as they may be prone to proarrhythmic effects of antiarrhythmic agents. Furthermore, such patients may be at high risk during surgical procedures, such as ICD implantation.

8.7. Transient Arrhythmias of Reversible Cause

Recommendations

Class I

1. **Myocardial revascularization should be performed, when appropriate, to reduce the risk of SCD in patients experiencing cardiac arrest due to VF or polymorphic VT in the setting of acute ischemia or MI.** ***(Level of Evidence: C)***
2. **Unless electrolyte abnormalities are proved to be the cause, survivors of cardiac arrest due to VF or polymorphic VT in whom electrolyte abnormalities are discovered in general should be evaluated and treated in a manner similar to that of cardiac arrest without electrolyte abnormalities.** ***(Level of Evidence: C)***
3. **Patients who experience sustained monomorphic VT in the presence of antiarrhythmic drugs or electrolyte abnormalities should be evaluated and treated in a manner similar to that of patients with VT without electrolyte abnormalities or antiarrhythmic drugs**

present. Antiarrhythmic drugs or electrolyte abnormalities should not be assumed to be the sole cause of sustained monomorphic VT. ***(Level of Evidence: B)***

4. **Patients who experience polymorphic VT in association with prolonged QT interval due to antiarrhythmic medications or other drugs should be advised to avoid exposure to all agents associated with QT prolongation. A list of such drugs can be found on the Web sites www.qtdrugs.org and www.torsades.org.** ***(Level of Evidence: B)***

The mortality of cardiac arrest survivors is high, even when the cause of the initial arrest appears to be a transient or correctable abnormality, and much of the mortality appears due to recurrent cardiac arrest (33,602). The most common putative reversible causes of arrest are acute ischemia and electrolyte imbalance. Other common potential causes to which cardiac arrest is attributed include proarrhythmic effects of antiarrhythmic drugs (603). No controlled trials have evaluated the effects of myocardial revascularization on VT or VF. However, observational studies suggest that:

- Sustained monomorphic VT in patients with prior MI is unlikely to be affected by revascularization (330).
- Myocardial revascularization is sufficient therapy only in patients surviving VF in association with myocardial ischemia when ventricular function is normal and there is no history of MI (604).

The short-term (hospital) mortality of patients in whom primary VF complicates the acute phase of MI is high. However, patients who survive the initial hospitalization after Q-wave MI have survival virtually identical to patients without VF in the acute phase of infarction (605). The low risk for late cardiac arrest appears to apply only to patients experiencing Q-wave infarction; patients with an infarction defined by biomarker elevations without development of new Q waves have a significantly higher risk of late cardiac arrest (606,607). Transient ischemia resulting from coronary artery spasm may cause polymorphic VT or VF (608). In such cases, treatment of coronary spasm is may be sufficient to prevent recurrent arrhythmia (609,610). Coronary artery spasm may increase the risk of ventricular arrhythmias and SCD.

Electrolyte abnormalities, including hypokalemia and hypomagnesemia, facilitate development of VT in predisposed patients receiving antiarrhythmic agents and other drugs associated with the LQTS. However, hypokalemia can also result from cardiac arrest and should not otherwise be assumed to be the cause of cardiac arrest, except under unusual circumstances (611). Correction of hypokalemia does not affect inducibility of monomorphic VT occurring after MI. Electrolyte abnormalities should not be assumed to be the cause of cardiac arrest, except in the presence of drug-induced LQTS.

In patients who develop polymorphic VT in association with drug-induced QT prolongation, withdrawal of the offending antiarrhythmic or other agent is usually sufficient to prevent arrhythmia recurrence. If ventricular function is normal, no therapy beyond drug withdrawal, avoidance of future drug exposure, and correction of electrolyte abnormalities is necessary. However, if ventricular function is abnormal, cardiac arrest or syncope should not be attributed solely to antiarrhythmic drugs, and evaluation and treatment should be similar to patients experiencing such events in the absence of antiarrhythmic drugs.

Occasionally, patients develop monomorphic sustained VT only in the presence of antiarrhythmic drugs without QT prolongation. In such cases, it may appear that the development of spontaneous VT is dependent on drug administration. In most patients exhibiting this behavior, the monomorphic VT is inducible by EP testing in the absence of antiarrhythmic drugs (612,613).

9. VENTRICULAR ARRHYTHMIAS ASSOCIATED WITH CARDIOMYOPATHIES

9.1. Dilated Cardiomyopathy (Nonischemic)

Recommendations

Class I

1. **EP testing is useful to diagnose bundle-branch reentrant tachycardia and to guide ablation in patients with nonischemic DCM.** ***(Level of Evidence: C)***
2. **EP testing is useful for diagnostic evaluation in patients with nonischemic DCM with sustained palpitations, wide-QRS-complex tachycardia, presyncope, or syncope.** ***(Level of Evidence: C)***
3. **An ICD should be implanted in patients with nonischemic DCM and significant LV dysfunction who have sustained VT or VF, are receiving chronic optimal medical therapy, and who have reasonable expectation of survival with a good functional status for more than 1 y.** ***(Level of Evidence: A)***
4. **ICD therapy is recommended for primary prevention to reduce total mortality by a reduction in SCD in patients with nonischemic DCM who have an LVEF less than or equal to 30% to 35%, are NYHA functional class II or III, who are receiving chronic optimal medical therapy, and who have reasonable expectation of survival with a good functional status for more than 1 y.** ***(Level of Evidence: B)*** **(See Section 1.2.)**

Class IIa

1. **ICD implantation can be beneficial for patients with unexplained syncope, significant LV dysfunction, and nonischemic DCM who are receiving chronic optimal medical therapy and who have reasonable expectation of survival with a good functional status for more than 1 y.** ***(Level of Evidence: C)***

2. **ICD implantation can be effective for termination of sustained VT in patients with normal or near normal ventricular function and nonischemic DCM who are receiving chronic optimal medical therapy and who have reasonable expectation of survival with a good functional status for more than 1 y.** ***(Level of Evidence: C)***

Class IIb

1. **Amiodarone may be considered for sustained VT or VF in patients with nonischemic DCM.** ***(Level of Evidence: C)***
2. **Placement of an ICD might be considered in patients who have nonischemic DCM, LVEF of less than or equal to 30% to 35%, who are NYHA functional *class I* receiving chronic optimal medical therapy, and who have reasonable expectation of survival with a good functional status for more than 1 y.** ***(Level of Evidence: C)*** **(See Section 1.2.)**

Considerations taken by the Writing Committee in formulating recommendations for this section are discussed in detail in the Introduction.

9.1.1. Risk Stratification

The 5-y mortality for DCM has been recently estimated at 20% with SCD accounting for approximately 30% (8% to 51%) of deaths (614,615). Ventricular arrhythmias, both symptomatic and asymptomatic, are common, but syncope and SCD are infrequent initial manifestations of the disease (616,617). The incidence of SCD is highest in patients with indicators of more advanced cardiac disease who are also at highest risk of all cause mortality. Although VT and/or VF is considered the most common mechanism of SCD, bradycardia, pulmonary embolus, electromechanical dissociation and other causes account for up to 50% of SCDs in patients with advanced HF (107,618,619). Risk stratification is difficult in DCM. SCD occurs less frequently in patients with less advanced cardiac disease but the proportion of SCD to all-cause death is higher in this group (617,618,620). Predictors of overall outcome also predict SCD and generally reflect severity of disease (EF, end-diastolic volume, older age, hyponatremia, pulmonary capillary wedge pressure, systemic hypotension, AF) (614). Unfortunately, they do not specifically predict arrhythmic death and are not useful in the patient with less severe disease (3,621). Even a low EF (less than 20%) may not have high positive predictive value for SCD (622–624). Syncope has been associated with a higher risk of SCD regardless of the proven etiology of the syncope (223,625) and patients with ICD implantation receive appropriate shocks comparable to a secondary prevention cohort (223,625,626). Premature ventricular complexes and NSVT correlate with the severity of cardiac disease and occur in the majority of patients with severe LV dysfunction (619,627,628). This limits the utility of ventricular arrhythmias as risk stratifiers as they would be expected to be sensitive but not specific. It has been suggested that the presence of NSVT may be more specific in the individual with better LV function (3). Induction of VT by EP testing has been shown to predict SCD (625) but unfortunately failure to induce VT misses most individuals destined to die suddenly (129,627,629,630). Microvolt TWA has been suggested to predict SCD in a cohort study of 137 patients with DCM (151). The study included 37 patients with an indication for ICD and most endpoints occurred in this group. Nonetheless, the positive predictive value was relatively modest (0.22), as was EF less than 35% (0.15). Idiopathic DCM has heterogeneous etiologies but is familial in at least 40% of cases, being usually autosomal dominant with variable penetrance but also X-linked (631–634). Unfortunately, genetic information is not currently useful for risk stratification.

9.1.2. Electrophysiological Testing

In DCM, EP testing plays a minor role in the evaluation and management of VT. This is related to low inducibility, low reproducibility of EP testing, and low predictive value of induced VT (203,204). The multicenter CAT trial included 104 patients with DCM and LVEF less than 30% without sustained VT/VF (635). NSVT during Holter monitoring was recorded in 52%. With use of a complete EP testing protocol, only 2.9% of patients had sustained VT and 9.6% had VF induced. However, symptomatic patients may have various supraventricular tachyarrhythmias, typical and atypical atrial flutter or AF, requiring EP testing for diagnostic purposes or to guide ablation. Bundle-branch reentry may be suspected in patients with DCM, intraventricular conduction defects during sinus rhythm, and LBBB pattern tachycardia (636).

9.1.3. Management

The treatment of DCM is often based on individual patient presentation and local physician experience. Pharmaceuticals that have improved overall mortality in patients with HF, such as beta blockers and ACE inhibitors, have also reduced SCD (622,637–640). Amiodarone is generally preferred to treat patients with symptomatic arrhythmias because of the absence of significant negative hemodynamic effects and low proarrhythmic potential, although controlled comparative trials of drugs are not available. Amiodarone has been suggested to improve mortality in uncontrolled trials (641). In controlled trials, amiodarone reduced the incidence of SCD in a population of patients with predominately nonischemic DCM (637) but not in a study of HF patients where the majority had CHD (638). The ICD has been shown to be superior to amiodarone for secondary prevention of VT and VF in studies where the majority of patients had CHD (266,642,643). The subgroup with nonischemic DCM in these studies benefited from the ICD more than did those with CHD (644).

The role of the ICD in primary prophylaxis has been controversial. The Cardiomyopathy Trial (CAT) enrolled patients with recently diagnosed DCM and was discontinued early due to futility largely because of a lower-than-expected incidence of all-cause mortality (635). This was a relatively small study (50 patients in the ICD arm and 54 in the control group), although the 5-y follow-up showed fewer deaths in the ICD group versus control (13 vs. 17, respectively). In the AMIOVERT study (645), 103 patients with DCM, EF less than 35%, and NSVT were randomized to amiodarone or ICD. The primary endpoint was total mortality, and the study was stopped prematurely due to futility. The Defibrillators in Nonischemic Cardiomyopathy Treatment Evaluation (DEFINITE) (646–648) randomized 458 patients with nonischemic cardiomyopathy, EF less than 35%, and frequent PVCs or NSVT to receive best medical therapy with or without ICD. There was a trend toward reduction of mortality with ICD therapy, but this was not significant.

The DEFINITE patients were randomized to receive best medical therapy with or without an ICD, and the primary endpoint was all-cause mortality. After 2 y, mortality was 13.8% in the standard therapy group versus 8.1% among those receiving an ICD, amounting to a 5.7% absolute reduction and a 35% relative risk reduction with ICD implantation. This failed to reach statistical significance ($p = 0.06$), but the findings are comparable to those of other similar trials (647,648). The SCD-HeFT compared amiodarone, ICD, and best medical therapy in 2521 patients with CHD or nonischemic cardiomyopathy who were in NYHA functional class II or III HF with EF less than 35%. The drug arm (amiodarone) was double blinded and placebo controlled. The median follow-up was 45.5 mo. The total mortality in the medical group was 7.2% per year over 5 y with a risk reduction of 23% in the ICD group versus placebo (CI 0.62 to 0.96, $p = 0.007$). Relative risk reduction was comparable for LV dysfunction due to prior MI and nonischemic groups, but absolute mortality was lower in the nonischemic group, resulting in a greater number to treat per life saved. There was no mortality difference between the amiodarone and placebo groups (8). Further risk stratification may decrease the number of individuals needed to treat to save a life in this population (649). With the exception of DEFINITE (25% in the ICD arm), trials assessing ICD in primary prophylaxis of DCM did not generally include asymptomatic patients with NYHA functional class I and therefore the efficacy of ICD in this population is not fully known (650). Because mortality is low in this subgroup, the benefit of ICD therapy is at best moderate.

9.1.4. Genetic Analysis

The clinical applicability of genetic analysis to DCM is still limited as knowledge in this area does not allow genotyping of most individuals clinically affected by the disease. Patients with DCM and AV block and patients with DCM and skeletal muscle diseases have a higher probability of being successfully genotyped. When a pathogenetic mutation is identified, it becomes possible to establish a presymptomatic diagnosis of the disease among family members and to provide them with genetic counseling to monitor progression of the disease and to assess the risk of transmitting the disease to offspring. Based on current knowledge, genetic analysis does not contribute to further risk stratification in DCM.

9.2. Hypertrophic Cardiomyopathy

Recommendations

Class I

ICD therapy should be used for treatment in patients with HCM who have sustained VT and/or VF and who are receiving chronic optimal medical therapy and who have reasonable expectation of survival with a good functional status for more than 1 y. ***(Level of Evidence: B)***

Class IIa

1. **ICD implantation can be effective for primary prophylaxis against SCD in patients with HCM who have 1 or more major risk factor (see Table 7) for SCD and who are receiving chronic optimal medical therapy and in patients who have reasonable expectation of survival with a good functional status for more than 1 y.** ***(Level of Evidence: C)***
2. **Amiodarone therapy can be effective for treatment in patients with HCM with a history of sustained VT and/or VF when an ICD is not feasible.** ***(Level of Evidence: C)***

Class IIb

1. **EP testing may be considered for risk assessment for SCD in patients with HCM.** ***(Level of Evidence: C)***

Table 7. Risk Factors for Sudden Cardiac Death in Hypertrophic Cardiomyopathy

Major Risk Factors	Possible in Individual Patients
Cardiac arrest (VF)	AF
Spontaneous sustained VT	Myocardial ischemia
Family history of premature sudden death	LV outflow obstruction
Unexplained syncope	High-risk mutation
LV thickness greater than or equal to 30 mm	Intense (competitive) physical exertion
Abnormal exercise BP	
Nonsustained spontaneous VT	

Modified with permission from Maron BJ, McKenna WJ, Danielson GK, et al. American College of Cardiology/European Society of Cardiology clinical expert consensus document on hypertrophic cardiomyopathy. A report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents and the European Society of Cardiology Committee for Practice Guidelines. J Am Coll Cardiol 2003;42:1687–713.

AF = atrial fibrillation; BP = blood pressure; LV = left ventricular; VF = ventricular fibrillation; VT = ventricular tachycardia.

2. **Amiodarone may be considered for primary prophylaxis against SCD in patients with HCM who have 1 or more major risk factor for SCD (see Table 7) if ICD implantation is not feasible.** ***(Level of Evidence: C)***

9.2.1. Risk Stratification

Most individuals with HCM are asymptomatic and the first manifestation may be SCD (651–657). SCD is usually related to ventricular arrhythmia with varying contribution of triggers such as ischemia, outflow obstruction, or AF (653–656,658). SCD is less frequently due to bradycardia (659). The annual mortality from HCM has been estimated as high as 6% from tertiary centers (653,660,661), but community-based studies suggest a more benign disease in the majority of individuals, with an annual mortality in the range of 1% or less (662–667). This relatively low incidence creates a challenge for risk stratification because the false-positive values for any stratifier may overwhelm the true-positive values (668). Features suggesting higher risk of SCD have been derived from observational studies (98,662,669–677). In one study, 23 of 480 patients died suddenly over a mean follow-up of 6.5 y (678). The risk of SCD was directly related to LV wall thickness with essentially no mortality over 20 y with wall thickness less than 20 mm and mortality of almost 40% for wall thickness greater than or equal to 30 mm. Patients with such extreme wall thickness were the youngest and frequently asymptomatic. Five of 12 patients in this category under the age of 18 died suddenly. Others have suggested that patients with extreme septal hypertrophy also have other risk factors, and the independent value of extreme septal hypertrophy is less clear (98,679). The degree of outflow obstruction has been shown to predict cardiovascular death (674,678) but not SCD (678). Athletes with HCM should not participate in most competitive sports with the possible exception of sports of low dynamic and low static intensity (680–682). Participation in low-to-moderate athletic activities may be allowed in selected low-risk patients (683).

Cardiac MRI (684) and CT (685) have been suggested to be helpful in assessing extent of disease and predicting SCD. A history of SCD in one or more family members has been considered to signify higher risk (653,660,686). This is intuitively logical and related closely to the suggestion that certain specific genetic abnormalities have been associated with increased risk of SCD (687–691); the role of genetic testing as a predictor of SCD is likely to increase (687). Syncope has been associated with increased risk of SCD (657,692–695). The severity of other symptoms such as dyspnea, chest pain, and effort intolerance has not been correlated with increased risk of SCD (695,696). A flat or hypotensive response to upright or supine exercise testing in patients younger than 40 y has been shown to be a risk factor for SCD, although the positive predictive value of this finding is low (658). A normal blood pressure response identifies a low-risk group (658,697–699). The presence of VT on Holter monitoring (665,696,700–702) has been associated with a higher risk of SCD, although the positive predictive accuracy is relatively low. The absence of VT appears to have good negative predictive value. VT induced in the EP laboratory (97) has also been associated with a higher risk of SCD, although others have suggested that VT induced in this setting with aggressive stimulation techniques is not specific (703,704).

A consensus document on HCM from the American College of Cardiology and European Society of Cardiology categorized known risk factors for SCD as "major" and "possible in individual patients" (705) (see Table 7).

It is clear that many of the risk factors listed in Table 7 are interdependent, and the major independent risk factors may prove to be the extent of disease and the genetic abnormality. The absence of risk factors identifies a low-risk group, but the positive predictive value of any single risk factor is limited. Risk stratification based on incorporation of multiple risk factors would likely improve positive predictive accuracy (693).

9.2.2. Electrophysiological Testing

The value of EP testing in HCM has been controversial (706). In 1989, Fananapazir et al. (707) showed by using 2 premature stimuli that only 16% of patients with cardiac arrest or syncope in the setting of HCM had inducible sustained VT. In a later study, the same group published data on 230 patients, including 155 patients reported earlier (97,707). Patients with inducible VT had a poorer prognosis than those without inducible VT. Induced VT was often polymorphic. The response to EP testing was considered to be an important predictive factor for outcome, together with a history of syncope or cardiac arrest. In a prospective study of 29 patients with HCM, 8 of them presenting with syncope, EP testing with up to 3 extrastimuli at 3 cycle lengths including LV stimulation failed to distinguish patients with from those without syncope (224). In patients who received an ICD for primary prevention, the estimated appropriate discharge rate was 5% per year (708).

9.2.3. Management

The mainstay of pharmacological management for the symptomatic patient has been beta blockers or verapamil, which probably exert their effect by reducing heart rate and decreasing contractility (653,660). Disopyramide has been similarly used presumably for its negative inotropic effect (709). AF can be especially problematic (710,711), with sudden clinical deterioration as a result of high ventricular rates and loss of atrial filling. In addition, it is associated with increased risk of embolism, HF, and death. The high rate of embolism warrants anticoagulation with warfarin even though this has not been validated in this group of patients by a large randomized trial. Amiodarone is widely used and considered the most effective antiarrhythmic agent, although large controlled comparative trials are not available (710,712). Medical therapy has not been proved to

be beneficial in the prevention of disease progression in the asymptomatic individual and is generally not indicated. Nonetheless, treatment with beta blockers and/or calcium antagonists is tempting even in asymptomatic individuals if they are younger and have severe hypertrophy or significant gradients (660). It is intuitively reasonable that optimal medical therapy and control of comorbidities will also reduce the risk of SCD, although this has not been rigidly demonstrated.

Although no randomized studies are available, the ICD has been used in patients with cardiac arrest, sustained VT, or VF, with a high percentage of patients receiving appropriate discharge during follow-up at a rate of 11% per year (708). The ICD implanted in a subgroup of patients for primary prophylaxis on the basis of perceived high risk for SCD (syncope, family history of SCD, NSVT, inducible VT, septal thickness greater than or equal to 30 mm) resulted in a lower rate of appropriate discharge of 5% per year (708). Amiodarone has been shown useful in prevention of SCD in nonrandomized studies (712,713), while other studies have suggested symptomatic improvement but have not shown complete prevention of SCD (714,715). Placebo-controlled studies or studies that compared ICD with amiodarone are not available, and the role of amiodarone in prevention of SCD is unclear. Amiodarone is unlikely to be superior to the ICD for this purpose, and a comparative study may never be done (716). The ICD is not indicated in the majority of asymptomatic patients with HCM, who will have a relatively benign course. Its role is individualized in the patient considered to be at high risk for SCD (3,717,718). Although precise risk stratification has not been validated, patients with multiple risk factors (especially severe septal hypertrophy, greater than or equal to 30 mm) and those with SCD (especially multiple SCDs) in close relatives appear to be at sufficiently high risk to merit consideration of ICD therapy.

9.2.4. Genetic Analysis

Genetic analysis is useful in families with HCM because whenever a pathogenetic mutation is identified, it becomes possible to establish a presymptomatic diagnosis of the disease among family members and to provide them with genetic counseling to assess the risk of disease development and transmission of the disease to offspring. Genetic analysis may contribute to risk stratification in selected circumstances.

9.3. Arrhythmogenic Right Ventricular Cardiomyopathy

Recommendations

Class I

ICD implantation is recommended for the prevention of SCD in patients with ARVC with documented sustained VT or VF who are receiving chronic optimal medical therapy and who have reasonable expectation of survival with a good functional status for more than 1 y. ***(Level of Evidence: B)***

Class IIa

1. **ICD implantation can be effective for the prevention of SCD in patients with ARVC with extensive disease, including those with LV involvement, 1 or more affected family member with SCD, or undiagnosed syncope when VT or VF has not been excluded as the cause of syncope, who are receiving chronic optimal medical therapy, and who have reasonable expectation of survival with a good functional status for more than 1 y.** ***(Level of Evidence: C)***
2. **Amiodarone or sotalol can be effective for treatment of sustained VT or VF in patients with ARVC when ICD implantation is not feasible.** ***(Level of Evidence: C)***
3. **Ablation can be useful as adjunctive therapy in management of patients with ARVC with recurrent VT, despite optimal antiarrhythmic drug therapy.** ***(Level of Evidence: C)***

Class IIb

EP testing might be useful for risk assessment of SCD in patients with ARVC. ***(Level of Evidence: C)***

9.3.1. Risk Stratification

ARVC ("dysplasia") is suspected in patients, typically a young man, with RV arrhythmias or in relatives of individuals with known ARVC. Syncope, presyncope, and, less frequently, biventricular failure are also observed (719,720). The ventricular arrhythmias have LBBB morphology that spans the spectrum of simple ventricular ectopy, sustained and NSVT, or VF. ARVC needs to be considered along with idiopathic RV outflow VT in the individual with ventricular ectopy and VT coming from the RV outflow region. In contrast to ARVC, idiopathic RV outflow VT is usually not associated with the ECG abnormalities seen with ARVC, is more common in women, and is initiated by isoproterenol infusion instead of by EP testing (721,722). The ECG in ARVC frequently shows precordial T-wave inversion, usually over V_1 to V_3, and QRS duration greater than 110 ms (721). Low voltage potentials following the QRS (epsilon waves) are characteristic but seen relatively infrequently, and late potentials are observed on the SAECG in greater than 50% of individuals (721,723,724).

Unfortunately, SCD is frequently the first manifestation of the disease (96,725,726). A standardized diagnostic scheme has been formulated to establish a clinical diagnosis on a point score basis (727). The annual incidence of SCD has varied, ranging from 0.08% to 9% (720,728–730). In an autopsy series, 24 of 27 patients were determined to have died suddenly and 3 to have died of congestive HF (731). SCD occurs relatively frequently during exercise or during stress, but SCD with no apparent provocation is not uncommon (732). In one Italian series, up to 25% of SCD

in athletes was related to ARVC (733). Although SCD usually occurs in individuals with grossly visible RV abnormalities, it can occur in those with only microscopic abnormalities and no obvious RV enlargement (734). RV dilation, precordial repolarization abnormalities, and LV involvement have been associated with risk of sudden death (730,735,736). Certain genetic types may be associated with higher risk of SCD (737). SCD in 1 or more family members intuitively suggests a higher risk of SCD in an affected individual, but this has not been well quantified (170).

9.3.2. Electrophysiological Testing

The arrhythmic manifestations of the disease are variable (96). The prognostic role of EP testing in patients presenting with isolated PVCs or NSVT is not known. The response to EP testing may be influenced by the severity of the disease. Progression of disease has to be considered. EP testing has been evaluated in a limited number of patients for risk stratification. Di Biase et al. (738) used EP testing in 17 patients with "mild" dysplasia and induced VT only in patients with spontaneous sustained VT. VT was induced in 90% of 12 patients with spontaneous sustained VT (739). The positive predictive value for recurrent VT was only 55%. Sustained VT could not be induced in 20 patients presenting with NSVT (736). In this study, inducibility was 88% in 24 of 27 patients presenting with sustained VT. EP testing, in general, is used to reproduce clinical VT and to guide ablation (740,741).

9.3.3. Management

The treatment of ARVC is often based on individual patient presentation and local physician experience. The ICD has been used in patients with unexplained syncope, sustained VT, or VF with a high incidence of appropriate shocks (742). Although there are no specific large randomized trials in ARVC to support this, the situation is sufficiently "similar" to those disease states such as previous MI where these indications are well established (266,718,741,743). ICD treatment in individuals with a known family history of SCD or unexplained syncope is intuitively compelling but not rigidly proved. The impact of medical therapy on mortality is not established. RF ablation has been used in selected patients for VT in medically refractory patients (744). Elimination of 1 or more clinical tachycardias by RF ablation is useful for management of symptoms but may not be sufficient to prevent SCD. Operative therapy in the form of total electrical RV disconnection has proved successful in medically refractory patients with normal LV function but does carry a risk of postoperative right HF (745). Heart transplantation and ventricular assist devices are an option in patients with biventricular failure.

9.3.4. Genetic Analysis

Genetic analysis is useful in families with RV cardiomyopathy, because whenever a pathogenetic mutation is identified, it becomes possible to establish a presymptomatic diagnosis of the disease among family members and to provide them with genetic counseling to monitor the development of the disease and to assess the risk of transmitting the disease to offspring. Based on current knowledge, genetic analysis does not contribute to risk stratification in RV cardiomyopathy.

9.4. Neuromuscular Disorders

Recommendations

Class I

Patients with neuromuscular disorders who have ventricular arrhythmias should generally be treated in the same manner as patients without neuromuscular disorders. ***(Level of Evidence: A)***

Class IIb

Permanent pacemaker insertion may be considered for neuromuscular diseases such as myotonic muscular dystrophy, Kearns-Sayre syndrome, Erb dystrophy, and peroneal muscular atrophy with any degree of AV block (including first-degree AV block) with or without symptoms, because there may be unpredictable progression of AV conduction disease. ***(Level of Evidence: B)***

The inherited neuromuscular disorders may predispose to atrial arrhythmias, conduction defects, advanced AV block, monomorphic VT, polymorphic VT, and SCD (746–755). An exhaustive list of the inherited neuromuscular disorders is beyond the scope of this guideline. Table 8 lists some of the more common disorders associated with cardiovascular manifestations, produced in some cases by degeneration of the specialized conduction tissue and in others by degenerative changes in atrial and myocardial tissue predisposing to cardiomyopathy and ventricular arrhythmias. In many cases, the resting ECG is abnormal, with first-degree AV block, bundle-branch block, Q waves, ST-T abnormalities, or PVCs (753,754).

The clinical presentation, indicating the potential substrate for SCD, is quite variable, ranging from asymptomatic to the symptoms of syncope, lightheadedness, and palpitations. There are no large series of asymptomatic patients treated with devices and the timing of pacemaker/ICD implantation is not clear based on the available literature. In general, the more advanced the cardiac involvement is (conduction or structural), the more likely it is that a serious arrhythmia will occur. SCD is a well-recognized complication of some of the neuromuscular diseases and progression of the conduction abnormalities may be unpredictable (756–762). Once cardiac involvement occurs, particularly with the muscular dystrophies, the clinician should maintain a low threshold for investigating symptoms or ECG findings to determine the need for pacemaker insertion, invasive EP studies, or ICD implantation. Screening for underlying cardiovascular manifestations with a resting 12-lead ECG or echocardiogram to

Table 8. Frequency of Events in Neuromuscular Disorders Associated With Heart Disease

	Inheritance	HB	VA	CM
Muscular dystrophies				
Duchenne	X-linked	+	+	+++
Becker	X-linked	+	+	+++
X-linked dilated CM	X-linked	—	+	+++
Limb-girdle 1B	AD	+++	+++	++
Limb-girdle 2C-2F	AR	+	+	+++
Myotonic MD	AD	+++	+++	+
Emery-Dreifuss MD and associated disorders	X-linked, AD, AR	+++	+++	++
Other conditions				
Friedreich's ataxia	AR	—	+	+++
Kearns-Sayre syndrome	—	+++	++	+

+ to +++ represents a comparison between the various medical conditions and the relative frequency of an event.
AD = autosomal dominant; AR = autosomal recessive; CM = cardiomyopathy; HB = heart block; MD = muscular dystrophy; VA = ventricular arrhythmias; + = low-frequency event; ++ = intermediate-frequency event; +++ = high-frequency event.

determine cardiac involvement should be part of the routine clinical assessment, independent of symptom status. The relative likelihood of a patient with an inherited neuromuscular disorder developing a conduction disturbance, ventricular arrhythmia, or cardiomyopathy is listed in Table 8. In general, the indications for device therapy in patients with Duchenne, Becker, X-linked cardiomyopathies, limb-girdle 2C to 2F, and Friedreich ataxia should follow standard pacing/ICD guidelines as for patients with dilated cardiomyopathies. The reader is referred to the ACC/AHA/NASPE 2002 Guidelines Update for Implantation of Cardiac Pacemakers and Antiarrhythmic Devices for a comprehensive listing of indications (1). In an asymptomatic subject with normal ECG and no cardiovascular manifestations, pacemaker or ICD implantation is generally not indicated.

Indications for pharmacological or device therapy in patients with myasthenia gravis, Guillain-Barre syndrome, or an acute cerebrovascular event are quite different than those for the above-mentioned inherited neuromuscular disorders. Treatment is often temporary to manage the acute event and not usually required on a long-term basis.

10. HEART FAILURE

Recommendations

Class I

1. **ICD therapy is recommended for secondary prevention of SCD in patients who survived VF or hemodynamically unstable VT, or VT with syncope and who have an LVEF less than or equal to 40%, who are receiving chronic optimal medical therapy, and who have a reasonable expectation of survival with a good functional status for more than 1 y.** ***(Level of Evidence: A)***
2. **ICD therapy is recommended for primary prevention to reduce total mortality by a reduction in SCD in patients with LV dysfunction due to prior MI who are at least 40 d post-MI, have an LVEF less than or equal to 30% to 40%, are NYHA functional class II or III receiving chronic optimal medical therapy, and who have reasonable expectation of survival with a good functional status for more than 1 y.** ***(Level of Evidence: A)*** **(See Section 1.2.)**
3. **ICD therapy is recommended for primary prevention to reduce total mortality by a reduction in SCD in patients with nonischemic heart disease who have an LVEF less than or equal to 30% to 35%, are NYHA functional class II or III, are receiving chronic optimal medical therapy, and who have reasonable expectation of survival with a good functional status for more than 1 y.** ***(Level of Evidence: B)*** **(See Section 1.2.)**
4. **Amiodarone, sotalol, and/or other beta blockers are recommended pharmacological adjuncts to ICD therapy to suppress symptomatic ventricular tachyarrhythmias (both sustained and nonsustained) in otherwise optimally treated patients with HF.** ***(Level of Evidence: C)***
5. **Amiodarone is indicated for the suppression of acute hemodynamically compromising ventricular or supraventricular tachyarrhythmias when cardioversion and/or correction of reversible causes have failed to terminate the arrhythmia or prevent its early recurrence.** ***(Level of Evidence: B)***

Class IIa

1. **ICD therapy combined with biventricular pacing can be effective for primary prevention to reduce total mortality by a reduction in SCD in patients with NYHA functional class III or IV, are receiving optimal medical therapy, in sinus rhythm with a QRS complex of at least 120 ms, and who have reasonable expectation of survival with a good functional status for more than 1 y.** ***(Level of Evidence: B)***
2. **ICD therapy is reasonable for primary prevention to reduce total mortality by a reduction in SCD in patients with LV dysfunction due to prior MI who are at least 40 d post-MI, have an LVEF of less than or equal to 30% to 35%, are NYHA functional class I,**

are receiving chronic optimal medical therapy, and have reasonable expectation of survival with a good functional status for more than 1 y. ***(Level of Evidence: B)*** **(See Section 1.2.)**

3. **ICD therapy is reasonable in patients who have recurrent stable VT, a normal or near normal LVEF, and optimally treated HF and who have a reasonable expectation of survival with a good functional status for more than 1 y.** ***(Level of Evidence: C)***
4. **Biventricular pacing in the absence of ICD therapy is reasonable for the prevention of SCD in patients with NYHA functional class III or IV HF, an LVEF less than or equal to 35%, and a QRS complex equal to or wider than 160 ms (or at least 120 ms in the presence of other evidence of ventricular dyssynchrony) who are receiving chronic optimal medical therapy and who have reasonable expectation of survival with a good functional status for more than 1 y.** ***(Level of Evidence: B)***

Class IIb

1. **Amiodarone, sotalol, and/or beta blockers may be considered as pharmacological alternatives to ICD therapy to suppress symptomatic ventricular tachyarrhythmias (both sustained and nonsustained) in optimally treated patients with HF for whom ICD therapy is not feasible.** ***(Level of Evidence: C)***
2. **ICD therapy may be considered for primary prevention to reduce total mortality by a reduction in SCD in patients with nonischemic heart disease who have an LVEF of less than or equal to 30% to 35%, are NYHA functional class I receiving chronic optimal medical therapy, and who have a reasonable expectation of survival with a good functional status for more than 1 y.** ***(Level of Evidence: B)*** **(See Section 1.2.)**

Considerations taken by the Writing Committee in formulating recommendations for this section are discussed in detail in the Introduction.

Ventricular arrhythmias and SCD are common in patients with symptomatic acute and chronic HF and LV systolic dysfunction. The cause of HF likely influences the mechanisms and types of ventricular arrhythmias. The guidelines and comments in this section refer to patients with the symptomatic HF; not just abnormal LVEF (refer to the ACC/AHA Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult for definitions (6).

Arrhythmia management in the setting of acute HF takes place concurrently with attempts at hemodynamic stabilization. Evaluation of arrhythmias in the setting of acute HF necessitates a search for correctable mechanical problems such as catheters placed for hemodynamic monitoring that are causing ventricular or supraventricular arrhythmias. In addition, meticulous attention needs to be given to such factors as pharmacological agents used in the management of acute heart failure and electrolyte and oxygen status. Given its relatively rapid onset of action and its superior safety profile in patients with HF, the use of intravenous amiodarone for the management of life-threatening arrhythmias during acute HF has gained widespread acceptance.

In the acutely ill patient with HF, SVT and AF or atrial flutter may impose hemodynamic decompensation, and aggressive therapy may be needed. Vagotonic measures rarely work in the setting of acute HF. Poorly tolerated SVT may be better treated acutely by synchronous cardioversion, which may be accomplished at relatively low energies (e.g., 50 to 100 J biphasic). Verapamil may be effective at suppressing reentrant SVTs that are dependent on the AV node. Care should be taken to avoid excessive myocardial suppression related to the negative inotropic effects of verapamil. Intravenous amiodarone may be more effective at rate control of AF or atrial flutter and may restore sinus rhythm. In HF patients, amiodarone either alone or with electrical cardioversion is effective at slowing the heart rate and achieving cardioversion (763,764).

In the setting of acute HF, ventricular arrhythmias may be especially poorly tolerated and early cardioversion should be performed, rather than attempting pharmacological termination of arrhythmia. Patients with advanced myocardial disease often have intraventricular conduction delays, making the distinction of ventricular from supraventricular arrhythmias challenging. Regardless of the origin of an unstable arrhythmia, cardioversion is appropriate. Amiodarone is preferred for longer-term administration and is generally well tolerated hemodynamically (765). Catheter ablation may be an appropriate adjunctive therapy in selected patients.

NSVT can be documented on 24-h ambulatory ECG monitoring in 30% to 80% of chronic HF patients without arrhythmia symptoms (25,766,767). Although NSVT is associated with increased mortality risk in this population, the weight of evidence does not show a specific link between NSVT and SCD (25,766,768), although one trial has suggested a link (767). There is no evidence that suppression of NSVT has a favorable effect on prognosis in patients with HF (638). Thus, asymptomatic NSVT should not be treated by antiarrhythmic medication. If NSVT causes symptoms that require therapy, amiodarone is probably the safest agent to use for treatment, although amiodarone treatment in NYHA functional class III patients in the SCD-HeFT trial was associated with possibly increased mortality (8,248).

Polymorphic VT in association with or not in association with QT prolongation may occur during exacerbation of HF. These arrhythmias may resolve with the treatment of HF.

SCD accounts for approximately 50% of deaths in patients with HF. However, there is little evidence that empiric antiarrhythmic therapy can reduce the risk of SCD. Earlier trials of empiric therapy with amiodarone have

yielded conflicting results, with some demonstrating reduced mortality and others showing no improvement in survival (637,638). The SCD-HeFT trial showed no survival benefit to patients with HF (NYHA functional class II and III) and LVEF less than or equal to 35% treated with amiodarone empirically (8).

ICD therapy did not improve the survival of patients with HF due to nonischemic DCM in 2 small trials (635,645). However, the SCD-HeFT trial demonstrated a 23% reduction in total mortality with ICD treatment in comparison to placebo (8). These results are consistent with the results of DEFINITE and earlier trials of patients with CHD and LV dysfunction, some of whom had symptomatic HF (192,267,268). ICD in combination with biventricular pacing may improve survival and improve symptoms of patients with advanced HF (NYHA functional class III and IV) over short-term follow-up (1 to 2 y).

Biventricular pacing may be used to synchronize the contraction of the LV in patients with abnormal ventricular activation. Cardiac resynchronization therapy has been shown to improve hemodynamics, increase LVEF, extend exercise tolerance, and improve quality of life (769,770). In patients with a poor functional status (NYHA functional class III or IV), reduced ventricular function (LVEF less than or equal to 35%), and a wide-QRS complex (at least 120 ms), biventricular pacing without ICD therapy has consistently led to a reduction of mortality and hospital admissions for the treatment of HF (771,772). It has therefore been strongly recommended (class I) elsewhere (6) that biventricular pacing should be considered for the treatment of such patients. This guideline considers therapies for the management of ventricular arrhythmias and SCD. In 1 recent study (772) that recruited patients with NYHA class III through IV HF, an EF equal to or less than 35%, and a QRS complex equal to or greater than 160 ms (or at least 120 ms in the presence of other evidence of ventricular dyssynchrony), sudden death was also significantly reduced when biventricular pacing was applied. However, in another study (771) that recruited similar patients, except that the QRS complex had simply to equal or exceed 120 ms, sudden death was not prevented by resynchronization therapy alone. The value of biventricular pacing without additional ICD support for the reduction of sudden death remains controversial (773,774).

11. GENETIC ARRHYTHMIA SYNDROMES

11.1. General Concepts for Risk Stratification

LQTS, Brugada syndrome, and catecholaminergic polymorphic ventricular tachycardia (CPVT) (Online Mendelian Inheritance in Man [OMIM] Nos. 192500, 152427, 603830, 600919, 176261, 603796, 601144, and 604772) (775) are inherited arrhythmogenic diseases. They share genetically determined susceptibility to VT and SCD in the absence of recognizable structural abnormalities of the heart. These syndromes are by definition rare diseases, because they have an estimated prevalence below 5 in 10 000 (Definition 1295/1999/EC of the European Parliament [770]).

Given the limited number of individuals affected by these diseases, certain aspects should be considered before developing recommendations for risk stratification and management of patients with these diseases.

- Most of the data available for these conditions derive from large registries that have followed patients over time, recording outcome information. No randomized studies are available, and most likely they will never be conducted in these uncommon conditions. Therefore, the level of evidence for recommendation in these conditions is B or C depending on the size of the available registries and on the duration of the follow-up of enrolled patients. (This Writing Committee has decided to consider Level of Evidence: B for data collected by the registries on LQTS because they are based on large number of patients with a long follow-up and to use a Level of Evidence: C for the Brugada syndrome and CPVT registries, which have a much shorter observation time for enrolled patients.)
- Data on the natural history of these diseases are potentially biased by the fact that it is more likely that a highly symptomatic case is referred to a registry. This potential bias is likely to be more pronounced in the more recent registries (ARVC, Brugada syndrome, and CPVT) than in those that have been collecting patient information for decades (LQTS).
- Some concepts applied for risk stratification are common to the different inherited arrhythmogenic diseases. For example, the severity of the ECG phenotype is generally a marker of increased risk of SCD in most of these diseases. In LQTS, the "severe" phenotype is represented by the presence of a QTc exceeding 500 ms (103,776), in the Brugada syndrome by the spontaneous presence of ST-segment elevation in the right precordial leads (104,777), and in CPVT by VT induced by exercise stress testing (105,778).
- Because these diseases are characterized by electrical abnormalities occurring in the structurally intact heart, the use of the ICD is always indicated with a class I indication in the secondary prevention of cardiac arrest. Its use in primary prevention is more debated, considering the young age of patients at diagnosis. In LQTS and in CPVT, pharmacological therapy with beta blockers is effective in reducing the risk of cardiac events. In these diseases, therefore, beta blockers are recommended as first-line treatment in all affected individuals, class I indication, and the use of the ICD is recommended for higher-risk subgroups (104,105,777,779). In the Brugada syndrome, no effective pharmacological treatment is known and therefore the use of prophylactic ICD should be targeted to high-risk patients (104,777).

- Genetic information is progressively entering clinical practice and is being integrated in the risk stratification schemes (103,780).
- In general, a family history of SCD has not proved useful in stratifying risk in affected patients.
- Avoidance of competitive sports is recommended by some, but not others, for all patients affected by inherited arrhythmogenic disorders even when physical activity is not considered to be the trigger for arrhythmic episodes, such as in patients with Brugada syndrome and LQT3 (see Section 13.1).

A concise overview of clinical manifestations and the recommendations for risk stratification and management of the individual diseases is outlined in the following subsections.

11.1.1. Long QT Syndrome

Recommendations

Class I

1. **Lifestyle modification is recommended for patients with an LQTS diagnosis (clinical and/or molecular). *(Level of Evidence: B)***
2. **Beta blockers are recommended for patients with an LQTS clinical diagnosis (i.e., in the presence of prolonged QT interval). *(Level of Evidence: B)***
3. **Implantation of an ICD along with use of beta blockers is recommended for LQTS patients with previous cardiac arrest and who have reasonable expectation of survival with a good functional status for more than 1 y. *(Level of Evidence: A)***

Class IIa

1. **Beta blockers can be effective to reduce SCD in patients with a molecular LQTS analysis and normal QT interval. *(Level of Evidence: B)***
2. **Implantation of an ICD with continued use of beta blockers can be effective to reduce SCD in LQTS patients experiencing syncope and/or VT while receiving beta blockers and who have reasonable expectation of survival with a good functional status for more than 1 y. *(Level of Evidence: B)***

Class IIb

1. **Left cardiac sympathetic neural denervation may be considered for LQTS patients with syncope, torsades de pointes, or cardiac arrest while receiving beta blockers. *(Level of Evidence: B)***
2. **Implantation of an ICD with the use of beta blockers may be considered for prophylaxis of SCD for patients in categories possibly associated with higher risk of cardiac arrest such as LQT2 and LQT3 and who have reasonable expectation of survival with a good functional status for more than 1 y. *(Level of Evidence: B)***

11.1.1.1. Causes and Risk Factors

The LQTS is an inherited disease characterized by prolonged ventricular repolarization (QT interval) and by ventricular tachyarrhythmias that may manifest as syncopal events. Cardiac arrhythmias are often elicited by stress and emotion, although in some cases they may also occur at rest or during sleep (781). Two patterns of inheritance have been identified: the more common autosomal dominant Romano-Ward and Timothy syndromes (782,783) and the much rarer autosomal recessive cases. The latter are usually more severe, often but not always involving consanguineous marriages, and are often associated with congenital deafness (the Jervell Lange-Nielsen syndrome [784]). Mutations in 8 genes have been identified: 7 of them encode cardiac ion channel subunits (785–790) and 1 encodes an anchoring protein that has been implicated in controlling ion channel targeting specific membrane sites (791). The distinguishing features of some of the genetic variants of the disease have been identified and incorporated in risk stratification algorithms.

11.1.1.2. Risk Stratification

Even before the identification of the genetic subtypes, QT interval duration was identified as the strongest predictor of risk for cardiac events (syncope, SCD) in LQTS (776), and it remains so. A normal QT interval in an ungenotyped family member portends a good prognosis (792). A QTc exceeding 500 ms (corresponding to the upper QTc quartile among affected genotyped individuals) identifies patients with the highest risk of becoming symptomatic by age 40 (103). Patients with the Jervell Lange-Nielsen and other homozygous syndromes and patients with LQTS associated with syndactyly (790,793) are at higher risk. A family history of SCD has not proved to be a risk factor for SCD (779, 794).

Genetic testing is often useful in probands with a clinical diagnosis of LQTS to provide more accurate risk stratification and to guide therapeutic strategies.

Symptoms in LQTS range from SCD to syncope and near syncope. Patients resuscitated from SCD have an especially ominous prognosis, with a relative risk of 12.9 of experiencing another cardiac arrest (779). In addition, affected patients may be identified because of QT prolongation detected incidentally or because they are relatives of affected individuals and are found to be mutation carriers in genetic screening; prognosis in such family members tends to be better than that for the proband. Risk is increased during the immediate postpartum period (795).

It has been shown that the interplay between genetic defect, QT duration, and gender may provide an algorithm for risk stratification (103). Patients with the highest risk of becoming symptomatic are LQT1 and LQT2 patients with a QTc greater than 500 ms and males with LQT3 irrespective of QT interval duration (103). LQT3 patients may represent a group at higher risk (780). Among LQT2

patients, those with a mutation resulting in a change in the pore region of the protein (796) appear to be at higher risk of cardiac events than are those with mutations in other regions of the gene. Beta blockers are highly effective in LQT1, whereas they offer incomplete protection in LQT2 and LQT3 (797).

11.1.1.3. Ventricular Arrhythmias

Syncope in LQTS patients is usually attributed to severe ventricular arrhythmias (although other causes can occur). Syncopal events are usually associated with stress, emotion, or exercise; however, gene-specific triggers for cardiac events have been identified in the 3 most common genetic variants of the disease. Individuals affected by the LQT1 form of the disease (mutations in the *KCNQ1* or *KvLQT1* gene encoding the ion channel that conducts the potassium current I_{Ks}) are more susceptible to cardiac events occurring during exercise (798) and particularly during swimming (799,800). LQT2 patients harbor mutations in the *KCNH2* (or *HERG*) gene encoding the channel conducting the potassium current I_{Kr} are susceptible to cardiac events occurring during rest or emotion, and characteristically with acoustic stimuli (800,801). Finally, LQT3 patients carrying mutations in the *SCN5A* gene encoding the cardiac sodium channel are susceptible to cardiac events occurring at rest and during sleep (798). A description of the long QT subtypes is given in Table 9.

The mean age for first manifestation of the disease is 12 y, but there is a wide range from the first year of life to as late as the fifth through sixth decades. Documentation of the arrhythmia during cardiac events is relatively uncommon in LQTS: when arrhythmias are recorded, the characteristic polymorphic VT, "torsades de pointes," is identified (781,802); SCD may be the first manifestation of the disease.

11.1.1.4. Lifestyle Changes

It is recommended that all patients affected by LQTS avoid competitive sports activity (682). For LQT1 patients, swimming should be specifically limited or performed under supervision. LQT2 patients should avoid exposure to acoustic stimuli especially during sleep (avoidance of telephone and alarm clock on the night stand). All patients with LQTS should avoid drugs known to prolong the QT interval and those that deplete potassium and magnesium.

Table 9. Long QT Syndrome Subtypes

Variant	Gene	Chromosome	Function
LQT1	*KCNQ1*	11p15.5	I_{Ks} alpha subunit
LQT2	*KCNH2*	7q35-35	I_{Kr} alpha subunit
LQT3	*SCN5A*	3p21-23	I_{Na} alpha subunit
LQT4	*ANK2*	4q25-2	Targeting protein
LQT5	*KCNE1*	21p22.1-22-2	I_{Ks} beta subunit
LQT6	*KCNE2*	21p22.1-22-2	I_{Kr} beta subunit
LQT7	*KCNJ2*	17p23.1-24.2	I_{K1}
LQT8	*CACNA1C*	12p13.3	I_{Ca} alpha subunit
JLN1	*KCNQ1*	11p15.5	I_{Ks} alpha subunit
JLN2	*KCNE1*	21p22.1-22-2	I_{Kr} beta subunit

11.1.1.5. Andersen Syndrome

In 1971, Andersen et al. (803) reported the case of an 8-y-old with short stature, hypertelorism, broad nasal root, and defect of the soft and hard palate. The definition of Andersen syndrome was used for the first time in 1994 by Tawil et al. (804) to describe a clinical disorder consisting of 3 major features: potassium-sensitive periodic paralysis, ventricular arrhythmias, and dysmorphic features (similar to those described by Andersen in 1971). The presence of a varying degree of QT interval prolongation was pointed out in the first systematic description of the disease (804). Subsequently, Sansone et al. (805) strengthened its crucial diagnostic significance. Besides showing QT interval prolongation, Andersen syndrome patients may also present with repolarization abnormalities consisting in a late repolarization component resembling an enlarged U wave. Bidirectional VT has been also reported as a distinguishing pattern of arrhythmias in Andersen syndrome. Andersen syndrome is also referred to as LQT7 even if it has been debated whether it should be considered part of the spectrum of the LQTSs (806). Despite SCD being reported (807), arrhythmias do not appear to be a major cause of death in Andersen syndrome and the disease often has a benign outcome (805,808).

The genetic background of Andersen syndrome was recently elucidated through genomewide linkage analysis by Plaster et al. (804), who successfully linked this disorder to the locus 17q23 in a large family. A candidate gene screening was carried out in the critical region and a missense mutation was identified in the *KCNJ2* gene. Additional mutations were subsequently identified in 8 unrelated individuals, thus providing the proof that *KCNJ2* is the cause of at least some of the Andersen syndrome cases. *KCNJ2* encodes an inwardly rectifier potassium channel, Kir2.1, that is highly expressed in the heart, where it appears to act as a determinant factor of phase 4 repolarization and of resting membrane potential. Mutations in *KCNJ2* are found in approximately 40% of patients with Andersen syndrome.

Little is known about risk stratification and management of patients with Andersen syndrome. Patients seem to have ventricular arrhythmias but not a high incidence of cardiac arrest. The benefit of prophylactic treatment with beta blockers has not been defined even if most patients with prolonged QT are usually treated with these agents on empiric grounds. The beneficial role of calcium channel blockers has also been proposed based on the arrhythmia suppression observed in a single patient (809).

11.1.1.6. Genetic Analysis

Genetic analysis is very important for identifying all mutation carriers within an LQTS family. Once identified, silent carriers of LQTS genetic defects may be treated with beta blockers for prophylaxis of life-threatening arrhythmias. Furthermore, silent mutation carriers should receive

genetic counseling to learn about the risk of transmitting LQTS to offspring.

In patients affected by LQTS, genetic analysis is useful for risk stratification (103) and for making therapeutic decisions (810). Although genetic analysis is not yet widely available, it is advisable to try to make it accessible to LQTS patients.

11.1.2. Short QT Syndrome

The first report of a clinical condition characterized by abnormally short repolarization was made by Gussak et al. in 2000 (140). These authors described 2 siblings and their mother, all with a persistently short QT interval (260 to 275 ms) with peaked and narrow T waves in the absence of structural heart disease. These authors proposed that a QT interval shorter than 300 ms is diagnostic for SQTS. In 2003, Gaita et al. (811), reported 2 families with SQTS and showed that all affected patients had a QTc less than 300 ms with a QT interval less than 280 ms. Shortly thereafter, a novel form of SQTS in patients with a QTc up to 320 ms was identified (812). At present, it is still undefined whether the diagnosis of SQTS should be based on QT or QTc and which is the sensitivity and specificity of different QT/QTc interval cutoff values.

Morphological T-wave abnormalities accompany the abbreviated repolarization in SQTS. Several patients have tall and peaked T waves or asymmetrical T waves with a normal ascending phase and a very rapid descending limb. Clinical parameters for diagnosis are not yet known, so genetic analysis seems useful to confirm diagnosis in suspected cases.

Up to now, only 23 cases of SQTS from 6 different families have been reported (813) and the present experience suggests that the disease may be highly lethal. It should be considered, however, that when only a very limited cohort of patients is available, the severity of a disease tends to be overestimated, because symptomatic patients are identified because of their life-threatening arrhythmias while asymptomatic patients remain underdiagnosed. No information is available on whether specific triggers may precipitate cardiac events, as cardiac arrest has occurred both at rest and under stress. Mutations in at least 3 genes encoding for cardiac ion channel proteins highly expressed in the cardiac muscle may cause SQTS.

The first identified SQTS gene is *KCNH2* (814), which was found to harbor mutation leading to a remarkable increase in the I_{Kr} current. Bellocq et al. (815) reported another gain-of-function mutation affecting the *KCNQ1* gene in a 70-y-old man presenting with idiopathic VF and short QT interval at the ECG. The third gene is *KCNJ2*, identified as the cause of abnormally short ventricular repolarization with a peculiar T-wave morphology (extremely fast terminal limb and a quasi-normal ST segment and ascending T-wave phase) by Priori et al. (816).

It is interesting to note that all 3 SQTS genes (*KCNH2*, *KCNQ1*, and *KCNJ2*) also cause LQTS. The ECG phenotypes depend on the opposite biophysical consequences of the underlying mutations, with loss-of-function mutations being associated with LQTS and gain-of-function mutation being the cause of SQTS.

EP investigations have shown that both atrial and ventricular effective refractory periods are shortened in SQTS and programmed electrical stimulation usually induces ventricular tachyarrhythmias. Whether inducibility of ventricular arrhythmias is predictive of adverse clinical outcome remains unclear (Table 10).

The management of patients with SQTS is still poorly defined (817). In patients with mutation on the *KCNH2* gene, it has been suggested that quidinidine may be effective in suppressing inducibility at programmed electrical stimulation, but whether this also confers long-term prevention of cardiac arrest is unknown. For the other genetic forms of SQTS, the efficacy of quinidine is less clear and the use of the ICD may be considered, even if it may be associated with an increased risk of inappropriate shocks due to T-wave oversensing (817).

11.1.2.1. Genetic Analysis

Genetic analysis may help identify silent carriers of SQTS-related mutations; however, the risk of cardiac events in genetically affected individuals with a normal ECG is currently not known. Similarly, given the limited number of patients with SQTS so far identified, at present, genetic analysis does not contribute to risk stratification.

11.1.3. Brugada Syndrome

Recommendations

Class I

An ICD is indicated for Brugada syndrome patients with previous cardiac arrest receiving chronic optimal medical therapy and who have reasonable expectation of survival with a good functional status for more than 1 y. ***(Level of Evidence: C)***

Class IIa

1. **An ICD is reasonable for Brugada syndrome patients with spontaneous ST-segment elevation in V_1, V_2, or V_3 who have had syncope with or without mutations demonstrated in the *SCN5A* gene and who have**

Table 10. Genetic Variants of Short QT Syndrome

Locus Name	Chromosomal Locus	Inheritance	Gene Symbol	Protein	Reference
SQTS1	7q3p2135-q36	Autosomal dominant	*KCNH2*	I_{Kr} potassium channel alpha subunit (HERG)	Brugada et al. (813)
SQTS2	11p15.5	Autosomal dominant	*KCNQ1*	I_{Ks} potassium channel alpha subunit (KvLQT1)	Bellocq et al. (814)
SQTS3	17q23.1-q24.2	Autosomal dominant	*KCNJ2*	I_{K1} potassium channel (Kir2.1)	Priori et al. (815)

reasonable expectation of survival with a good functional status for more than 1 y. *(Level of Evidence: C)*

2. **Clinical monitoring for the development of a spontaneous ST-segment elevation pattern is reasonable for the management of patients with ST-segment elevation induced only with provocative pharmacological challenge with or without symptoms. *(Level of Evidence: C)***
3. **An ICD is reasonable for Brugada syndrome patients with documented VT that has not resulted in cardiac arrest and who have reasonable expectation of survival with a good functional status for more than 1 y. *(Level of Evidence: C)***
4. **Isoproterenol can be useful to treat an electrical storm in the Brugada syndrome. *(Level of Evidence: C)***

Class IIb

1. **EP testing may be considered for risk stratification in asymptomatic Brugada syndrome patients with spontaneous ST elevation with or without a mutation in the *SCN5A* gene. *(Level of Evidence: C)***
2. **Quinidine might be reasonable for the treatment of electrical storm in patients with Brugada syndrome. *(Level of Evidence: C)***

11.1.3.1. Causes and Risk Factors

The Brugada syndrome is associated with a characteristically abnormal ECG and a high risk of SCD in individuals with a structurally normal heart (818). The Brugada pattern ECG shows J-point segment elevation in leads V_1 to V_3 and RBBB in some patients; the ECG pattern can be present always or intermittently. Occasionally, J-point elevation has been reported in other (e.g., inferior) leads. The disease is transmitted with an autosomal dominant pattern of inheritance. The clinical expression of the phenotype is modified by gender as 90% of the affected individuals with a diagnostic ECG are male. Only 1 Brugada syndrome disease gene has been identified so far, the cardiac sodium channel gene (*SCN5A*) (819); non-*SCN5A* loci have also been reported but the disease gene(s) at these loci remain to be identified. Cardiac events (syncope or cardiac arrest) occur predominantly in males in the third and fourth decades of life, although presentation with cardiac arrest in neonates or children have been reported (104,777,820). Fever is a predisposing factor for cardiac arrest in the Brugada syndrome (800,818,821–824).

11.1.3.2. Risk Stratification

Because implantation of an ICD is the only prophylactic measure able to prevent SCD, risk stratification is of major importance in these patients.

11.1.3.3. Family History

As with LQTS, there are no data showing that family history predicts cardiac events among family members. Therefore, it should not be assumed that asymptomatic individuals with the characteristic ECG but without family history are at low risk or that family members of an individual with SCD are at increased risk (104).

11.1.3.4. Electrocardiography

ST-segment elevation can occur spontaneously or be exposed by administration of sodium channel blockers such as flecainide, procainamide, or ajmaline (825). There is agreement that patients with a spontaneous pattern have a worse prognosis than individuals in whom the typical ECG is observed only after pharmacological drug challenge (104,777).

11.1.3.5. Clinical Symptoms

Patients with history of syncope and the ECG pattern of spontaneous ST-segment elevation have a 6-fold higher risk of cardiac arrest than patients without syncope and the spontaneous ECG pattern (104).

11.1.3.6. Electrophysiological Testing

The role of EP testing for risk stratification is debated. Brugada et al. (206,207) suggested that EP testing has a pivotal role in risk stratification: in their large study, EP testing had a low positive predictive value (23%), but over a 3-y follow-up, it had a very high negative predictive value (93%). By contrast, Priori et al. (104,826) reported that EP testing has a low accuracy in predicting individuals who will experience cardiac arrest. Priori et al. (104,208) proposed that noninvasive risk stratification based on the ECG and symptoms provides an accurate alternative for risk stratification.

11.1.3.7. Genetic Defect

Because only a single gene has been linked to the Brugada syndrome, there is still insufficient information about the contribution of genetic defects in predicting clinical outcome. Mutations in the SCN5A gene do not identify a subset of patients at higher risk of cardiac events (104).

11.1.3.8. Ventricular Arrhythmias

SCD is caused by rapid polymorphic VT or VF frequently occurring at rest or during sleep. Patients with Brugada syndrome usually do not have ventricular extrasystoles or nonsustained runs of VT at Holter recording. Therefore, the therapeutic approach for these patients is centered on the prevention of cardiac arrest. Basic science studies and clinical studies suggest a role for block of the transient outward potassium current by quinidine in reducing arrhythmia frequency (827,828). Quinidine and isoproterenol may be useful in patients with arrhythmia storm even in the presence of an ICD (139,395,829).

11.1.3.9. Genetic Analysis

Genetic analysis may help identify silent carriers of Brugada syndrome-related mutations so that they can remain under clinical monitoring to detect early manifestations of the syndrome. Furthermore, once identified, silent mutation carriers should receive genetic counseling and discussion of the risk of transmitting the disease to off-

spring. Based on current knowledge, genetic analysis does not contribute to risk stratification.

11.1.4. Catecholaminergic Polymorphic Ventricular Tachycardia

Recommendations

Class I

1. **Beta blockers are indicated for patients who are clinically diagnosed with CPVT on the basis of the presence of spontaneous or documented stress-induced ventricular arrhythmias.** ***(Level of Evidence: C)***
2. **Implantation of an ICD with use of beta blockers is indicated for patients with CPVT who are survivors of cardiac arrest and who have reasonable expectation of survival with a good functional status for more than 1 y.** ***(Level of Evidence: C)***

Class IIa

1. **Beta blockers can be effective in patients without clinical manifestations when the diagnosis of CPVT is established during childhood based on genetic analysis.** ***(Level of Evidence: C)***
2. **Implantation of an ICD with the use of beta blockers can be effective for affected patients with CPVT with syncope and/or documented sustained VT while receiving beta blockers and who have reasonable expectation of survival with a good functional status for more than 1 y.** ***(Level of Evidence: C)***

Class IIb

Beta blockers may be considered for patients with CPVT who were genetically diagnosed in adulthood and never manifested clinical symptoms of tachyarrhythmias. ***(Level of Evidence: C)***

11.1.4.1. Causes and Risk Factors

CPVT is characterized by ventricular tachyarrhythmias that develop during physical activity or acute emotion in the presence of an unremarkable resting ECG (778). The first episodes often manifest during childhood, although late-onset cases have been described (830).

The disease can be transmitted as an autosomal dominant as well as an autosomal recessive trait. Half of the autosomal dominant cases are caused by mutations in the gene encoding the cardiac ryanodine receptor (RyR2), responsible for calcium release from the stores of the sarcoplasmic reticulum (831,832). The recessive form is caused by mutations in the gene encoding calsequestrin (*CASQ2*), a calcium-buffering protein in the sarcoplasmic reticulum (833).

11.1.4.2. Risk Stratification

Too few patients with CPVT have been reported to allow the definition of a risk stratification scheme. Beta blockers appear to be effective. Patients who have had an episode of VF are considered at higher risk and are usually implanted with an ICD along with beta-blocker therapy. The recurrence of sustained VT or of hemodynamically nontolerated VT while receiving beta blockers is usually considered a marker of higher risk and an ICD is often recommended in these patients. EP testing is not useful for management and risk stratification because CPVT patients are usually not inducible (105,778).

11.1.4.3. Ventricular Arrhythmias

Supraventricular and ventricular arrhythmias are usually reproducibly induced by exercise stress when the heart rate reaches a threshold of 120 to 130 beats per minute. Isolated PVCs usually develop first and are followed shortly after by short runs of NSVT. If the patient continues to exercise, the duration of VT runs progressively increase and VT may become sustained. A beat-to-beat alternating QRS axis that rotates by 180°, "bidirectional VT," is the typical pattern of CPVT-related arrhythmias. CPVT patients can also present with irregular polymorphic VT or VF (105,778).

Beta blockers prevent recurrences of syncope in the majority of patients (105,778), even if VT and SVT usually can still be elicited during exercise stress test. If syncope occurs in a patient taking a beta blocker, the implantation of an ICD is recommended (105). However, ICD therapy requires careful programming of the device to prevent needless therapy for nonsustained episodes of ventricular tachyarrhythmia.

11.1.4.4. Genetic Analysis

Genetic analysis may help identify silent carriers of catecholaminergic VT-related mutations; once identified silent carriers may be treated with beta blockers to reduce the risk of cardiac events and may receive appropriate genetic counseling to assess the risk of transmitting the disease to offspring. Based on current knowledge, genetic analysis does not contribute to risk stratification.

12. ARRHYTHMIAS IN STRUCTURALLY NORMAL HEARTS

12.1. Idiopathic Ventricular Tachycardia

Recommendations

Class I

Catheter ablation is useful in patients with structurally normal hearts with symptomatic, drug-refractory VT arising from the RV or LV or in those who are drug intolerant or who do not desire long-term drug therapy. ***(Level of Evidence: C)***

Class IIa

1. **EP testing is reasonable for diagnostic evaluation in patients with structurally normal hearts with palpitations or suspected outflow tract VT.** ***(Level of Evidence: B)***

2. **Drug therapy with beta blockers and/or calcium channel blockers (and/or IC agents in RVOT VT) can be useful in patients with structurally normal hearts with symptomatic VT arising from the RV.** ***(Level of Evidence: C)***
3. **ICD implantation can be effective therapy for the termination of sustained VT in patients with normal or near normal ventricular function and no structural heart disease who are receiving chronic optimal medical therapy and who have reasonable expectation of survival for more than 1 y.** ***(Level of Evidence: C)***

12.1.1. Demographics and Presentation of Outflow Tract Ventricular Tachycardia

VT arising from the RV is the most common form of VT in apparently healthy people and is associated with a good prognosis in those without overt structural heart disease (291,294,297,377,834–844). This VT usually has a left bundle-branch, inferior-axis morphology. It often presents as nonischemic exercise-induced and/or repetitive monomorphic VT. Symptoms tend to be mild and syncope is rare (722). Left ventricular outflow tract (LVOT) VT can arise in the absence of overt structural abnormalities and accounts for a small percentage of the overall cases of VT. The ECG recorded during sinus rhythm in patients with RVOT tachycardia helps distinguish it from the more serious condition of RV dysplasia where the ECG is more often abnormal (722). RVOT has long been thought to be idiopathic in nature, but this characterization has relied on conventional imaging and diagnostic techniques such as stress testing, echocardiography, and coronary angiography (297,834,835,843,845–847). More recently, MRI has been applied to the evaluation of patients with VT arising from the RV in the absence of defined abnormalities on conventional testing particularly to exclude ARVC (210,262). LVOT VT can be classified by site of origin to either an endocardial origin; coronary cusp origin; or epicardial origin (232). VT arising from the LVOT and from the LV septum typically presents in the third to fifth decades of life (694). LVOT VT is more common in men than in women. This VT may be incessant and may be provoked by exercise.

12.1.2. Mechanisms

Several EP mechanisms have been associated with RVOT VT, including abnormal automaticity and triggered activity. The most common form of RVOT VT is related to triggered activity arising from delayed afterdepolarizations and is thought to be dependent on intracellular calcium overload and cyclic adenosine monophosphate (377, 840,841). RVOT VT is frequently adenosine sensitive, may terminate with vagal maneuvers, and is facilitated by catecholamines. As such, it is often not easily inducible at baseline EP testing and may require rapid burst pacing or stimulation by isoproterenol (210,722). LV VT arising from the outflow tract may be reentrant but can also result from enhanced automaticity. Incessant LV VT has been related to a triggered mechanism associated with delayed afterdepolarizations (4,694). Idiopathic LV tachycardia can be verapamil sensitive, adenosine sensitive, and propranolol sensitive (697–702).

12.1.3. Electrophysiological Testing

EP is motivated by the need to establish precise diagnosis to guide curative catheter ablation (209,210). Outflow tract VT in the absence of concomitant cardiac disease does not carry an adverse prognosis, although syncope can occur (848). The prognostic value of inducibility of ventricular arrhythmias has not been systematically evaluated. Inducibility of 80% has been reported in 35 patients with RVOT when EP testing was performed with up to 3 extrastimuli and isoproterenol infusion if required (300). In another study, a rate of induction of only 3% was observed, but this increased to by 80% with isoproterenol infusion alone (210). Induction with burst pacing has also been useful (297).

VTs arising from the LVOT or aortic cusps have been described. These appear to be mechanistically and prognostically similar to RVOT VT. Induction of LVOT VT by EP testing is not consistent, although the arrhythmia may be provoked. It can be provoked during isoproterenol infusion (378).

12.1.4. Management

Clinical treatment of RVOT or LVOT VT often involves beta and calcium channel blockers. Type IC antiarrhythmic drugs have been found to be useful in RVOT VT (297,837,849–852). In patients who remain symptomatic or for whom drug therapy fails, catheter ablation of the arrhythmia focus in the RVOT should be considered. Acute success rates for RVOT ablation have been reported in excess of 90% (210,722). However, long-term success varies and may depend on the degree or presence of other abnormalities.

12.1.5. Demographics and Presentation of Other Idiopathic Left Ventricular Tachycardias

So-called idiopathic LV VT can arise from the LVOT or from the fascicles of the specialized conduction system. Fascicular VT can be classified into 3 types according to origin and QRS morphology during VT. Left posterior fascicular VT typically has an RBBB and superior axis morphology and is the more common form of fascicular VT. VT arising from the left anterior fascicle has an RBBB and right-axis deviation configuration and is less common. Rarely, fascicular VT will arise from fascicular location high in the septum and has a narrow QRS and normal axis configuration. This VT presents in the third to fifth decades of life (695) and is equally distributed between the sexes.

12.1.6. Mechanisms and Treatment

Left fascicular VT typically is reentrant and may respond to beta or calcium channel blockers. However, in patients who do not tolerate medical treatment or for whom medical treatment has failed, ablation can be considered. Ablation of posterior fascicular VT is guided by recording made either

during sinus rhythm or in VT demonstrating a discrete potential preceding the earliest ventricular electrogram (703,704,709,853). Newer 3-dimensional mapping devices that do not require the presence of sustained VT can facilitate ablation in these patients (710).

12.2. Electrolyte Disturbances

Recommendations

Class I

Potassium (and magnesium) salts are useful in treating ventricular arrhythmias secondary to hypokalemia (or hypomagnesmia) resulting from diuretic use in patients with structurally normal hearts. ***(Level of Evidence: B)***

Class IIa

1. **It is reasonable to maintain serum potassium levels above 4.0 mM/L in any patient with documented life-threatening ventricular arrhythmias and a structurally normal heart.** ***(Level of Evidence: C)***
2. **It is reasonable to maintain serum potassium levels above 4.0 mM/L in patients with acute MI.** ***(Level of Evidence: B)***
3. **Magnesium salts can be beneficial in the management of VT secondary to digoxin toxicity in patients with structurally normal hearts.** ***(Level of Evidence: B)***

Although changes in extracellular potassium, extracellular and intracellular magnesium (especially with associated hypokalemia), and intracellular calcium are all associated with EP changes that are arrhythmogenic, life-threatening ventricular arrhythmias in patients with structural heart disease should not be attributed solely to changes in these ionic concentrations. Changes in potassium concentration may occur after cardiac arrest or may accompany certain disease states such as periodic paralysis.

A rapid rise in extracellular potassium, hypokalemia (less than 3.5 mM), and hypomagnesemia are all associated with ventricular arrhythmias and SCD in patients with structurally normal hearts (some of whom may have underlying channelopathies) and in an AMI setting (591,854–867). Hypomagnesemia is classically associated with polymorphic VT or torsades de pointes, which together with ventricular arrhythmias in an AMI setting may respond to intravenous magnesium (868–871). Hypokalemia with or without hypomagnesemia may be responsible for ventricular arrhythmias in subjects with hypertension and congestive cardiac failure (precipitated by the use of thiazide and loop diuretics) (855,856,872), acute starvation (873), acute alcohol toxicity/withdrawal, and those with ventricular arrhythmias associated with digoxin and other Vaughan Williams class 1 antiarrhythmic drugs (865,874,875). Significant hypocalcemia can prolong the QT interval.

Changes in the extracellular ionic concentrations of calcium required to produce EP changes that may contribute to ventricular arrhythmias are not encountered in clinical practice. Occasionally, hyperparathyroidism can cause important elevations in serum calcium concentrations. Intracellular fluctuations in calcium concentration influenced by drugs (e.g., digitalis glycosides), exercise (e.g., catecholamines), and reperfusion following myocardial ischemia, however, can trigger EP changes that may lead to life-threatening arrhythmias. The protective effects of beta blockade in the latter settings may in part be due to the inhibition of calcium influx into myocytes.

12.3. Physical and Toxic Agents

12.3.1. Alcohol

Recommendations

Class I

1. **Complete abstinence from alcohol is recommended in cases where there is a suspected correlation between alcohol intake and ventricular arrhythmias.** ***(Level of Evidence: C)***
2. **Persistent life-threatening ventricular arrhythmias despite abstinence from alcohol should be treated in the same manner that such arrhythmias are treated in patients with other diseases, including an ICD, as required, in patients receiving chronic optimal medical therapy and who have reasonable expectation of survival for more than 1 y.** ***(Level of Evidence: C)***

The relationship between alcohol ingestion and VT/SCD is indisputable; what is controversial however, is its exact nature (876). A number of studies claim a J-shaped relationship with risk lowest in individuals with low alcohol intake (i.e., 2 to 6 drinks per week) compared with those who rarely or never consume alcohol (877) and those with a high alcohol intake (i.e., more than 3 to 5 drinks per day) (878,879) and binge drinking habits, the "holiday heart syndrome" (880–883). The reason for this relationship is probably the protective effects of low to moderate alcohol consumption on the risk of CHD (884). This is contested by a meta-analysis where lower protective and harmful effects were found in women, in men living in countries outside the Mediterranean area, and in studies where fatal events were used as the outcome. Furthermore, unlike low-risk patients without CHD, in middle-aged men with established CHD, low to moderate alcohol intake (1 to 14 units per week) was not associated with any significant benefit (885). Alcohol ingestion may therefore reduce the incidence of VT/SCD due to coronary events, but its effect on life-threatening arrhythmias correlates directly with the amount and duration of alcohol intake and even small quantities may be significant in susceptible individuals.

The mechanisms associated with alcohol-induced VT/SCD are complex and not entirely related to the presence of alcohol-induced cardiomyopathy. Alcohol has a negative inotropic effect mediated by direct interaction with cardiac muscle cells, although this action is often masked by the indirect actions from enhanced release of catecholamines (886). EP

studies have shown alcohol to induce various arrhythmias including VT in patients with and without cardiomyopathy (887,888). LVH and remodeling is an early response to heavy drinking (889); one third of alcoholics demonstrate diastolic dysfunction correlating with consumption (890) and 20% to 26% develop DCM within 5 y (891). In these patients, myocyte and nuclear hypertrophy, interstitial fibrosis, and myocyte necrosis provide the substrate for arrhythmogenesis (892). QTc is prolonged in patients with proved alcoholic liver disease in the absence of electrolyte disturbances and may act as the trigger to life-threatening arrhythmias (893).

12.3.2. Smoking

Recommendations

Class I

Smoking should be strongly discouraged in all patients with suspected or documented ventricular arrhythmias and/or aborted SCD. *(Level of Evidence: B)*

Cigarette smoking is an independent risk factor for SCD regardless of underlying CHD (58,894–897). The vast majority of these deaths are arrhythmic. In females who smoke 25 or more cigarettes per day, the risk of ventricular arrhythmia and SCD is increased 4-fold, similar to that conferred by a history of MI (62). It is a long-term risk factor (898) and continues to be so in survivors of out-of-hospital cardiac arrest who fail to give up smoking (74). Cessation of smoking significantly reduces risk of SCD. There are no data available to allow identification of individuals at greatest risk.

12.3.3. Lipids

Recommendations

Class I

Statin therapy is beneficial in patients with CHD to reduce the risk of vascular events, possibly ventricular arrhythmias, and SCD. *(Level of Evidence: A)*

Class IIb

n-3 polyunsaturated fatty acid supplementation may be considered for patients with ventricular arrhythmias and underlying CHD. *(Level of Evidence: B)*

The association of high total, very low-density lipoprotein (VLDL), or low-density lipoprotein (LDL) cholesterol levels, a low HDL cholesterol level together with high triglyceride and apolipoprotein B levels with increased risk of VT/SCD is almost entirely due to concurrent CHD. Appropriate lipid management strategies, especially the use of statins, reduces the risk of SCD by preventing recurrent fatal MI and ventricular arrhythmia (899–901). The effect of lipid lowering on SCD in primary prevention has not been addressed, but a relative risk reduction of 30% to 40% would be expected in parallel with the reduction in the risk of CHD death (902,903).

Free fatty acid or nonesterified fatty acid levels are also an independent risk factors for SCD but not fatal MI (94). However, the widely held belief from clinical studies that dietary n-3 PUFA may confer protection from arrhythmic death in subjects with and without documented underlying CHD (904,905), in patients who have manifest previously (904–911), has been challenged by a small multicenter, double-blinded, randomized, placebo-controlled trial of n-3 PUFA in 200 patients with ICD and a recent episode of ventricular arrhythmia (262). This study showed a trend toward a higher incidence of VT/VF in patients randomized to fish oil, a trend that correlated with n-3 PUFA levels. An actuarial analysis of time to recurrent events showed significantly more events in patients randomized to fish oil.

13. VENTRICULAR ARRHYTHMIAS AND SUDDEN CARDIAC DEATH RELATED TO SPECIFIC POPULATIONS

13.1. Athletes

Recommendations

Class I

1. **Preparticipation history and physical examination, including family history of premature or SCD and specific evidence of cardiovascular diseases such as cardiomyopathies and ion channel abnormalities, is recommended in athletes. *(Level of Evidence: C)***
2. **Athletes presenting with rhythm disorders, structural heart disease, or other signs or symptoms suspicious for cardiovascular disorders should be evaluated as any other patient but with recognition of the potential uniqueness of their activity. *(Level of Evidence: C)***
3. **Athletes presenting with syncope should be carefully evaluated to uncover underlying cardiovascular disease or rhythm disorder. *(Level of Evidence: B)***
4. **Athletes with serious symptoms should cease competition while cardiovascular abnormalities are being fully evaluated. *(Level of Evidence: C)***

Class IIb

Twelve-lead ECG and possibly echocardiography may be considered as preparticipation screening for heart disorders in athletes. *(Level of Evidence: B)*

It is generally accepted that preparticipation screening for medical conditions should be a requirement for clearance to participate in competitive athletics, but there are no uniformly accepted standards for screening. Because the risk of SCD among athletes appears to exceed the risk in comparably aged populations (912), attention to cardiovascular screening is of special importance.

Competitive athletics has been defined as "participation in an organized team or individual sport that requires regular competition against others as a central component, that places a high premium on excellence and achievement and requires some form of systematic training" (913,914). Preparticipation screening of athletes has been discussed in various conferences, and policy statements, although (802,915,916) the screening programs vary greatly in different countries. The major causes of SCD in athletes are HCM (36%) , coronary artery anomalies (19%), ARVC, and myocarditis. In Italy, the incidence of the former as a cause of SCD has been reduced considerably due to an ECG and echocardiographic screening program (917).

13.1.1. Screening and Management

13.1.1.1. Screening

Preparticipation cardiovascular screening focuses in general on a young population group (aged less than 30 y), among whom most anomalies will be congenital, although some might be acquired disorders (680,915, 918). The multiple mechanisms and diseases involved in sudden death in young athletes have been reviewed (919). Drug intake may have an important effect on the cardiovascular system and may lead to coronary artery spasm (cocaine), modification of repolarization by drugs in susceptible individuals (i.e., antibiotics, antiarrhythmics, antidepressant agents), and blunted heart rate response during exercise (beta blockers) (920). Special consideration is required in athletes who are middle-aged and older (914).

Screening of athletes is a difficult task. The low incidence of anomalies makes screening not very cost effective, although one study has suggested that ECG screening is more cost effective than echocardiographic screening (921,922). Routine physical examination might not reveal clinically significant anomalies, and personal or family histories have limited value. The resting ECG can disclose rhythm disturbances, abnormal repolarization syndromes such as the LQTS, the Brugada syndrome, the WPW syndrome, and the depolarization and repolarization abnormalities associated with HCM. However, nonspecific variations commonly observed on ECGs recorded from adolescents and young athletes may be confounding. Echocardiography may show structural anomalies but will not disclose anomalies of the coronary arteries.

Nonetheless, it is recommended that all candidates undergo screening tests, such as ECG and, when appropriate, echocardiography (e.g., abnormal ECG, family history), beyond the history and physical examination. The impact of additional screening requires further clarification; the financial burden for subsequent investigation in case of suspected anomalies might be considerable.

13.1.1.2. Management of Arrhythmias, Cardiac Arrest, and Syncope in Athletes

In athletes, risk factors might be aggravated or attenuated but not abolished by regular physical activity. For legal and ethical reasons, athletes receiving cardiovascular drugs and devices such as pacemakers and ICDs are generally not allowed to participate in high-grade competition. Exceptions, such as beta adrenergic−blocking agents, depend on legal and regulatory guidelines. According to the World Anti-Doping Code established by the World Anti-Doping Agency (WADA), one of the bodies of the International Olympic Committee and accepted by all international sports federations, beta blockers and diuretics are prohibited in some particular sports. The list of particular sports can be found on the WADA World Wide Web site at www.wada-ama.org and is available as a downloadable file (923).

Athletes presenting with syncope or presyncope should not participate in competitive sports until the cause is determined to be both benign and treatable. Increase of PVCs during exercise requires careful evaluation. They might be caused by structural anomalies, including coronary artery anomalies, abnormal origin of coronary artery, mitral valve prolapse, ARVC, and HCM or DCM. Endurance training is commonly accompanied by sinus bradycardia, junctional rhythm, and Wenckebach AV conduction on ECG. These are generally adaptive responses in apparently normal individuals. The distinction between adaptive LV chamber enlargement and a mild form of cardiomyopathy might be difficult. Athletes with nonsustained and asymptomatic exercise-induced ventricular arrhythmias may participate in low-intensity competitive sports provided that no structural heart disease has been demonstrated (924). Recommendations for disqualification from high-intensity sports have been stated in an advisory paper (914) and a Bethesda Conference (682,802).

Athletes presenting with rhythm disorders, cardiac anomalies, or syncope should be treated as any other patients. One must keep in mind that high-grade physical activity may aggravate the anomaly.

13.2. Gender and Pregnancy

Recommendations

Class I

1. **Pregnant women developing hemodynamically unstable VT or VF should be electrically cardioverted or defibrillated. (*Level of Evidence: B*) (See Section 7.)**
2. **In pregnant women with the LQTS who have had symptoms, it is beneficial to continue beta-blocker medications throughout pregnancy and afterward, unless there are definite contraindications. *(Level of Evidence: C)***

13.2.1. QT Interval

Typically, women have longer QT intervals than do men, and this difference is more pronounced at slower heart rates. The corrected QT interval in males decreases at puberty and then gradually increases as androgen levels fall. By age 50, gender differences in QT intervals have largely equalized (925). A similar shortening of the QT interval at puberty has been noted in males genotypically characterized with LQTSs (926). These observations strongly support a hormonal effect on QT and hence arrhythmia susceptibility. In

women with the congenital LQTS, the risk of cardiac arrest is greater during the postpartum period compared with before or during pregnancy (795). The relative tachycardia seen during pregnancy may serve to shorten the QT interval and be protective. Beta blockers have a major benefit during the postpartum period when the heart rate naturally falls. Beta blockers can generally be used safely during pregnancy. Most are excreted in breast milk. Use during pregnancy is generally well tolerated by both the mother and the fetus, although a decrease in fetal heart rate can be seen. Several studies have demonstrated an increased susceptibility in women to torsades de pointes, likely related to the longer baseline QT interval and perhaps to differences in drug pharmacodynamics (927). The incidence of both congenital and acquired forms of long QT intervals and resultant torsades de pointes is higher in women than in men (776, 928). In the Long QT Registry, 70% of the subjects and 58% of affected family members are women (929). Until puberty, males in the registry were found to be more likely than females to have cardiac arrests or syncope, but subsequently, the incidence of these potentially fatal events predominated in females (926). Several studies have shown that drug-induced torsades de pointes is more common in women than in men (930–933). ICD therapy should be strongly considered in patients with long-term QT syndromes who are drug resistant and those with marked potential for life-threatening arrhythmias (1).

13.2.2. Pregnancy and Postpartum

Recommendations on management of cardiovascular diseases during pregnancy, including ventricular arrhythmias, have been summarized elsewhere (934). Palpitations are extremely common during pregnancy, and several studies have shown an increase in the symptoms of SVT during pregnancy (935–937). While most palpitations are benign during pregnancy, new-onset VT is of concern (938,939). Although the presence of structural heart disease should be sought in these women, often VT occurs in the absence of overt structural heart disease and may be related to elevated catecholamines (938). As such, these arrhythmias may be beta blocker sensitive. In women presenting with new-onset VT during the last 6 wk of pregnancy or in the early postpartum period, the possibility of postpartum cardiomyopathy should be ruled out (940). In women with non-long QT-related sustained VT during pregnancy, antiarrhythmic therapy may be indicated with intravenous lidocaine acutely or procainamide long term. Amiodarone can have deleterious effects on the fetus, including hypothyroidism, growth retardation, and premature birth. Prophylactic therapy with a cardioselective beta blocker may be effective. Sotalol can be considered if beta-blocker therapy is ineffective (941). For women with known structural heart disease, pregnancy may present significant risk. Pulmonary edema, stroke, or cardiac death can occur in up to 13% of such pregnancies (942). Independent predictors of risk in women with heart disease include prior history of arrhythmias, cyanosis, poor functional class, LV systolic dysfunction, and LV outflow obstruction (942). Potentially life-threatening ventricular tachyarrhythmias should be terminated by electrical cardioversion. Beta 1-selective beta blockers alone, amiodarone alone (noting cautions about birth defects above), or in combination may be used, and ICD may be needed as its presence does not contraindicate future pregnancies.

13.2.3. Special Concerns Regarding Specific Arrhythmias

WPW syndrome and orthodromic AV reciprocating tachycardia are more common in men than in women (943,944). In addition, in patients with WPW syndrome manifest pathways are more common in men. Conversely, antidromic AV ventricular reciprocating tachycardia is more common in women than in men. However, AF degenerating to VF is more common in men than in women (100). For symptomatic WPW syndrome, the treatment of choice is RF ablation. The outcomes are similar in both sexes (945–947). Management of symptomatic WPW during pregnancy may require initiation of antiarrhythmic drugs to block the accessory pathway and, in some, long-term monitoring.

The incidence of SCD at any age is greater in men than in women (948). In part, this may be related to the more common occurrence of coronary disease in men. However, even matched cohorts without CHD show a male preponderance. Classic predictors such as obesity, LVH, hyperlipidemia, and tobacco use are associated with CHD and VT more in men than in women (898). For women, hyperglycemia, elevated hematocrit, and decreased vital capacity are more important predictors for CHD and VT (898). The impact of diabetes is seen in both sexes but is much more pronounced in women. While NSVT and PVCs have been associated with increased risk of sudden death in men with or without CHD, no such association has been seen in women (898). Similarly, while PVCs post-MI in men have been associated with increased mortality, this does not hold true for women (949).

13.3. Elderly Patients

Recommendations

Class I

1. **Elderly patients with ventricular arrhythmias should generally be treated in the same manner as younger individuals.** ***(Level of Evidence: A)***
2. **The dosing and titration schedule of antiarrhythmic drugs prescribed to elderly patients should be adjusted to the altered pharmacokinetics of such patients.** ***(Level of Evidence: C)***

Class III

Elderly patients with projected life expectancy less than 1 y due to major comorbidities should not receive ICD therapy. ***(Level of Evidence: C)***

13.3.1. Epidemiology

Ventricular arrhythmias are common in elderly populations, and the incidence increases in the presence of structural heart disease (404,950–952). It must be noted that the elderly are a heterogeneous group. In different studies, elderly patients are defined anywhere from greater than 60 y to greater than 85 y of age. This lack of uniformity raises concerns regarding the applicability of study results to the entire elderly population.

Ventricular arrhythmias can be found in 70% to 80% of persons over the age of 60 y and complex ventricular ectopy is common in this age group, although many such persons are often asymptomatic (953–956). Complex ventricular arrhythmias often presage new major coronary events and SCD in patients with CHD and other types of structural heart disease (957,958). The incidence of SCD increases with advancing age (959,960). In elderly patients with CHD, the proportion of cardiac deaths that are sudden decreases (36,961), whereas the proportion of "out of hospital" SCD increases progressively with advancing age (36,414).

Although greater than 80% of patients who die suddenly from cardiac causes have CHD, elderly patients with DCM and valvular heart disease are also at risk (957,961). SCD has also been documented in elderly patients with HCM (662), ARVC (962), and surgically repaired tetralogy of Fallot (963), particularly in patients with LV dysfunction. Brugada syndrome and congenital LQTS are uncommon causes of SCD in elderly patients (929,964).

In the peri-infarction period, cardiac arrest (used as SCD surrogate) is more common in elderly patients. Data from the Second National Registry of Myocardial Infarction (NRMI-2) indicate that age greater than 75 y was associated with a higher likelihood of in-hospital cardiac arrest with an odds ratio of 1.6 (CI 1.5 to 1.7) (965).

13.3.2. Pharmacological Therapy

The management of ventricular arrhythmias and the prevention of SCD in elderly patients do not differ appreciably from those recommended for the general population. However, when prescribing antiarrhythmic drugs to elderly patients, one must take into account the physiological changes that occur with advancing age and adjust drug regimens accordingly. Such changes include decreased renal and hepatic clearance and altered volume of distribution of pharmacological agents. Additionally, changes in body composition and the presence of comorbidities must be considered. Therefore, drug therapy should be initiated at lower than the usual dose and titration of the drug should take place at longer intervals and smaller doses.

The empiric use of most antiarrhythmic drugs to treat NSVT and other complex ventricular ectopy has been shown to be ineffective in preventing SCD and is even deleterious under certain circumstances (966–970). Advanced age has been found to increase the susceptibility to adverse cardiac events from class IC antiarrhythmic drugs (969). Amiodarone is the only antiarrhythmic drug shown to improve prognosis in survivors of cardiac arrest, based on a meta-analysis of 15 randomized trials (971) (see Section 6.3.1 for further discussion).

Amiodarone, however, is a drug associated with numerous side effects particularly in elderly patients who are prone to develop side effects and who are commonly on multiple drugs increasing the risk of drug interactions (404,972). Therefore, when considering amiodarone therapy for the prevention of SCD in an elderly patient who is receiving multiple drugs for comorbid conditions, the treating physician must weigh the potential benefit of such therapy against its potential side effects and decide whether amiodarone, device therapy, or no therapy is most appropriate for this particular patient.

Beta blockers, along with several agents that do not possess classic antiarrhythmic properties (e.g., ACE inhibitors, angiotensin receptor blockers, statins), have been shown in many studies to reduce all-cause mortality and SCD after AMI in all age groups, including the elderly (110,973–976). In the Beta Blocker Heart Attack trial, subgroup analysis demonstrated that the greatest benefit of beta blockers occurred in the group aged 60 to 69 y (973). The combination of beta blockers and amiodarone may reduce all-cause mortality and SCD to a greater extent than amiodarone alone (404,405), and in a post-hoc analysis of the CAST data, patients treated with an antiarrhythmic drug who were also receiving beta blockers had a lower SCD rate than those treated only with an antiarrhythmic drug (977). Beta blockers have also been shown to reduce all-cause mortality and SCD in patients with severe HF (978,979). In these studies, subgroup analysis showed equivalent benefit from beta blocker therapy in younger and older patients.

Despite the demonstrated efficacy in reducing all-cause mortality and SCD, beta blockers are underused in the elderly. A retrospective analysis of the use of beta blockers after MI in patients greater than age 65 y found that only 21% of 3737 patients without contraindications were so treated. Patients who received these agents had a 43% lower 2-y mortality than patients not so treated (980). Similarly, a study of clinical practices and sources of therapeutic variation found a strong, independent negative association between age and odds of treatment with beta blockers after MI (981). These findings are a matter of great public health concern.

13.3.3. Device Therapy

Several randomized, prospective trials have demonstrated the efficacy of ICDs in reducing SCD in patients with CHD at high risk for SCD (primary prevention) and in patients resuscitated from SCD (secondary prevention) compared with antiarrhythmic drug therapy (192,266–268,642,643).

All of the above-referenced studies included substantial numbers of patients over the age of 65 y. Subgroup analysis in AVID and MADIT II trials demonstrated equivalent benefits from ICD implantation in older and younger patients (266,268). In the Cardiac Arrest Study Hamburg (CASH) study, patients older than 65 y derived a greater benefit from ICD implantation than younger patients (643).

It is therefore appropriate to infer that the results of these trials are applicable to elderly patients across the board.

Data comparing the efficacy and complications of ICD therapy in older and younger patients are sparse. In a retrospective study comparing the efficacy of ICD therapy in patients over age 65 with that of patients under 65 (982), no significant difference in surgical morbidity or length of hospital stay following ICD implantation was noted between the 2 groups. Furthermore, similar survival rates were calculated for the 2 groups at 1, 2, and 3 y post−ICD implantation.

Similarly in an observational study (983) of 450 patients who received either epicardial (46%) or transvenous (54%) ICDs, the 3-, 5-, and 7-y survival for arrhythmic mortality was similar for younger and older patients. Perioperative morbidity was also similar in all patient groups.

Despite these documented benefits of ICD implantation, many physicians have been hesitant to subject elderly patients to such interventions and the role of device therapy in this age group has been controversial. However, several observational studies have shown that the invasive approach in managing patients with life-threatening ventricular arrhythmias is equally beneficial in the elderly and in younger patients (984–986). From 1985 to 1995, the use of ICDs in older patients grew from 1% to 13%; this was associated with improved medium-term survival (987).

Very elderly patients with multiple comorbidities and limited life expectancy may not be appropriate candidates for ICD therapy even if they meet standard criteria. In such circumstances, the clinical judgment of the primary treating physician and the desires of the patient and/or his or her family take precedence over general guideline recommendations. Nevertheless, there is evidence from a study (988) that octogenarians who die suddenly can be highly functional even in the month before their death. This information supports the concept that SCD often strikes fully functional elderly patients who could benefit from an ICD implantation if they meet appropriate criteria.

13.4. Pediatric Patients

Recommendations

Class I

1. **An ICD should be implanted in pediatric survivors of a cardiac arrest when a thorough search for a correctable cause is negative and the patients are receiving optimal medical therapy and have reasonable expectation of survival with a good functional status for more than 1 y.** ***(Level of Evidence: C)***
2. **Hemodynamic and EP evaluation should be performed in the young patient with symptomatic, sustained VT.** ***(Level of Evidence: C)***
3. **ICD therapy in conjunction with pharmacological therapy is indicated for high-risk pediatric patients with a genetic basis (ion channel defects or cardiomyopathy) for either SCD or sustained ventricular arrhythmias. The decision to implant an ICD in a child must consider the risk of SCD associated with the disease, the potential equivalent benefit of medical therapy, as well as risk of device malfunction, infection, or lead failure and that there is reasonable expectation of survival with a good functional status for more than 1 y.** ***(Level of Evidence: C)***

Class IIa

1. **ICD therapy is reasonable for pediatric patients with spontaneous sustained ventricular arrhythmias associated with impaired (LVEF of 35% or less) ventricular function who are receiving chronic optimal medical therapy and who have reasonable expectation of survival with a good functional status for more than 1 y.** ***(Level of Evidence: B)***
2. **Ablation can be useful in pediatric patients with symptomatic outflow tract or septal VT that is drug resistant, when the patient is drug intolerant or wishes not to take drugs.** ***(Level of Evidence: C)***

Class III

1. **Pharmacological treatment of isolated PVCs in pediatric patients is not recommended.** ***(Level of Evidence: C)***
2. **Digoxin or verapamil should not be used for treatment of sustained tachycardia in infants when VT has not been excluded as a potential diagnosis.** ***(Level of Evidence: C)***
3. **Ablation is not indicated in young patients with asymptomatic NSVT and normal ventricular function.** ***(Level of Evidence: C)***

The incidence of SCD due to cardiovascular disease is significantly less in pediatric than in adult patients. Current estimates are that deaths due to cardiovascular disease in individuals younger than 25 y of age account for less than 1% of all cardiac mortality (36). Due to this low event rate, population-based epidemiological studies have been required to define the incidence of unexpected, sudden death in pediatric patients. These studies have been relatively consistent, with an event rate between 1.3 and 4 deaths per 100 000 patient years (49,989–991). A definite or probable cardiac cause has been estimated in 70% of young, unexpected sudden death victims (433). This compares with the estimated SCD rate of 100 per 100 000 patient years in adult patients (992). Given the low incidence of events, no randomized clinical trials have been performed to define either risk stratification for SCD in the young or the role of primary prevention therapies. Therefore, the level of evidence for most recommendations in young patients is class C.

Despite these limitations, several groups of young patients have been identified who are at an increased risk of SCD compared with the general population. These include patients with congenital heart disease, coronary artery anomalies, cardiomyopathies, and primary arrhythmic diagnoses such as the LQTSs (993). The risk of SCD and significance of ventricular arrhythmias in these patients are discussed in the individual sections in this report regarding these topics. This section

discusses ventricular arrhythmias in the general pediatric population and its significance as a risk factor for SCD.

SCD in pediatric patients with WPW syndrome is uncommon and occurs primarily in patients with prior syncope, multiple accessory pathways, or short refractory periods. Therefore, in selected patients, an EP study may be indicated and ablation performed if the patient is symptomatic or the refractory period of the accessory pathway is equal to or less than 240 ms (279).

Isolated PVCs are common in infants, with 15% of all newborns reported as having some ventricular ectopy during 24-h ambulatory ECG monitoring. The prevalence of ventricular ectopy decreases to less than 5% in children but then increases to 10% by 10 y of age and 25% during late adolescence and early adulthood (994–996). For the vast majority of young patients with ventricular ectopy, the primary objective is to exclude any associated functional or structural heart disease, in which case PVCs may have prognostic significance (434,997). Simple ventricular ectopy in the absence of heart disease has not been demonstrated to have adverse prognostic significance.

Sustained ventricular arrhythmias may also occur in infants, most commonly, it is an accelerated idioventricular rhythm. By definition, this is a ventricular rhythm no more than 20% faster than the sinus rate and occurring in the absence of other heart disease (998). This arrhythmia typically resolves spontaneously during the first months of life. This is in contrast to the rare infant with incessant VT, which may be due to discrete myocardial tumors or cardiomyopathy (999,1000). VF and SCD have been reported in these infants, most often following the administration of intravenous digoxin or verapamil for a presumptive diagnosis of SVT (1001,1002). These ventricular arrhythmias may respond to antiarrhythmic treatment or be amenable to surgical resection. Sustained VT in infants may also be caused by hyperkalemia or associated with one of the LQTSs, particularly those forms with AV block or digital syndactyly (790,1003,1004).

There is considerable debate regarding the sudden infant death syndrome (SIDS) and potential role of the LQTS in causing some of these deaths (1005,1006). However, population-based studies have demonstrated a 40% decline in the incidence of SIDS associated with avoidance of sleeping in the prone position, supporting apnea, or impaired respiratory regulation as the primary cause of SIDS in most cases (1007). Definition of the cause(s) of SIDS remains an area of ongoing investigation and includes autonomic dysfunction and ventricular arrhythmias due to genetic causes.

Beyond the first year of life, most children with complex ectopy or hemodynamically tolerated VT appear to have a good prognosis (233,1008). The cause of these arrhythmias remains unknown, and they often spontaneously resolve. Pharmacological suppression of these ventricular arrhythmias is generally ineffective and may increase the risk of an adverse outcome.

RVOT and LVOT tachycardia and LV septal tachycardia may be diagnosed during childhood or adolescence. The criteria for diagnoses of these specific arrhythmias are discussed in Section 12. The general prognosis for these arrhythmias is mostly benign, with treatment for symptomatic patients with catheter ablation offering a high rate of cure. As with other pediatric arrhythmias, a primary objective is to exclude any associated cardiovascular disease. Catecholaminergic or exercise-induced polymorphic VT is one exception to the benign prognosis for hemodynamically tolerated VT in patients with an otherwise normal heart. Although patients with this form of VT may not be overtly symptomatic, they are at risk for SCD (105). Also, symptomatic ventricular arrhythmias may be the initial presentation of cardiomyopathy in young patients (834,1009).

The role and benefit of ICD implantation for the prevention of SCD in young children with advanced ventricular dysfunction have not been defined. In older children and adolescents, prophylactic ICD implantation may be considered, based on data derived from adult randomized clinical trials of similar patients (8,248).

The treatment of potentially life-threatening ventricular arrhythmias in children is disease specific (e.g., beta blockade for LQTSs, catheter or surgical ablation for focal VTs, and heart transplantation for end-stage cardiomyopathies). When indicated, ICDs with transvenous lead systems are generally feasible in children older than 10 y (1). However, there is concern regarding the longevity of intravascular leads when potentially used for decades of life (1010). The use of ICDs in younger children and those with complex congenital heart disease remains challenging and often requires the use of epicardial or subcutaneous array systems. The higher incidence of lead failure and ICD infection or erosion in these patients mandates the judicious use of these devices in young patients (1011).

13.5. Patients With Implantable Cardioverter-Defibrillators

Recommendations

Class I

1. **Patients with implanted ICDs should receive regular follow-up and analysis of the device status.** ***(Level of Evidence: C)***
2. **Implanted ICDs should be programmed to obtain optimal sensitivity and specificity.** ***(Level of Evidence: C)***
3. **Measures should be undertaken to minimize the risk of inappropriate ICD therapies.** ***(Level of Evidence: C)***
4. **Patients with implanted ICDs who present with incessant VT should be hospitalized for management.** ***(Level of Evidence: C)***

Class IIa

1. **Catheter ablation can be useful for patients with implanted ICDs who experience incessant or frequently recurring VT.** ***(Level of Evidence: B)***
2. **In patients experiencing inappropriate ICD therapy, EP evaluation can be useful for diagnostic and therapeutic purposes.** ***(Level of Evidence: C)***

The placement of an ICD does not, in itself, decrease the incidence of arrhythmias, although the patient is protected from the consequences of the arrhythmias.

13.5.1. Supraventricular Tachyarrhythmias

SVT may trigger ICD action due to fulfilling programmed ventricular or SVT detection criteria. The effect of atrial tachyarrhythmia on ventricular rate response is crucial. As long as the ventricular rate fits within the tachycardia detection window, meaningful programming of the detection algorithms may prevent device action for VT. If ventricular rate falls within the VF detection window, appropriate therapy should not be withheld (see Section 7.6 for further discussion). Sophisticated algorithms enhance specificity of VT therapy and help to avoid VT therapies based on rate criteria alone (1012–1014). Beta blockade is also a valuable therapy that will prevent many unwanted device interventions due to supraventricular arrhythmias. Additional investigations such as Holter recordings, patient-activated loop recorders, and EP studies might be required to guide the management of these arrhythmias.

13.5.2. Supraventricular Tachycardia in Patients With Ventricular Implantable Cardioverter-Defibrillators

Episode analysis relies mainly on the information from the ventricular lead of the ICD, although in some instances atrial activity is also sensed (see later) (1015). Careful analysis of detected episodes, the effects of antitachycardia pacing on the cycle length intervals, and the mode of termination or acceleration are important for classification of the detected tachycardia. Enhanced discrimination algorithms help to reduce inappropriate VT therapies based on the rate criterion alone. AF is the most frequent culprit of arrhythmia. Rapid ventricular rate during SVTs may provoke ventricular antitachycardia pacing. Device action may be proarrhythmic, as inappropriate antitachycardia pacing may cause VT or VF (1016).

13.5.3. Dual-Chamber Implantable Cardioverter-Defibrillators

Dual-chamber ICDs provide improved atrial diagnostic features with recording of local atrial electrograms, regularity of atrial signals, and cycle lengths. This may provide additional features to avoid inappropriate VT/VF therapies, but inappropriate ventricular tachyarrhythmia sensing still occurs in 10% to 15% of cases (1017). Oversensing of far-field signals by the atrial electrodes(s) may prompt inappropriate therapies for SVTs, such as antitachycardia pacing or automatic cardioversion. In case of programmed internal atrial cardioversion therapies, even low-energy shocks may be painful and compromise quality of life (1018). High-rate atrial antitachycardia pacing may induce (transient) AF. Efficacy of advanced atrial pacing or cardioversion therapies varies greatly in function of episode duration, atrial cycle length, and atrial tachycardia mechanism (1013,1019,1020). Acute efficacy of atrial antitachycardia pacing may be as high as 40% (1013).

13.5.4. Arrhythmia Storm in Implantable Cardioverter-Defibrillator Patients

The term *arrhythmia storm* refers to a situation when numerous device discharges occur due to recurrent repetitive arrhythmias. A vicious cycle between device action and cardiac dysfunction may lead to further deterioration. The management must address all aspects to correct the situation (see Section 7.6 for further discussion).

13.6. Drug-Induced Arrhythmias

13.6.1. Introduction

Because the problem of drug-induced arrhythmias is sporadic, randomized, double-blind clinical trials have, with very few exceptions, not been performed. Specific syndromes of drug-induced arrhythmias, with diverse mechanisms and management strategies, are described in the sections that follow. Treatment guidelines focus on avoiding drug treatment in high-risk patients, recognizing the syndromes of drug-induced arrhythmia and withdrawal of the offending agent(s). The efficacy of specific therapies is often inferred from anecdotal evidence or preclinical, mechanism-based studies.

High drug concentrations due to overdose or drug interactions generally increase the risk of drug-induced arrhythmias. The largest increases in concentrations occur when a drug is eliminated by a single pathway and that pathway is susceptible to inhibition by the administration of a second drug. Table 11 lists examples of drug interactions that may cause arrhythmias through this mechanism. Interactions can also reduce plasma concentrations of antiarrhythmic drugs and thereby exacerbate the arrhythmia being treated. Additive pharmacological effects may also result in arrhythmias.

13.6.2. Digitalis Toxicity

Recommendations

Class I

An antidigitalis antibody is recommended for patients who present with sustained ventricular arrhythmias, advanced AV block, and/or asystole that are considered due to digitalis toxicity. ***(Level of Evidence: A)***

Class IIa

1. **Patients taking digitalis who present with mild cardiac toxicity (e.g., isolated ectopic beats only) can be managed effectively with recognition, continuous monitoring of cardiac rhythm, withdrawal of digitalis, restoration of normal electrolyte levels (including serum potassium greater than 4 mM/L), and oxygenation.** ***(Level of Evidence: C)***
2. **Magnesium or pacing is reasonable for patients who take digitalis and present with severe toxicity (sustained ventricular arrhythmias, advanced AV block, and/or asystole).** ***(Level of Evidence: C)***

Table 11. Drug Interactions Causing Arrhythmias

Drug	Interacting Drug	Effect
Increased Concentration of Arrhythmogenic Drug		
Digoxin	Some antibiotics	By eliminating gut flora that metabolize digoxin, some antibiotics may increase digoxin bioavailability. Note: some antibiotics also interfere with P-glycoprotein (expressed in the intestine and elsewhere), another effect that can elevate digoxin concentration
Digoxin	Amiodarone Quinidine Verapamil	Increased digoxin bioavailability, reduced biliary and renal excretion due to P-glycoprotein inhibition
	Cyclosporine Itraconazole Erythromycin	Digoxin toxicity
Quinidine	Ketoconazole	Increased drug levels
Cisapride	Itraconazole	
Terfenadine, astemizole	Erythromycin* Clarithromycin Some calcium blockers* Some HIV protease inhibitors (especially ritanovir)	
Beta blockers propafenone	Quinidine (even ultra-low dose)	Increased beta blockade
	Fluoxetine	Increased beta blockade
Flecainide	Some tricyclic antidepressants	Increased adverse effects Decreased analgesia (due to failure of biotransformation to the active metabolite morphine)
Dofetilide	Verapamil Cimetidine Trimethoprim Ketoconazole Megestrol	Increased plasma dofetilide concentration due to inhibition of renal excretion
Decreased Concentration of Antiarrhythmic Drug		
Digoxin	Antacids	Decreased digoxin effect due to decreased absorption
	Rifampin	Increased P-glycoprotein activity
Quinidine, mexiletine	Rifampin, barbiturates	Induced drug metabolism
Synergistic Pharmacological Activity Causing Arrhythmias		
QT-prolonging antiarrhythmics	Diuretics	Increased torsades de pointes risk due to diuretic-induced hypokalemia
Beta blockers	Amiodarone, clonidine, digoxin, diltiazem, verapamil	Bradycardia when used in combination
Digoxin	Amiodarone, beta blockers, clonidine, diltiazem, verapamil	
Verapamil	Amiodarone, beta blockers, clonidine, digoxin, diltiazem	
Diltiazem	Amiodarone, beta blockers, clonidine, digoxin, verapamil	
Clonidine	Amiodarone, beta blockers, digoxin, diltiazem, verapamil	
Amiodarone	Beta blockers, clonidine, digoxin, diltiazem, verapamil	
Sildenafil	Nitrates	Increased and persistent vasodilation; risk of myocardial ischemia

*These may also accumulate to toxic levels with co-administration of inhibitor drugs like ketoconazole. Data are from Roden DM, Anderson ME. Proarrhythmia. In: Kass RS, Clancey CE, editors. Handbook of Experimental Pharmacology: vol. 171. Basis and Treatment of Cardiac Arrhythmias. Boston: Springer Verlag, 2006:288–304 (1021).

Class IIb

Dialysis for the management of hyperkalemia may be considered for patients who take digitalis and present with severe toxicity (sustained ventricular arrhythmias; advanced AV block, and/or asystole). ***(Level of Evidence: C)***

Class III

Management by lidocaine or phenytoin is not recommended for patients taking digitalis and who present with severe toxicity (sustained ventricular arrhythmias, advanced AV block, and/or asystole). ***(Level of Evidence: C)***

13.6.2.1. Clinical Presentation

Certain arrhythmias are typical: enhanced atrial, junctional, or ventricular automaticity (with ectopic beats or tachycardia) often combined with AV block. Overdose of digitalis causes severe 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. Contributing factors may include hypothyroidism, hypokalemia, or renal dysfunction.

13.6.2.2. Specific Management

In mild cases, management includes discontinuing the drug, monitoring rhythm and maintaining normal serum potassium. Occasionally, temporary pacing may be needed. For more severe intoxication (serum digoxin concentration greater than 4 to 5 ng/mL, and with serious arrhythmias), the treatment of choice is digoxin-specific Fab antibody (1022). In one series of 150 severely intoxicated patients, response was rapid (30 min to 4 h), and 54% of patients presenting with a cardiac arrest survived hospitalization. Side effects include worsening of the underlying disease (increased ventricular rate during AF, exacerbation of HF) and hypokalemia. Digoxin concentration monitoring is unreliable after antidigoxin antibody. There is little role for previously used therapies such as lidocaine or phenytoin.

13.6.3. Drug-Induced Long QT Syndrome

Recommendations

Class I

In patients with drug-induced LQTS, removal of the offending agent is indicated. (*Level of Evidence: A*)

Class IIa

1. **Management with intravenous magnesium sulfate is reasonable for patients who take QT-prolonging drugs and present with few episodes of torsades de pointes in which the QT remains long. *(Level of Evidence: B)***
2. **Atrial or ventricular pacing or isoproterenol is reasonable for patients taking QT-prolonging drugs who present with recurrent torsades de pointes. *(Level of Evidence: B)***

Class IIb

Potassium ion repletion to 4.5 to 5 mmol/L may be reasonable for patients who take QT-prolonging drugs and present with few episodes of torsades de pointes in whom the QT remains long. *(Level of Evidence: C)*

13.6.3.1. Clinical Features

Marked QT prolongation, often accompanied by the morphologically distinctive polymorphic VT torsades de pointes, occurs in 1% to 10% of patients receiving QT-prolonging antiarrhythmic drugs and much more rarely in patients receiving "noncardiovascular" drugs with QT-prolonging potential. While many drugs have been associated with isolated cases of torsades de pointes, Table 12 lists those generally recognized as having QT-prolonging potential. An up-to-date list is maintained at www.torsades.org and www.qtdrugs.org.

Most cases of drug-induced torsades de pointes display a "short-long-short" series of cycle length changes prior to initiation of tachycardia. QT intervals, uncorrected for rate, are generally greater than 500 ms, prominent U waves are common, and marked QTU prolongation may be evident only on postpause beats. Major risk factors for drug-induced torsades de pointes are listed in Table 13; often more than one is present. Drugs can expose subclinical congenital LQTS; in addition, some studies have implicated commoner DNA variants (polymorphisms, with frequencies ranging up to 15% of some populations) (70,1023).

Presentations of drug-induced QT prolongation include incidental detection in an asymptomatic patient, palpitations due to frequent extrasystoles and nonsustained ventricular arrhythmias, syncope due to prolonged episodes of torsades de pointes, or SCD. The extent to which SCD in patients receiving QT-prolonging therapies represents torsades de pointes is uncertain. The QT-prolonging agent D-sotalol increased mortality in a large randomized clinical trial (SWORD [Survival With Oral D-sotalol]), an effect that may have been due to torsades de pointes (970). In the Danish Investigators of Arrhythmia and Mortality on Dofetilide (DIAMOND) trial, 3.3% of patients with severe HF had torsades de pointes during the first 72 h of dofetilide therapy (1024). High concentrations of erythromycin achieved by intravenous therapy have been associated with torsades de pointes, and a review of SCD in a

Table 12. Examples of Drugs Causing Torsades de Pointes*

Frequent (greater than 1%)
(e.g.,) hospitalization for monitoring recommended during drug initiation in some circumstances)
- Disopyramide
- Dofetilide
- Ibutilide
- Procainamide
- Quinidine
- Sotalol
- Ajmaline

Less frequent
- Amiodarone
- Arsenic trioxide
- Bepridil
- Cisapride
- Anti-infectives: clarithromycin, erythromycin, halofantrine, pentamidine, sparfloxacin
- Antiemetics: domperidone, droperidol
- Antipsychotics: chlorpromazine, haloperidol, mesoridazine, thioridazine, pimozide
- Opioid dependence agents: methadone

*See www.torsades.org for up-to-date listing. Adapted with permission from Roden DM. Drug-induced prolongation of the QT interval. N Engl J Med 2004;350:1013–22. Copyright © 2004 Massachusetts Medical Society (1025).

Table 13. Risk Factors for Drug-Induced Torsades de Pointes

- Female gender
- Hypokalemia
- Bradycardia
- Recent conversion from atrial fibrillation
- Congestive heart failure
- Digitalis therapy
- High drug concentrations (*exception: quinidine*), often due to drug interactions
- Rapid rate of intravenous drug administration
- Baseline QT prolongation
- Ventricular arrhythmia
- Left ventricular hypertrophy
- Congenital long QT syndrome
- Certain DNA polymorphisms
- Severe hypomagnesemia
- Concomitant use of 2 or more drugs that prolong the QT interval
- Combination of QT-prolonging drug with its metabolic inhibitor

Adapted with permission from Roden DM. Drug-induced prolongation of the QT interval. N Engl J Med 2004;350:1013–22. Copyright © 2004 Massachusetts Medical Society (1025).
DNA = deoxyribonucleic acid.

Medicaid database implicated the combination of oral erythromycin and drugs blocking its metabolism as increasing SCD (603).

13.6.3.2. Management

Monitoring high-risk patients during initiation of QT-prolonging antiarrhythmic drugs and recognition of the syndrome when it occurs are the first steps. Maintaining serum potassium between 4.5 and 5 mEq/L shortens QT (1026, 1027); no specific data are available on the efficacy of potassium repletion to prevent torsades de pointes. Intravenous magnesium can suppress episodes of torsades de pointes without necessarily shortening QT, even when serum magnesium is normal (1028). Magnesium toxicity (areflexia progressing to respiratory depression) can occur when concentrations reach 6 to 8 mEq/L but is a very small risk with the doses usually used in torsades de pointes, 1 to 2 g intravenously. Temporary pacing is highly effective in managing torsades de pointes that is recurrent after potassium repletion and magnesium supplementation. Isoproterenol can also be used to increase heart rate and abolish postectopic pauses. Anecdotes have reported that lidocaine (1029), verapamil (1030), and even occasionally amiodarone (1031) have been effective. However, amiodarone may itself cause torsades de pointes, albeit much less commonly than with other QT-prolonging antiarrhythmics (1032).

13.6.4. Sodium Channel Blocker–Related Toxicity

Recommendations

Class I

In patients with sodium channel blocker–related toxicity, removal of the offending agent is indicated. *(Level of Evidence: A)*

Class IIa

1. **Stopping the drug, reprogramming the pacemaker or repositioning leads can be useful in patients taking sodium channel blockers who present with elevated defibrillation thresholds or pacing requirement. *(Level of Evidence: C)***
2. **In patients taking sodium channel blockers who present with atrial flutter with 1:1 AV conduction, withdrawal of the offending agent is reasonable. If the drug needs to be continued, additional A-V nodal blockade with diltiazem, verapamil, or beta blocker or atrial flutter ablation can be effective. *(Level of Evidence: C)***

Class IIb

Administration of a beta blocker and a sodium bolus may be considered for patients taking sodium channel blockers if the tachycardia becomes more frequent or more difficult to cardiovert. *(Level of Evidence: C)*

13.6.4.1. Clinical Features

Arrhythmias caused by sodium channel-blocking drugs are included in Table 14. Antiarrhythmic drugs are the most common precipitants, although other agents, notably tricyclic antidepressants and cocaine, may produce some of their toxicities through these mechanisms. Sodium channel–blocking drugs with slower rates of dissociation

Table 14. Syndromes of Drug-Induced Arrhythmia and Their Management

Drugs	Clinical Setting	Management*
Digitalis	Mild cardiac toxicity (isolated arrhythmias only)	
	Severe toxicity: sustained ventricular arrhythmias; advanced AV block; asystole	Anti-digitalis antibody Pacing Dialysis for hyperkalemia
QT-prolonging drugs	Torsades de pointes: few episodes, QT remains long	IV magnesium sulfate ($MgSO_4$) Replete potassium (K^+) to 4.5 to 5 mEq/L
	Recurrent torsades de pointes	Ventricular pacing Isoproterenol
Sodium channel blockers	Elevated defibrillation or pacing requirement	Stop drug; reposition leads
	Atrial flutter with 1:1 AV conduction	Diltiazem, verapamil, beta blocker (IV)
	Ventricular tachycardia (more frequent; difficult to cardiovert)	Beta blocker; sodium
	Brugada syndrome	Stop drug; treat arrhythmia

*Always includes recognition, continuous monitoring of cardiac rhythm, withdrawal of offending agents, restoration of normal electrolytes (including serum potassium to greater than 4 mEq/L), and oxygenation. The order shown is not meant to represent the preferred sequence when more than one treatment is listed.
AV = atrioventricular; IV = intravenous.

tend to generate these adverse effects more commonly; these include agents such as flecainide, propafenone, and quinidine that (as a consequence of the slow dissociation rate) tend to prolong QRS durations even at normal heart rates and therapeutic dosages (1033).

In large clinical trials, sodium channel–blocking drugs have increased mortality among patients convalescing from MI. This effect was best demonstrated in CAST (967), but similar trends were also seen with earlier trials of mexiletine (1034) and disopyramide (1035). Analysis of the CAST database has indicated that patients at risk for recurrent myocardial ischemia are especially susceptible to SCD during sodium channel–blocking drugs (1036).

In patients treated for sustained VT, these agents may provoke more frequent, and often more difficult to cardiovert, episodes of sustained VT. While the drugs generally slow the rate of VT, occasionally the arrhythmia becomes disorganized and may be resistant to cardioversion; deaths have resulted. It seems likely that at least some of the excess mortality in CAST and other trials reflect such provocation or exacerbation of sustained ventricular arrhythmias. Sodium channel–blocking drugs increase defibrillation energy requirement and pacing thresholds (1037,1038); as a consequence, patients may require reprogramming or revision of pacing or ICD systems or changes in their drug regimens. Sodium channel blockers can "convert" AF to slow atrial flutter, which can show 1:1 AV conduction with wide-QRS complexes. This drug-induced arrhythmia can be confused with VT (1039).

Sodium channel blockers can occasionally precipitate the typical Brugada syndrome ECG (1040). This has been reported not only with antiarrhythmic drugs but also with tricyclic antidepressants (1041) and cocaine (1042). Whether this represents exposure of individuals with clinically inapparent Brugada syndrome (see Section 11.1.3) or one end of a broad spectrum of responses to sodium channel–blocking drugs is not known. The extent to which latent Brugada syndrome may have played a role in the CAST result is also unknown.

13.6.4.2. Management

Sodium channel-blocking drugs should not be used in patients with MI or sustained VT due to structural heart disease. The extent to which this prohibition on sodium channel blockers in patients with structural heart disease extends to tricyclic antidepressants that also block sodium channels is unknown (1043).

The major indication for these drugs is atrial arrhythmias in patients without structural heart disease; this excludes at least those studied in CAST (recent or remote MI) and by mechanistic considerations extends to those with other forms of ventricular dysfunction. When used for AF, AV nodal–blocking drugs should be coadministered to prevent rapid ventricular rates should atrial flutter occur; amiodarone may be an exception. Patients presenting with atrial flutter and rapid rates (and in whom VT is not a consideration) should be treated by slowing of AV conduction with drugs such as intravenous diltiazem. Ablation of the atrial flutter and continuation of the antiarrhythmic drug may be an option for long-term therapy (1044).

Animal and clinical anecdotes suggest that administration of sodium, as sodium chloride or sodium bicarbonate, may be effective in the reversing conduction slowing or frequent or cardioversion-resistant VT (1045,1046). Beta blockers have also been used successfully (1047).

13.6.5. Tricyclic Antidepressant Overdose

13.6.5.1. Clinical Features

Tricyclic antidepressants are second only to analgesics as a cause of serious overdose toxicity. Typical cardiac manifestations include sinus tachycardia, PR and QRS prolongation, and occasionally a Brugada syndrome-like ECG (1041). Hypotension, fever, and coma are other common manifestations of serious toxicity. Torsades de pointes have been associated with tricyclic antidepressant use, but this seems to be very rare.

13.6.5.2. Management

QRS duration can be shortened in experimental animals and in humans by administration of $NaHCO_3$ or NaCl boluses (1048). Antiarrhythmic drugs, including beta blockers, are generally avoided. Supportive measures, such as pressors, activated charcoal, and extracorporeal circulation, may be required.

13.6.6. Sudden Cardiac Death and Psychiatric or Neurological Disease

The incidence of SCD is increased in patients with seizure disorders (1049) and schizophrenia. It is uncertain whether this reflects specific abnormalities, such as autonomic dysfunction or an unusually high prevalence of cardiovascular disease, or the therapies used to treat the disease (1049–1052). Drug interactions may also contribute (1053). Antipsychotic agents well known to produce marked QT prolongation and torsades de pointes include thioridazine and haloperidol. Another group of generally newer antipsychotic drugs also prolong the QT interval, but fewer cases of torsades de pointes have been reported. It is not known whether this reflects intrinsic differences between drugs producing marked QT prolongation versus those producing lesser degrees of QT prolongation or differences in patient exposures to newer versus older drugs (238,1054).

13.6.7. Other Drug-Induced Toxicity

Recommendations

Class I

1. **High intermittent doses and cumulative doses exceeding the recommended levels should be avoided in patients receiving anthracyclines such as doxorubicin. *(Level of Evidence: B)***
2. **All patients receiving 5-fluorouracil therapy should receive close supervision and immediate discontinuation of the infusion if symptoms or signs of myocardial ischemia occur. Further treatment with 5-fluorouracil must be avoided in these individuals. *(Level of Evidence: C)***

3. **Patients with known cardiac disease should have a full cardiac assessment including echocardiography, which should be undertaken prior to use of anthracyclines such as doxorubicin, and regular long-term follow-up should be considered.** ***(Level of Evidence: C)***

Anthracycline cardiotoxicity is dose dependent, with intermittent high doses and higher cumulative doses increasing the risk of cardiomyopathy and lethal arrhythmias (1055,1056). Risk factors include younger age, female gender, and use of trastuzimab (1055,1057–1059). This form of cardiomyopathy can occur acutely soon after treatment, within a few months of treatment (the so-called subacute form), or many years later (1056,1060–1066). There is an increase in ventricular ectopy in patients receiving doxorubicin during the acute infusion period, but this is very rarely of any significance (1067,1068). Some studies have suggested reduced HRV, abnormalities in area ratios on SAECG, and increased QTc may be indicators of impending cardiomyopathy and electrical instability, but these have yet to be substantiated (1066,1069,1070). Long-term intermittent cardiac assessment of patients is therefore necessary and cardiac decompensation should be treated conventionally. There is, however, little evidence of reversibility in the anthracycline-induced myopathic process.

5-Fluorouracil causes lethal and potentially fatal arrhythmias irrespective of underlying coronary disease during the acute infusion period, the vast majority occurring during the first administration (1071). Cardiac monitoring during the infusion period, especially the first, is recommended for all patients receiving 5-fluorouracil therapy. Symptoms, with or without corresponding ECG changes compatible with cardiac ischemia, should lead to an immediate discontinuation of the infusion. Ischemia should be treated conservatively or conventionally with anticoagulants, nitrates, and calcium channel and beta blockade as required (1071). Although this cardiotoxicity is reversible, 5-fluorouracil sensitizes individuals and should be avoided in the future (1071). Cesium, well -recognized to produce torsades de pointes in animal models, has also been used as "alternate therapy" for malignancy and when torsades de pointes has been reported (1072).

Toad venom, an ingredient of some traditional Chinese medicines, produces clinical toxicity resembling that of digoxin, and in animal models, digoxin-specific antibodies are successful in reversing the toxicity (1073). Other herbal products, including foxglove tea, have been reported to produce similar effects (1074,1075).

Cocaine has both slow offset sodium channel–blocking properties and QT-prolonging (I_{Kr}-blocking) properties. Arrhythmias associated with cocaine ingestion include wide-complex tachycardias suggestive of sodium channel block (and responding to sodium infusion) as well as torsades de pointes. Cocaine also causes other cardiovascular complications that can lead to arrhythmias, notably myocarditis, and coronary spasm.

Dietary supplements containing ephedra alkaloids (including "ma huang") are no longer marketed because they appeared to have an infrequent association with serious cardiovascular toxicity, including SCD (1076–1078). The mechanism is unknown but may involve direct myocardial sympathomimetic stimulation, coronary spasm, and/or severe hypertension in susceptible individuals. Ephedrine, the active component, is also detected in a number of street drugs. Coronary spasm has been reported with multiple other medications and can present as VF: certain anticancer drugs (5-fluorouracil [1079–1082]), capecitabine (1083), triptans used in the treatment of migraines (1084), recreational agents (e.g., ecstasy [1085], cocaine), inadvertent vascular administration of pressor catecholamines, and anaphylaxis due to any one of a wide range of drugs (see Section 7.5 for further discussion).

Bradyarrhythmias are common (and desired) pharmacological effects of digoxin, verapamil, diltiazem, and beta blockers. Severe bradyarrhythmias may occur with usual doses in sensitized individuals, particularly those receiving combinations, or in suicidal or accidental overdose. Marked sinus bradycardia is also common with clonidine.

14. CONCLUSIONS

SCD continues to be a major cause of mortality in all developed countries. Using an evidence-based approach, this document attempts to summarize the latest information addressing the problem, with the goal of providing recommendations consistent with previous documents. However, it is important to stress that the field is evolving and recommendations will certainly change as more is learned about the problem. The lengthy list of references serves as an indication of the large amount of research addressing SCD already, and undoubtedly, the list will grow in the future. Timely updates of this information will be critical as clinicians try to care for patients at risk of SCD (1021,1025).

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APPENDIX 1. Author Relationships With Industry for the ACC/AHA/ESC 2006 Guidelines for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death

Committee Member	Research Grant	Speakers Bureau	Stock Ownership	Board of Directors	Consultant/Advisory Member
Martin Borggrefe, MD	• Medtronic Inc.	None	None	None	• Procter & Gamble • Impulse Dynamics • Synecor
Alfred E. Buxton, MD	• Medtronic Inc. • Guidant Corp. • St. Jude Medical	None	None	None	• Medtronic Inc. • General Electric
A. John Camm, MD	• Pfizer Inc.	• St. Jude Medical • Medtronic Inc. • Vitatron	• Cameron Health (small number of share options, less than US $5000)	None	• Vitatron • St. Jude Medical • Procter & Gamble • Servier • GlaxoSmithKline • Guidant Corp. • Wyeth • Johnson & Johnson • Sanofi-Aventis • Cardiome • Astellas • Cryocor • Point • CV Therapeutics Inc.
Bernard R. Chaitman, MD	• Pfizer Inc. • Aventis Inc. • Berlex • Procter & Gamble • CV Therapeutics Inc.	• Pfizer Inc. • Merck Inc.	None	None	• Aventis Inc. • CV Therapeutics Inc.
Martin Fromer, MD	None	None	None	None	None
Gabriel Gregoratos, MD	None	• Pfizer Inc.	None	None	• CV Therapeutics Inc. • GlaxoSmithKline
George J. Klein, MD	None	None	None	• Cryocath Technologies	• Medtronic Inc.
Arthur J. Moss, MD	• Guidant Corp. • Medtronic Inc.	None	None	None	• CV Therapeutics Inc.
Robert J. Myerburg, MD	None	• Berlex • Procter & Gamble • Guidant Corp. • Reliant Pharmaceuticals	None	None	• Berlex • Procter & Gamble • Reliant Pharmaceuticals • Medifacts Corp.
Silvia G. Priori, MD	• Medtronic Inc.	None	None	None	• Pfizer Inc. • CV Therapeutics Inc. • Guidant Corp. • Medtronic Inc.
Miguel A. Quinones, MD	None	None	None	None	• Procter & Gamble
Dan M. Roden, MD	• Co-investigator for colleagues who have grants from Medtronic Inc., St. Jude Medical, receives no compensation from these grants	None	• No stocks valued greater than $10,000	None	• Abbott • Alza • Arpida • Astra-Zeneca • Bristol-Myers Squibb • EBR Systems • First Genetic Trust • Lexicon • Lundbeck • Medtronic Inc.

APPENDIX 1. Continued

Committee Member	Research Grant	Speakers Bureau	Stock Ownership	Board of Directors	Consultant/Advisory Member
Dan M. Roden, MD (continued)					• Merck Inc. • NPS Pharmaceuticals • Novartis • Pfizer Inc. • Johnson & Johnson • GlaxoSmithKline • CV Therapeutics Inc. • Genzyme • Sanofi-Synthelabo Groupe • Solvay Pharmaceuticals • Thornton Medical • Wyeth • Yamanouchi
Michael J. Silka, MD	None	None	None	None	• General Electric
Cynthia M. Tracy, MD	• Medtronic Inc. • Guidant Corp.	None	None	None	None
Douglas P. Zipes, MD	• Medtronic Inc.	None	• MVMD	None	• Michael Marcus and Associates Science Partners, LLC, limited partner • GMP Companies Inc. • Medtronic Inc. • Aderis Pharmaceuticals Inc. • Terumo Cardiovascular Systems Corp. • Life Sentry • CV Therapeutics Inc. • Burrill and Company • Genzyme • Cardiofocus • Solvay Pharmaceuticals • Physical Logic

This table represents the relevant relationships of authors with industry to this topic that were reported orally at the initial writing committee meeting in May 2003 and updated in conjunction with all meetings and conference calls of the writing committee. It does not reflect any actual or potential relationships at the time of publication.

APPENDIX 2. External Peer Review Relationships With Industry for the ACC/AHA/ESC 2006 Guidelines for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death

Committee Member*†	Representation	Research Grant	Speakers Bureau	Stock Ownership	Board of Directors	Consultant/Advisory Member
Dr. John Di Marco	• Official Reviewer—AHA	• Guidant	• Guidant	None	None	• Novartis
Dr. John Field	• Official Reviewer—AHA	None	None	None	None	None
Dr. Bruce Lindsay	• Official Reviewer—ACCF Board of Trustees	None	None	None	None	• Guidant • Medtronic
Dr. Richard L. Page	• Official Reviewer—ACC/AHA Task Force on Practice Guidelines	None	None	None	None	• Procter & Gamble (no longer very active, less than $10,000 last 2 years)
Dr. Karl Stajduhar	• Official Reviewer—ACCF Board of Governors	• Sanofi	None	None	None	None
Dr. Elliott M. Antman	• Content Reviewer—ACC/AHA Task Force on Practice Guidelines	None	None	None	None	None
Dr. Angelo Auricchio	• Content Reviewer—ESC	None	None	None	None	None
Dr. Jean-Jacques Blanc	• Content Reviewer—ESC	None	None	None	None	None
Dr. Guenther Breithardt	• Content Reviewer—ESC	• Guidant • Medtronic • Biotran	• Guidant • Medtronic			• Guidant • Medtronic • Abbott • Johnson & Johnson
Dr. Mark Carlson	• Content Reviewer—ACCF Clinical EP Committee	None	None	• Atricure	None	• Atricure • Cameron Health • St. Jude Medical • St. Jude Medical
Dr. Paolo Della Bella	• Content Reviewer—ESC	None	None	None	None	None
Dr. Andrew Epstein	• Content Reviewer—ACC/AHA/HRS Pacemaker Guidelines	• Guidant • Medtronic • St. Jude Medical	• Guidant • Medtronic • St. Jude Medical	None	None	None
Dr. Sharon Hunt	• Content Reviewer—ACC/AHA HF Guidelines, ACC/AHA Task Force on Practice Guidelines	None	None	None	None	None
Dr. Guillaume Jondeau	• Content Reviewer—ESC	None	None	None	None	None
Dr. Alan Kadish	• Content Reviewer—Individual Reviewer	• St. Jude Medical	St. Jude Medical	• Medtronic • St. Jude Medical	None	None
Dr. Cecilia Linde	• Content Reviewer—ESC	• Medtronic	None	None	None	• St. Jude Medical
Dr. Jonathan Linder	• Content Reviewer—ACCF Task Force on Clinical Expert Consensus Documents	None	None	• Targeson	None	None

APPENDIX 2. Continued

Committee Member	Representation	Research Grant	Speakers Bureau	Stock Ownership	Board of Directors	Consultant/Advisory Member
Dr. Christine Albert	• Content Reviewer—AHA, ECG & Arrhythmias Committee	None	None	None	None	None
Dr. Carina Blomstrom-Lundquist	• Content Reviewer—ESC, ACC/AHA/ESC Supraventricular Arrhythmias Guidelines	None	None	None	None	None
Dr. Ali Oto	• Content Reviewer—ESC	None	None	None	None	None
Dr. Alexander Parkomenko	• Content Reviewer—ESC	None	None	None	None	None
Dr. Richard Sutton	• Content Reviewer—ESC	None	None	None	None	None
Dr. Josep Brugada Terradellas	• Content Reviewer—ESC	None	None	None	None	None
Dr. Panos Vardas	• Content Reviewer—ESC	None	None	None	None	None
Dr. Sami Viskin	• Content Reviewer—ESC	None	None	None	None	None
Dr. David Wilber	• Content Reviewer—Individual Reviewer	• Biosense/Webster • BAND • Guidant • Medtronic • St. Jude Medical	• Medtronic	None	None	• Biosense/Webster • Guidant
Dr. Antonio ZaZa	• Content Reviewer—ESC	None	None	None	None	None
Dr. L. Brent Mitchell	• Organizational Reviewer—HRS	None	None	None	None	None
Dr. Thomas Munger	• Organizational Reviewer—HRS	None	None	None	None	None

This table represents the relevant relationships of peer reviewers with industry to this topic that were disclosed at the time of peer review of this guideline. It does not necessarily reflect relationships with industry at the time of publication. *Participation in the peer review process does not imply endorsement of the document. †Names are listed in alphabetical order within each category of review.

APPENDIX 3

Ventricular Arrhythmias and SCD Acronyms and Abbreviations

ACE = angiotensin-converting enzyme

ACLS = advanced cardiac life support

ACS = acute coronary syndromes

AED = automated external defibrillator

AF = atrial fibrillation

AMI = acute myocardial infarction

AMIOVERT = Amiodarone Versus Implantable Cardioverter-Defibrillator

ARVC = arrhythmogenic right ventricular cardiomyopathy

AV = atrioventricular

AVID = Antiarrhythmics Versus Implantable Defibrillators

BEST-ICD = Beta-Blocker Strategy plus Implantable Cardioverter Defibrillator

CABG Patch Trial = Coronary Artery Bypass Graft Patch Trial

CASH = Cardiac Arrest Study Hamburg

CAST = Cardiac Arrhythmia Suppression Trial

CAT = Cardiomyopathy Trial

CHD = coronary heart disease

CPVT = catecholaminergic polymorphic ventricular tachycardia

CT = computed tomography

DCM = dilated cardiomyopathy

DEFINITE = Defibrillators in Nonischemic Cardiomyopathy Treatment Evaluation

DIAMOND = Danish Investigators of Arrhythmia and Mortality on Dofetilide

EF = ejection fraction

EP = electrophysiological

HCM = hypertrophic cardiomyopathy

HF = heart failure

HRV = heart rate variability

ICD = implantable cardioverter-defibrillator

LIFE = Losartan Intervention for Endpoint Reduction in Hypertension

LV = left ventricle, ventricular

LVEF = left ventricular ejection fraction

LVOT = left ventricular outflow tract

LQTS = long QT syndrome

MADIT II = Multicenter Automatic Defibrillator Implantation Trial II

MI = myocardial infarction

MRI = magnetic resonance imaging

MUSTT = Multicenter UnSustained Tachycardia Trial

NRMI-2 = Second National Registry of Myocardial Infarction

NSTEMI = non–ST-elevation myocardial infarction

NSVT = nonsustained ventricular tachycardia

NYHA = New York Heart Association

PAH = pulmonary arterial hypertension

PVC = premature ventricular complex

RBBB = right bundle-branch block

RF = radiofrequency

RV = right ventricle, ventricular

RVOT = right ventricular outflow tract

SAECG = signal-averaged electrocardiography

SCD = sudden cardiac death

SCD-HeFT = Sudden Cardiac Death in Heart Failure Trial

SCN5A = cardiac sodium channel gene

SIDS = sudden infant death syndrome

SNP = single nucleotide polymorphism

SOLVD = Studies Of Left Ventricular Dysfunction

SPECT = single-photon emission computed tomography

SVT = supraventricular tachycardia

SWORD = Survival With Oral D-sotalol

TWA = T-wave alternans

VF = ventricular fibrillation

VT = ventricular tachycardia

WADA = World Anti-Doping Agency

WPW = Wolff-Parkinson-White

REFERENCES

1. Gregoratos G, Abrams J, Epstein AE, et al. ACC/AHA/NASPE 2002 guidelines update for implantation of cardiac pacemakers and antiarrhythmia devices: summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/NASPE Committee to Update the 1998 Pacemaker Guidelines). Circulation 2002;106:2145–61.
2. Antman EM, Anbe DT, Armstrong PW, et al. ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction; a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1999 Guidelines for the Management of Patients With Acute Myocardial Infarction). J Am Coll Cardiol 2004;44:E1–211.
3. Priori SG, Aliot E, Blomstrom-Lundqvist C, et al. Task Force on Sudden Cardiac Death of the European Society of Cardiology. Eur Heart J 2001;22:1374–450.
4. Priori SG, Aliot E, Blomstrom-Lundqvist C, et al. Update of the guidelines on sudden cardiac death of the European Society of Cardiology. Eur Heart J 2003;24:13–5.
5. Nieminen MS, Bohm M, Cowie MR, et al. Executive summary of the guidelines on the diagnosis and treatment of acute heart failure: the Task Force on Acute Heart Failure of the European Society of Cardiology. Eur Heart J 2005;26:384–416.

5a. Swedberg K, Cleland J, Dargie H, et al. Executive summary of the guidelines for the diagnosis and treatment of chronic heart failure: the Task Force for the diagnosis and treatment of Chronic Heart Failure of the European Society of Cardiology. Eur Heart J 2005;11:1115–40.

6. Hunt SA. ACC/AHA 2005 guideline update for the diagnosis and management of chronic heart failure in the adult: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure). J Am Coll Cardiol 2005;46:e1–82.
7. Buxton AE. A report of the American College of Cardiology Task Force on Clinical Data Standards (Electrophysiolology Writing Committee). Manuscript in preparation.

7a. Poole JE, Bardy GH. Sudden Cardiac Death. In: Zipes DP, Jalife J, editors. Cardiac Electrophysiology: From Cell to Bedside. 3rd edition. Philadelphia, PA: WB Saunders Company, 2000:615–40.

8. Bardy GH, Lee KL, Mark DB, et al. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. N Engl J Med 2005;352:225–37.
9. Myerburg RJ, Interian A JR. Mitrani RM, et al. Frequency of sudden cardiac death and profiles of risk. Am J Cardiol 1997;80:10F–9F.
10. Myerburg RJ, Mitrani R, Interian A Jr., et al. Interpretation of outcomes of antiarrhythmic clinical trials: design features and population impact. Circulation 1998;97:1514–21.
11. Bonow R, Clark EB, Curfman GD, et al. Task Force on Strategic Research Direction: Clinical Science Subgroup key science topics report. Circulation 2002;106:e162–e166.
12. Hiss RG, Lamb LE. Electrocardiographic findings in 122,043 individuals. Circulation 1962;25:947–61.
13. Hinkle LE Jr., Carver ST, Stevens M. The frequency of asymptomatic disturbances of cardiac rhythm and conduction in middle-aged men. Am J Cardiol 1969;24:629–50.
14. Kennedy HL, Whitlock JA, Sprague MK, et al. Long-term follow-up of asymptomatic healthy subjects with frequent and complex ventricular ectopy. N Engl J Med 1985;312:193–7.
15. Viskin S, Belhassen B. Polymorphic ventricular tachyarrhythmias in the absence of organic heart disease: classification, differential diagnosis, and implications for therapy. Prog Cardiovasc Dis 1998;41:17–34.
16. Chiang BN, Perlman LV, Ostrander LD Jr., et al. Relationship of premature systoles to coronary heart disease and sudden death in

the Tecumseh Epidemiologic Study. Ann Intern Med 1969;70:1159–66.
17. Bikkina M, Larson MG, Levy D. Prognostic implications of asymptomatic ventricular arrhythmias: the Framingham Heart Study. Ann Intern Med 1992;117:990–6.
18. Engstrom G, Hedblad B, Janzon L, et al. Ventricular arrhythmias during 24-h ambulatory ECG recording: incidence, risk factors and prognosis in men with and without a history of cardiovascular disease. J Intern Med 1999;246:363–72.
19. Jouven X, Zureik M, Desnos M, et al. Long-term outcome in asymptomatic men with exercise-induced premature ventricular depolarizations. N Engl J Med 2000;343:826–33.
20. Frolkis JP, Pothier CE, Blackstone EH, et al. Frequent ventricular ectopy after exercise as a predictor of death. N Engl J Med 2003;348:781–90.
21. Bigger JT Jr., Fleiss JL, Kleiger R, et al. The relationships among ventricular arrhythmias, left ventricular dysfunction, and mortality in the 2 years after myocardial infarction. Circulation 1984;69: 250–8.
22. Ruberman W, Weinblatt E, Goldberg JD, et al. Ventricular premature complexes and sudden death after myocardial infarction. Circulation 1981;64:297–305.
23. Ruberman W, Weinblatt E, Frank CW, et al. Repeated 1 hour electrocardiographic monitoring of survivors of myocardial infarction at 6 month intervals: arrhythmia detection and relation to prognosis. Am J Cardiol 1981;47:1197–204.
24. Huikuri HV, Makikallio TH, Raatikainen MJ, et al. Prediction of sudden cardiac death: appraisal of the studies and methods assessing the risk of sudden arrhythmic death. Circulation 2003;108:110–5.
25. Teerlink Jr., Jalaluddin M, Anderson S, et al. Ambulatory ventricular arrhythmias in patients with heart failure do not specifically predict an increased risk of sudden death. PROMISE (Prospective Randomized Milrinone Survival Evaluation) Investigators. Circulation 2000;101:40–6.
26. Volpi A, Cavalli A, Franzosi MG, et al. One-year prognosis of primary ventricular fibrillation complicating acute myocardial infarction. The GISSI (Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto miocardico) investigators. Am J Cardiol 1989; 63:1174–8.
27. Liberthson RR, Nagel EL, Hirschman JC, et al. Prehospital ventricular defibrillation. Prognosis and follow-up course. N Engl J Med 1974;291:317–21.
28. Jensen GV, Torp-Pedersen C, Hildebrandt P, et al. Does in-hospital ventricular fibrillation affect prognosis after myocardial infarction? Eur Heart J 1997;18:919–24.
29. Behar S, Kishon Y, Reicher-Reiss H, et al. Prognosis of early versus late ventricular fibrillation complicating acute myocardial infarction. Int J Cardiol 1994;45:191–8.
30. Ottani F, Galvani M, Nicolini FA, et al. Elevated cardiac troponin levels predict the risk of adverse outcome in patients with acute coronary syndromes. Am Heart J 2000;140:917–27.
31. Al-Khatib SM, Granger CB, Huang Y, et al. Sustained ventricular arrhythmias among patients with acute coronary syndromes with no ST-segment elevation: incidence, predictors, and outcomes. Circulation 2002;106:309–12.
32. Cheema AN, Sheu K, Parker M, et al. Nonsustained ventricular tachycardia in the setting of acute myocardial infarction: tachycardia characteristics and their prognostic implications. Circulation 1998; 98:2030–6.
33. Wyse DG, Friedman PL, Brodsky MA, et al. Life-threatening ventricular arrhythmias due to transient or correctable causes: high risk for death in follow-up. J Am Coll Cardiol 2001;38:1718–24.
34. Gillum RF. Sudden coronary death in the United States: 1980–1985. Circulation 1989;79:756–65.
35. Escobedo LG, Zack MM. Comparison of sudden and nonsudden coronary deaths in the United States. Circulation 1996;93:2033–6.
36. Zheng ZJ, Croft JB, Giles WH, et al. Sudden cardiac death in the United States, 1989 to 1998. Circulation 2001;104:2158–63.
37. Cobb LA, Fahrenbruch CE, Olsufka M, et al. Changing incidence of out-of-hospital ventricular fibrillation, 1980–2000. JAMA 2002; 288:3008–13.
38. American Heart Association. Heart Disease and Stroke Statistics—2005 Update. Dallas, TX: American Heart Association; 2004.
39. Myerburg RJ, Kessler KM, Castellanos A. Sudden cardiac death: epidemiology, transient risk, and intervention assessment. Ann Intern Med 1993;119:1187–97.
40. Kuller L, Lilienfeld A, Fisher R. An epidemiological study of sudden and unexpected deaths in adults. Medicine (Baltimore) 1967;46:341–61.
41. de Vreede-Swagemakers JJ, Gorgels AP, Dubois-Arbouw WI, et al. Out-of-hospital cardiac arrest in the 1990's: a population-based study in the Maastricht area on incidence, characteristics and survival. J Am Coll Cardiol 1997;30:1500–5.
42. Gillum RF. Geographic variation in sudden coronary death. Am Heart J 1990;119:380–9.
43. Myerburg RJ. Sudden cardiac death: exploring the limits of our knowledge. J Cardiovasc Electrophysiol 2001;12:369–81.
44. Huikuri HV, Castellanos A, Myerburg RJ. Sudden death due to cardiac arrhythmias. N Engl J Med 2001;345:1473–82.
45. Braunwald E. Shattuck lecture—cardiovascular medicine at the turn of the millennium: triumphs, concerns, and opportunities. N Engl J Med 1997;337:1360–9.
46. Myerburg RJ, Kessler KM, Castellanos A. Sudden cardiac death. Structure, function, and time-dependence of risk. Circulation 1992; 85:I2–10.
47. Solomon SD, Zelenkofske S, McMurray JJ, et al. Sudden death in patients with myocardial infarction and left ventricular dysfunction, heart failure, or both. N Engl J Med 2005;352:2581–8.
48. Holmberg M, Holmberg S, Herlitz J. Incidence, duration and survival of ventricular fibrillation in out-of-hospital cardiac arrest patients in Sweden. Resuscitation 2000;44:7–17.
49. Wren C, O'Sullivan JJ, Wright C. Sudden death in children and adolescents. Heart 2000;83:410–3.
50. Kuisma M, Suominen P, Korpela R. Paediatric out-of-hospital cardiac arrests—epidemiology and outcome. Resuscitation 1995;30: 141–50.
51. Steinberger J, Lucas RV Jr., Edwards JE, et al. Causes of sudden unexpected cardiac death in the first two decades of life. Am J Cardiol 1996;77:992–5.
52. Boerwinkle E, Ellsworth DL, Hallman DM, et al. Genetic analysis of atherosclerosis: a research paradigm for the common chronic diseases. Hum Mol Genet 1996;5:1405–10.
53. Faber BC, Cleutjens KB, Niessen RL, et al. Identification of genes potentially involved in rupture of human atherosclerotic plaques. Circ Res 2001;89:547–54.
54. Topol EJ, McCarthy J, Gabriel S, et al. Single nucleotide polymorphisms in multiple novel thrombospondin genes may be associated with familial premature myocardial infarction. Circulation 2001; 104:2641–4.
55. Spooner PM, Albert C, Benjamin EJ, et al. Sudden cardiac death, genes, and arrhythmogenesis: consideration of new population and mechanistic approaches from a National Heart, Lung, and Blood Institute workshop, part II. Circulation 2001;103:2447–52.
56. Myerburg RJ. Scientific gaps in the prediction and prevention of sudden cardiac death. J Cardiovasc Electrophysiol 2002;13:709–23.
57. Friedlander Y, Siscovick DS, Weinmann S, et al. Family history as a risk factor for primary cardiac arrest. Circulation 1998;97:155–60.
58. Jouven X, Desnos M, Guerot C, et al. Predicting sudden death in the population: the Paris Prospective Study I. Circulation 1999;99: 1978–83.
59. Schatzkin A, Cupples LA, Heeren T, et al. The epidemiology of sudden unexpected death: risk factors for men and women in the Framingham Heart Study. Am Heart J 1984;107:1300–6.
60. Schatzkin A, Cupples LA, Heeren T, et al. Sudden death in the Framingham Heart Study. Differences in incidence and risk factors by sex and coronary disease status. Am J Epidemiol 1984;120:888–99.
61. Gillum RF. Sudden cardiac death in Hispanic Americans and African Americans. Am J Public Health 1997;87:1461–6.
62. Albert CM, Chae CU, Grodstein F, et al. Prospective study of sudden cardiac death among women in the United States. Circulation 2003;107:2096–101.
63. De Buyzere G, Ambrosioni E, Borch-Johnsen K, et al. European guidelines on cardiovascular disease prevention in clinical practice: Third Joint Task Force of European and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted

by representatives of eight societies and by invited experts). Eur J Cardiovasc Prev Rehabil 2003;10:S1–S10.
64. Becker LB, Han BH, Meyer PM, et al. Racial differences in the incidence of cardiac arrest and subsequent survival. The CPR Chicago Project. N Engl J Med 1993;329:600–6.
65. Grundy SM, Balady GJ, Criqui MH, et al. Primary prevention of coronary heart disease: guidance from Framingham: a statement for healthcare professionals from the AHA Task Force on Risk Reduction. American Heart Association. Circulation 1998;97:1876–87.
66. Holmes DR Jr., Davis K, Gersh BJ, et al. Risk factor profiles of patients with sudden cardiac death and death from other cardiac causes: a report from the Coronary Artery Surgery Study (CASS). J Am Coll Cardiol 1989;13:524–30.
67. Blake GJ, Ridker PM. C-reactive protein and other inflammatory risk markers in acute coronary syndromes. J Am Coll Cardiol 2003;41:37S–42S.
68. Casscells W, Naghavi M, Willerson JT. Vulnerable atherosclerotic plaque: a multifocal disease. Circulation 2003;107:2072–5.
69. Nissen SE, Tuzcu EM, Schoenhagen P, et al. Statin therapy, LDL cholesterol, C-reactive protein, and coronary artery disease. N Engl J Med 2005;352:29–38.
70. Splawski I, Timothy KW, Tateyama M, et al. Variant of SCN5A sodium channel implicated in risk of cardiac arrhythmia. Science 2002;297:1333–6.
71. Haider AW, Larson MG, Benjamin EJ, et al. Increased left ventricular mass and hypertrophy are associated with increased risk for sudden death. J Am Coll Cardiol 1998;32:1454–9.
72. Kannel WB, Thomas HE Jr.. Sudden coronary death: the Framingham Study. Ann N Y Acad Sci 1982;382:3–21.
73. Essebag V, Eisenberg MJ. Expanding indications for defibrillators after myocardial infarction: risk stratification and cost effectiveness. Card Electrophysiol Rev 2003;7:43–8.
74. Hallstrom AP, Cobb LA, Ray R. Smoking as a risk factor for recurrence of sudden cardiac arrest. N Engl J Med 1986;314:271–5.
75. Jouven X, Empana JP, Schwartz PJ, et al. Heart-rate profile during exercise as a predictor of sudden death. N Engl J Med 2005;352:1951–8.
76. Albert CM, Mittleman MA, Chae CU, et al. Triggering of sudden death from cardiac causes by vigorous exertion. N Engl J Med 2000;343:1355–61.
77. Mittleman MA, Maclure M, Tofler GH, et al. Triggering of acute myocardial infarction by heavy physical exertion. Protection against triggering by regular exertion. Determinants of Myocardial Infarction Onset Study Investigators. N Engl J Med 1993;329:1677–83.
78. Siscovick DS, Weiss NS, Fletcher RH, et al. The incidence of primary cardiac arrest during vigorous exercise. N Engl J Med 1984;311:874–7.
79. Rozanski A, Blumenthal JA, Kaplan J. Impact of psychological factors on the pathogenesis of cardiovascular disease and implications for therapy. Circulation 1999;99:2192–217.
80. Krantz DS, Sheps DS, Carney RM, et al. Effects of mental stress in patients with coronary artery disease: evidence and clinical implications. JAMA 2000;283:1800–2.
81. Hemingway H, Malik M, Marmot M. Social and psychosocial influences on sudden cardiac death, ventricular arrhythmia and cardiac autonomic function. Eur Heart J 2001;22:1082–101.
82. Thomas SA, Friedmann E, Wimbush F, et al. Psychological factors and survival in the Cardiac Arrhythmia Suppression Trial (CAST): a reexamination. Am J Crit Care 1997;6:116–26.
83. Williams RB, Barefoot JC, Califf RM, et al. Prognostic importance of social and economic resources among medically treated patients with angiographically documented coronary artery disease. JAMA 1992;267:520–4.
84. de Vreede-Swagemakers JJ, Gorgels AP, Weijenberg MP, et al. Risk indicators for out-of-hospital cardiac arrest in patients with coronary artery disease. J Clin Epidemiol 1999;52:601–7.
85. Leor J, Poole WK, Kloner RA. Sudden cardiac death triggered by an earthquake. N Engl J Med 1996;334:413–9.
86. Lampert R, Joska T, Burg MM, et al. Emotional and physical precipitants of ventricular arrhythmia. Circulation 2002;106:1800–5.
87. Burke AP, Farb A, Malcom GT, et al. Plaque rupture and sudden death related to exertion in men with coronary artery disease. JAMA 1999;281:921–6.
88. Farb A, Tang AL, Burke AP, et al. Sudden coronary death. Frequency of active coronary lesions, inactive coronary lesions, and myocardial infarction. Circulation 1995;92:1701–9.
89. Theroux P, Fuster V. Acute coronary syndromes: unstable angina and non-Q-wave myocardial infarction. Circulation 1998;97:1195–206.
90. Burke AP, Farb A, Malcom GT, et al. Effect of risk factors on the mechanism of acute thrombosis and sudden coronary death in women. Circulation 1998;97:2110–6.
91. Jimenez RA, Myerburg RJ. Sudden cardiac death. Magnitude of the problem, substrate/trigger interaction, and populations at high risk. Cardiol Clin 1993;11:1–9.
92. Duflou J, Virmani R, Rabin I, et al. Sudden death as a result of heart disease in morbid obesity. Am Heart J 1995;130:306–13.
93. Alpert MA. Obesity cardiomyopathy: pathophysiology and evolution of the clinical syndrome. Am J Med Sci 2001;321:225–36.
94. Jouven X, Charles MA, Desnos M, et al. Circulating nonesterified fatty acid level as a predictive risk factor for sudden death in the population. Circulation 2001;104:756–61.
95. Luscher TF, Creager MA, Beckman JA, et al. Diabetes and vascular disease: pathophysiology, clinical consequences, and medical therapy: part II. Circulation 2003;108:1655–61.
96. Corrado D, Basso C, Thiene G, et al. Spectrum of clinicopathologic manifestations of arrhythmogenic right ventricular cardiomyopathy/dysplasia: a multicenter study. J Am Coll Cardiol 1997;30:1512–20.
97. Fananapazir L, Chang AC, Epstein SE, et al. Prognostic determinants in hypertrophic cardiomyopathy. Prospective evaluation of a therapeutic strategy based on clinical, Holter, hemodynamic, and electrophysiological findings. Circulation 1992;86:730–40.
98. Elliott PM, Poloniecki J, Dickie S, et al. Sudden death in hypertrophic cardiomyopathy: identification of high risk patients. J Am Coll Cardiol 2000;36:2212–8.
99. Sorgato A, Faggiano P, Aurigemma GP, et al. Ventricular arrhythmias in adult aortic stenosis: prevalence, mechanisms, and clinical relevance. Chest 1998;113:482–91.
100. Timmermans C, Smeets JL, Rodriguez LM, et al. Aborted sudden death in the Wolff-Parkinson-White syndrome. Am J Cardiol 1995;76:492–4.
101. Munger TM, Packer DL, Hammill SC, et al. A population study of the natural history of Wolff-Parkinson-White syndrome in Olmsted County, Minnesota, 1953–1989. Circulation 1993;87:866–73.
102. Spooner PM, Albert C, Benjamin EJ, et al. Sudden cardiac death, genes, and arrhythmogenesis: consideration of new population and mechanistic approaches from a National Heart, Lung, and Blood Institute workshop, part I. Circulation 2001;103:2361–4.
103. Priori SG, Schwartz PJ, Napolitano C, et al. Risk stratification in the long-QT syndrome. N Engl J Med 2003;348:1866–74.
104. Priori SG, Napolitano C, Gasparini M, et al. Natural history of Brugada syndrome: insights for risk stratification and management. Circulation 2002;105:1342–7.
105. Priori SG, Napolitano C, Memmi M, et al. Clinical and molecular characterization of patients with catecholaminergic polymorphic ventricular tachycardia. Circulation 2002;106:69–74.
106. Snapir A, Mikkelsson J, Perola M, et al. Variation in the alpha2B-adrenoceptor gene as a risk factor for prehospital fatal myocardial infarction and sudden cardiac death. J Am Coll Cardiol 2003;41:190–4.
107. Luu M, Stevenson WG, Stevenson LW, et al. Diverse mechanisms of unexpected cardiac arrest in advanced heart failure. Circulation 1989;80:1675–80.
108. Bayes de Luna A, Coumel P, Leclercq JF. Ambulatory sudden cardiac death: mechanisms of production of fatal arrhythmia on the basis of data from 157 cases. Am Heart J 1989;117:151–9.
109. Amiodarone Trials Meta-Analysis Investigators. Effect of prophylactic amiodarone on mortality after acute myocardial infarction and in congestive heart failure: meta-analysis of individual data from 6500 patients in randomised trials. Lancet 1997;350:1417–24.
110. Alberte C, Zipes DP. Use of nonantiarrhythmic drugs for prevention of sudden cardiac death. J Cardiovasc Electrophysiol 2003;14:S87–S95.
111. Raitt M, Connor W, Morris C, et al. Antiarrhythmic effects of n-3 polyunsaturated fatty acids in survivors of ventricular tachyarrhythmias (abstr). Circulation 2003;108:2723.

112. Zipes DP, Wellens HJ. Sudden cardiac death. Circulation 1998;98: 2334–51.
113. Gardner RA, Kruyer WB, Pickard JS, et al. Nonsustained ventricular tachycardia in 193 U.S. military aviators: long-term follow-up. Aviat Space Environ Med 2000;71:783–90.
114. Priori SG, Barhanin J, Hauer RN, et al. Genetic and molecular basis of cardiac arrhythmias: impact on clinical management parts I and II. Circulation 1999;99:518–28.
115. Priori SG, Barhanin J, Hauer RN, et al. Genetic and molecular basis of cardiac arrhythmias: impact on clinical management, part III. Circulation 1999;99:674–81.
116. Buxton AE, Lee KL, DiCarlo L, et al. Electrophysiologic testing to identify patients with coronary artery disease who are at risk for sudden death. Multicenter Unsustained Tachycardia Trial Investigators. N Engl J Med 2000;342:1937–45.
117. Rankovic V, Karha J, Passman R, et al. Predictors of appropriate implantable cardioverter-defibrillator therapy in patients with idiopathic dilated cardiomyopathy. Am J Cardiol 2002;89:1072–6.
118. Maron BJ. Risk stratification and prevention of sudden death in hypertrophic cardiomyopathy. Cardiol Rev 2002;10:173–81.
119. Zimetbaum P, Josephson ME. Evaluation of patients with palpitations. N Engl J Med 1998;338:1369–73.
120. Brignole M, Alboni P, Benditt DG, et al. Guidelines on management (diagnosis and treatment) of syncope-update 2004. Executive Summary. Eur Heart J 2004;25:2054–72.
121. Mittal S, Iwai S, Stein KM, et al. Long-term outcome of patients with unexplained syncope treated with an electrophysiologic-guided approach in the implantable cardioverter-defibrillator era. J Am Coll Cardiol 1999;34:1082–9.
122. Farmer DM, Swygman CA, Wang PJ, et al. Evidence that nonsustained polymorphic ventricular tachycardia causes syncope (data from implantable cardioverter defibrillators). Am J Cardiol 2003;91:606–9.
123. Steinberg JS, Beckman K, Greene HL, et al. Follow-up of patients with unexplained syncope and inducible ventricular tachyarrhythmias: analysis of the AVID registry and an AVID substudy. Antiarrhythmics Versus Implantable Defibrillators. J Cardiovasc Electrophysiol 2001;12:996–1001.
124. Andrews NP, Fogel RI, Pelargonio G, et al. Implantable defibrillator event rates in patients with unexplained syncope and inducible sustained ventricular tachyarrhythmias: a comparison with patients known to have sustained ventricular tachycardia. J Am Coll Cardiol 1999;34:2023–30.
125. Link MS, Saeed M, Gupta N, et al. Inducible ventricular flutter and fibrillation predict for arrhythmia occurrence in coronary artery disease patients presenting with syncope of unknown origin. J Cardiovasc Electrophysiol 2002;13:1103–8.
126. Fonarow GC, Feliciano Z, Boyle NG, et al. Improved survival in patients with nonischemic advanced heart failure and syncope treated with an implantable cardioverter-defibrillator. Am J Cardiol 2000;85:981–5.
127. Garcia-Moran E, Mont L, Cuesta A, et al. Low recurrence of syncope in patients with inducible sustained ventricular tachyarrhythmias treated with an implantable cardioverter-defibrillator. Eur Heart J 2002;23:901–7.
128. Pires LA, May LM, Ravi S, et al. Comparison of event rates and survival in patients with unexplained syncope without documented ventricular tachyarrhythmias versus patients with documented sustained ventricular tachyarrhythmias both treated with implantable cardioverter-defibrillators. Am J Cardiol 2000;85:725–8.
129. LeLorier P, Krahn AD, Klein GJ, et al. Comparison of patients with syncope with left ventricular dysfunction and negative electrophysiologic testing to cardiac arrest survivors and patients with syncope and preserved left ventricular function and impact of an implantable defibrillator. Am J Cardiol 2002;90:77–9.
130. Schwartz PJ, Moss AJ, Vincent GM, et al. Diagnostic criteria for the long QT syndrome. An update. Circulation 1993;88:782–4.
131. Anderson JL, Hallstrom AP, Epstein AE, et al. Design and results of the antiarrhythmics vs implantable defibrillators (AVID) registry. The AVID Investigators. Circulation 1999;99:1692–9.
132. Hariman RJ, Hu DY, Gallastegui JL, et al. Long-term follow-up in patients with incessant ventricular tachycardia. Am J Cardiol 1990; 66:831–6.
133. Mitchell LB, Pineda EA, Titus JL, et al. Sudden death in patients with implantable cardioverter defibrillators: the importance of post-shock electromechanical dissociation. J Am Coll Cardiol 2002;39: 1323–8.
134. De Bacquer D, De Backer G, Kornitzer M, et al. Prognostic value of ischemic electrocardiographic findings for cardiovascular mortality in men and women. J Am Coll Cardiol 1998;32:680–5.
135. Kors JA, de Bruyne MC, Hoes AW, et al. T-loop morphology as a marker of cardiac events in the elderly. J Electrocardiol 1998;31 Suppl:54–9.
136. Kors JA, de Bruyne MC, Hoes AW, et al. T axis as an indicator of risk of cardiac events in elderly people. Lancet 1998;352:601–5.
137. Schouten EG, Dekker JM, Meppelink P, et al. QT interval prolongation predicts cardiovascular mortality in an apparently healthy population. Circulation 1991;84:1516–23.
138. Algra A, Tijssen JG, Roelandt Jr., et al. QT interval variables from 24 hour electrocardiography and the two year risk of sudden death. Br Heart J 1993;70:43–8.
139. Maury P, Couderc P, Delay M, et al. Electrical storm in Brugada syndrome successfully treated using isoprenaline. Europace 2004;6: 130–3.
140. Gussak I, Brugada P, Brugada J, et al. Idiopathic short QT interval: a new clinical syndrome? Cardiology 2000;94:99–102.
141. Gibbons RJ, Balady GJ, Bricker JT, et al. ACC/AHA 2002 guideline update for exercise testing: summary article. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1997 Exercise Testing Guidelines). J Am Coll Cardiol 2002;40:1531–40.
142. Podrid PJ, Graboys TB. Exercise stress testing in the management of cardiac rhythm disorders. Med Clin North Am 1984; 68:1139–52.
143. Califf RM, McKinnis RA, McNeer JF, et al. Prognostic value of ventricular arrhythmias associated with treadmill exercise testing in patients studied with cardiac catheterization for suspected ischemic heart disease. J Am Coll Cardiol 1983;2:1060–7.
144. Young DZ, Lampert S, Graboys TB, et al. Safety of maximal exercise testing in patients at high risk for ventricular arrhythmia. Circulation 1984;70:184–91.
145. Linzer M, Pritchett EL, Pontinen M, et al. Incremental diagnostic yield of loop electrocardiographic recorders in unexplained syncope. Am J Cardiol 1990;66:214–9.
146. Krahn AD, Klein GJ, Yee R, et al. Use of an extended monitoring strategy in patients with problematic syncope. Reveal Investigators. Circulation 1999;99:406–10.
147. Steinberg JS, Berbari EJ. The signal-averaged electrocardiogram: update on clinical applications. J Cardiovasc Electrophysiol 1996;7: 972–88.
148. Cook Jr., Flack JE, Gregory CA, et al. Influence of the preoperative signal-averaged electrocardiogram on left ventricular function after coronary artery bypass graft surgery in patients with left ventricular dysfunction. The CABG Patch Trial. Am J Cardiol 1998;82:285–9.
149. Steinberg JS, Prystowsky E, Freedman RA, et al. Use of the signal-averaged electrocardiogram for predicting inducible ventricular tachycardia in patients with unexplained syncope: relation to clinical variables in a multivariate analysis. J Am Coll Cardiol 1994;23:99–106.
150. Ikeda T, Saito H, Tanno K, et al. T-wave alternans as a predictor for sudden cardiac death after myocardial infarction. Am J Cardiol 2002;89:79–82.
151. Hohnloser SH, Klingenheben T, Bloomfield D, et al. Usefulness of microvolt T-wave alternans for prediction of ventricular tachyarrhythmic events in patients with dilated cardiomyopathy: results from a prospective observational study. J Am Coll Cardiol 2003;41: 2220–4.
152. Hohnloser SH, Kuck KH, Dorian P, et al. Prophylactic use of an implantable cardioverter-defibrillator after acute myocardial infarction. N Engl J Med 2004;351:2481–8.
153. Bloomfield DM, Bigger JT, Steinman RC, et al. Microvolt T-wave alternans and the risk of death or sustained ventricular arrhythmias in patients with left ventricular dysfunction. J Am Coll Cardiol 2006;47:456–63.
154. Chow T, Kereiakes DJ, Bartone C, et al. Prognostic utility of microvolt T-wave alternans in risk stratification of patients with ischemic cardiomyopathy. J Am Coll Cardiol 2006;47:1820–7.

155. Bloomfield DM, Steinman RC, Namerow PB, et al. Microvolt T-wave alternans distinguishes between patients likely and patients not likely to benefit from implanted cardiac defibrillator therapy: a solution to the Multicenter Automatic Defibrillator Implantation Trial (MADIT) II conundrum. Circulation 2004;110:1885–9.
156. Zuanetti G, Neilson JM, Latini R, et al. Prognostic significance of heart rate variability in post-myocardial infarction patients in the fibrinolytic era. The GISSI-2 results. Gruppo Italiano per lo Studio della Sopravvivenza nell' Infarto Miocardico. Circulation 1996;94: 432–6.
157. La Rovere MT, Bigger JT Jr., Marcus FI, et al. Baroreflex sensitivity and heart-rate variability in prediction of total cardiac mortality after myocardial infarction. ATRAMI (Autonomic Tone and Reflexes After Myocardial Infarction) Investigators. Lancet 1998;351:478–84.
158. Malik M, Camm AJ, Janse MJ, et al. Depressed heart rate variability identifies postinfarction patients who might benefit from prophylactic treatment with amiodarone: a substudy of EMIAT (The European Myocardial Infarct Amiodarone Trial). J Am Coll Cardiol 2000;35:1263–75.
159. Camm AJ, Pratt CM, Schwartz PJ, et al. Mortality in patients after a recent myocardial infarction: a randomized, placebo-controlled trial of azimilide using heart rate variability for risk stratification. Circulation 2004;109:990–6.
160. Farrell TG, Paul V, Cripps TR, et al. Baroreflex sensitivity and electrophysiological correlates in patients after acute myocardial infarction. Circulation 1991;83:945–52.
161. Farrell TG, Odemuyiwa O, Bashir Y, et al. Prognostic value of baroreflex sensitivity testing after acute myocardial infarction. Br Heart J 1992;67:129–37.
162. Hohnloser SH, Klingenheben T, Li YG, et al. T wave alternans as a predictor of recurrent ventricular tachyarrhythmias in ICD recipients: prospective comparison with conventional risk markers. J Cardiovasc Electrophysiol 1998;9:1258–68.
163. Cheitlin MD, Alpert JS, Armstrong WF, et al. ACC/AHA guidelines for the clinical application of echocardiography. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Clinical Application of Echocardiography). Developed in collaboration with the American Society of Echocardiography. Circulation 1997;95: 1686–744.
164. Cheitlin MD, Armstrong WF, Aurigemma GP, et al. ACC/AHA/ASE 2003 guideline update for the clinical application of echocardiography—summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/ASE Committee to Update the 1997 Guidelines for the Clinical Application of Echocardiography). J Am Coll Cardiol 2003;42:954–70.
165. Schiller NB, Shah PM, Crawford M, et al. Recommendations for quantitation of the left ventricle by two-dimensional echocardiography. American Society of Echocardiography Committee on Standards, Subcommittee on Quantitation of Two-Dimensional Echocardiograms. J Am Soc Echocardiogr 1989;2:358–67.
166. Grothues F, Smith GC, Moon JC, et al. Comparison of interstudy reproducibility of cardiovascular magnetic resonance with two-dimensional echocardiography in normal subjects and in patients with heart failure or left ventricular hypertrophy. Am J Cardiol 2002;90:29–34.
167. Chuang ML, Hibberd MG, Salton CJ, et al. Importance of imaging method over imaging modality in noninvasive determination of left ventricular volumes and ejection fraction: assessment by two- and three-dimensional echocardiography and magnetic resonance imaging. J Am Coll Cardiol 2000;35:477–84.
168. Foster RE, Johnson DB, Barilla F, et al. Changes in left ventricular mass and volumes in patients receiving angiotensin-converting enzyme inhibitor therapy for left ventricular dysfunction after Q-wave myocardial infarction. Am Heart J 1998;136:269–75.
169. Kies P, Bootsma M, Bax J, et al. Arrhythmogenic right ventricular dysplasia/cardiomyopathy: screening, diagnosis, and treatment. Heart Rhythm 2006;3:225–34.
170. Marcus F, Towbin JA, Zareba W, et al. Arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVD/C): a multidisciplinary study: design and protocol. Circulation 2003;107:2975–8.
171. Lima JA, Desai MY. Cardiovascular magnetic resonance imaging: current and emerging applications. J Am Coll Cardiol 2004;44: 1164–71.
172. Diethelm L, Simonson JS, Dery R, et al. Determination of left ventricular mass with ultrafast CT and two-dimensional echocardiography. Radiology 1989;171:213–7.
173. Yamaoka O, Fujioka H, Haque T, et al. Low-dose dobutamine stress test for the evaluation of cardiac function using ultrafast computed tomography. Clin Cardiol 1993;16:473–9.
174. Thomson HL, Basmadjian AJ, Rainbird AJ, et al. Contrast echocardiography improves the accuracy and reproducibility of left ventricular remodeling measurements: a prospective, randomly assigned, blinded study. J Am Coll Cardiol 2001;38:867–75.
175. Rumberger JA, Simons DB, Fitzpatrick LA, et al. Coronary artery calcium area by electron-beam computed tomography and coronary atherosclerotic plaque area. A histopathologic correlative study. Circulation 1995;92:2157–62.
176. He ZX, Hedrick TD, Pratt CM, et al. Severity of coronary artery calcification by electron beam computed tomography predicts silent myocardial ischemia. Circulation 2000;101:244–51.
177. Klocke FJ, Baird MG, Lorell BH, et al. ACC/AHA/ASNC guidelines for the clinical use of cardiac radionuclide imaging—executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/ASNC Committee to Revise the 1995 Guidelines for the Clinical Use of Cardiac Radionuclide Imaging). J Am Coll Cardiol 2003;42:1318–33.
178. Wellens HJ, Schuilenburg RM, Durrer D. Electrical stimulation of the heart in patients with ventricular tachycardia. Circulation 1972;46:216–26.
179. Ross DL, Farre J, Bar FW, et al. Comprehensive clinical electrophysiologic studies in the investigation of documented or suspected tachycardias. Time, staff, problems and costs. Circulation 1980;61: 1010–6.
180. Freedman RA, Swerdlow CD, Soderholm-Difatte V, et al. Prognostic significance of arrhythmia inducibility or noninducibility at initial electrophysiologic study in survivors of cardiac arrest. Am J Cardiol 1988;61:578–82.
181. Wilber DJ, Garan H, Finkelstein D, et al. Out-of-hospital cardiac arrest. Use of electrophysiologic testing in the prediction of long-term outcome. N Engl J Med 1988;318:19–24.
182. Kuchar DL, Rottman J, Berger E, et al. Prediction of successful suppression of sustained ventricular tachyarrhythmias by serial drug testing from data derived at the initial electrophysiologic study. J Am Coll Cardiol 1988;12:982–8.
183. Fromer M, Shenasa M. A critical reappraisal of serial electrophysiologic drug testing for sustained ventricular tachycardia. Am Heart J 1987;114:1537–41.
184. Bachinsky WB, Linzer M, Weld L, et al. Usefulness of clinical characteristics in predicting the outcome of electrophysiologic studies in unexplained syncope. Am J Cardiol 1992;69:1044–9.
185. Swerdlow CD, Bardy GH, McAnulty J, et al. Determinants of induced sustained arrhythmias in survivors of out-of-hospital ventricular fibrillation. Circulation 1987;76:1053–60.
186. Spielman SR, Greenspan AM, Kay HR, et al. Electrophysiologic testing in patients at high risk for sudden cardiac death. I. Nonsustained ventricular tachycardia and abnormal ventricular function. J Am Coll Cardiol 1985;6:31–40.
187. Baerman JM, Morady F, de Buitleir M, et al. A prospective comparison of programmed ventricular stimulation with triple extrastimuli versus single and double extrastimuli during infusion of isoproterenol. Am Heart J 1989;117:342–7.
188. Summitt J, Rosenheck S, Kou WH, et al. Effect of basic drive cycle length on the yield of ventricular tachycardia during programmed ventricular stimulation. Am J Cardiol 1990;65:49–52.
189. Morady F, DiCarlo L, Winston S, et al. A prospective comparison of triple extrastimuli and left ventricular stimulation in studies of ventricular tachycardia induction. Circulation 1984;70:52–7.
190. Morady F, Kadish A, Rosenheck S, et al. Concealed entrainment as a guide for catheter ablation of ventricular tachycardia in patients with prior myocardial infarction. J Am Coll Cardiol 1991;17:678–89.

191. Zipes DP, Foster PR, Troup PJ, et al. Atrial induction of ventricular tachycardia: reentry versus triggered automaticity. Am J Cardiol 1979;44:1–8.
192. Moss AJ, Hall WJ, Cannom DS, et al. Improved survival with an implanted defibrillator in patients with coronary disease at high risk for ventricular arrhythmia. Multicenter Automatic Defibrillator Implantation Trial Investigators. N Engl J Med 1996;335:1933–40.
193. Pires LA, Lehmann MH, Buxton AE, et al. Differences in inducibility and prognosis of in-hospital versus out-of-hospital identified nonsustained ventricular tachycardia in patients with coronary artery disease: clinical and trial design implications. J Am Coll Cardiol 2001;38:1156–62.
194. Buxton AE, Lee KL, DiCarlo L, et al. Nonsustained ventricular tachycardia in coronary artery disease: relation to inducible sustained ventricular tachycardia. MUSTT Investigators. Ann Intern Med 1996;125:35–9.
195. Wyse DG, Talajic M, Hafley GE, et al. Antiarrhythmic drug therapy in the Multicenter UnSustained Tachycardia Trial (MUSTT): drug testing and as-treated analysis. J Am Coll Cardiol 2001;38:344–51.
196. Sesselberg HW, Moss AJ, Steinberg J, et al. Factors associated with ventricular inducibility in the MADIT-II study population. Am J Cardiol 2003;91:1002–4, A7.
197. Schmitt C, Barthel P, Ndrepepa G, et al. Value of programmed ventricular stimulation for prophylactic internal cardioverter-defibrillator implantation in postinfarction patients preselected by noninvasive risk stratifiers. J Am Coll Cardiol 2001;37:1901–7.
198. Buxton AE, Lee KL, Hafley GE, et al. Relation of ejection fraction and inducible ventricular tachycardia to mode of death in patients with coronary artery disease: an analysis of patients enrolled in the multicenter unsustained tachycardia trial. Circulation 2002;106: 2466–72.
199. Wilber DJ, Olshansky B, Moran JF, et al. Electrophysiological testing and nonsustained ventricular tachycardia. Use and limitations in patients with coronary artery disease and impaired ventricular function. Circulation 1990;82:350–8.
200. Schlapfer J, Rapp F, Kappenberger L, et al. Electrophysiologically guided amiodarone therapy versus the implantable cardioverter-defibrillator for sustained ventricular tachyarrhythmias after myocardial infarction: results of long-term follow-up. J Am Coll Cardiol 2002;39:1813–9.
201. Gurevitz O, Viskin S, Glikson M, et al. Long-term prognosis of inducible ventricular flutter: not an innocent finding. Am Heart J 2004;147:649–54.
202. Viskin S, Justo D, Halkin A, et al. Long QT syndrome caused by noncardiac drugs. Prog Cardiovasc Dis 2003;45:415–27.
203. Oseran DS, Gang ES, Hamer AW, et al. Mode of stimulation versus response: validation of a protocol for induction of ventricular tachycardia. Am Heart J 1985;110:646–51.
204. Milner PG, Dimarco JP, Lerman BB. Electrophysiological evaluation of sustained ventricular tachyarrhythmias in idiopathic dilated cardiomyopathy. Pacing Clin Electrophysiol 1988;11:562–8.
205. Bhandari AK, Shapiro WA, Morady F, et al. Electrophysiologic testing in patients with the long QT syndrome. Circulation 1985; 71:63–71.
206. Brugada J, Brugada R, Brugada P. Determinants of sudden cardiac death in individuals with the electrocardiographic pattern of Brugada syndrome and no previous cardiac arrest. Circulation 2003;108:3092–6.
207. Brugada P, Brugada R, Mont L, et al. Natural history of Brugada syndrome: the prognostic value of programmed electrical stimulation of the heart. J Cardiovasc Electrophysiol 2003;14:455–7.
208. Priori SG, Grillo M. To the editor. J Cardiovasc Electrophysiol 2003;14:1131–3.
209. Ito S, Tada H, Naito S, et al. Development and validation of an ECG algorithm for identifying the optimal ablation site for idiopathic ventricular outflow tract tachycardia. J Cardiovasc Electrophysiol 2003;14:1280–6.
210. O'Donnell D, Cox D, Bourke J, et al. Clinical and electrophysiological differences between patients with arrhythmogenic right ventricular dysplasia and right ventricular outflow tract tachycardia. Eur Heart J 2003;24:801–10.
211. Bass EB, Elson JJ, Fogoros RN, et al. Long-term prognosis of patients undergoing electrophysiologic studies for syncope of unknown origin. Am J Cardiol 1988;62:1186–91.
212. Denes P, Uretz E, Ezri MD, et al. Clinical predictors of electrophysiologic findings in patients with syncope of unknown origin. Arch Intern Med 1988;148:1922–8.
213. Doherty JU, Pembrook-Rogers D, Grogan EW, et al. Electrophysiologic evaluation and follow-up characteristics of patients with recurrent unexplained syncope and presyncope. Am J Cardiol 1985;55:703–8.
214. Click RL, Gersh BJ, Sugrue DD, et al. Role of invasive electrophysiologic testing in patients with symptomatic bundle branch block. Am J Cardiol 1987;59:817–23.
215. Morady F, Higgins J, Peters RW, et al. Electrophysiologic testing in bundle branch block and unexplained syncope. Am J Cardiol 1984;54:587–91.
216. Kushner JA, Kou WH, Kadish AH, et al. Natural history of patients with unexplained syncope and a nondiagnostic electrophysiologic study. J Am Coll Cardiol 1989;14:391–6.
217. Brignole M, Menozzi C, Moya A, et al. Mechanism of syncope in patients with bundle branch block and negative electrophysiological test. Circulation 2001;104:2045–50.
218. Fujimura O, Yee R, Klein GJ, et al. The diagnostic sensitivity of electrophysiologic testing in patients with syncope caused by transient bradycardia. N Engl J Med 1989;321:1703–7.
219. Krahn AD, Klein GJ, Yee R, et al. Randomized assessment of syncope trial: conventional diagnostic testing versus a prolonged monitoring strategy. Circulation 2001;104:46–51.
220. Alboni P, Brignole M, Menozzi C, et al. Diagnostic value of history in patients with syncope with or without heart disease. J Am Coll Cardiol 2001;37:1921–8.
221. Leitch JW, Klein GJ, Yee R, et al. Syncope associated with supraventricular tachycardia. An expression of tachycardia rate or vasomotor response? Circulation 1992;85:1064–71.
222. Lacroix D, Dubuc M, Kus T, et al. Evaluation of arrhythmic causes of syncope: correlation between Holter monitoring, electrophysiologic testing, and body surface potential mapping. Am Heart J 1991;122:1346–54.
223. Middlekauff HR, Stevenson WG, Stevenson LW, et al. Syncope in advanced heart failure: high risk of sudden death regardless of origin of syncope. J Am Coll Cardiol 1993;21:110–6.
224. Nienaber CA, Hiller S, Spielmann RP, et al. Syncope in hypertrophic cardiomyopathy: multivariate analysis of prognostic determinants. J Am Coll Cardiol 1990;15:948–55.
225. Menozzi C, Brignole M, Garcia-Civera R, et al. Mechanism of syncope in patients with heart disease and negative electrophysiologic test. Circulation 2002;105:2741–5.
226. Bailey JJ, Berson AS, Handelsman H, et al. Utility of current risk stratification tests for predicting major arrhythmic events after myocardial infarction. J Am Coll Cardiol 2001;38:1902–11.
227. Cannom DS, Prystowsky EN. Management of ventricular arrhythmias: detection, drugs, and devices. JAMA 1999;281:172–9.
228. Domanski MJ, Epstein A, Hallstrom A, et al. Survival of antiarrhythmic or implantable cardioverter defibrillator treated patients with varying degrees of left ventricular dysfunction who survived malignant ventricular arrhythmias. J Cardiovasc Electrophysiol 2002;13:580–3.
229. Hallstrom AP, Greene HL, Wilkoff BL, et al. Relationship between rehospitalization and future death in patients treated for potentially lethal arrhythmia. J Cardiovasc Electrophysiol 2001;12:990–5.
230. Fromer M, Wietholt D. Algorithm for the prevention of ventricular tachycardia onset: the Prevent Study. Am J Cardiol 1999;83:45D–7D.
231. Lerman BB, Stein KM, Markowitz SM, et al. Ventricular arrhythmias in normal hearts. Cardiol Clin 2000;18:265–91, vii.
232. Nogami A. Idiopathic left ventricular tachycardia: assessment and treatment. Card Electrophysiol Rev 2002;6:448–57.
233. Pfammatter JP, Paul T. Idiopathic ventricular tachycardia in infancy and childhood: a multicenter study on clinical profile and outcome. Working Group on Dysrhythmias and Electrophysiology of the Association for European Pediatric Cardiology. J Am Coll Cardiol 1999;33:2067–72.
234. Roden DM. Mechanisms and management of proarrhythmia. Am J Cardiol 1998;82:49I–57I.
235. Tresch DD. Evaluation and management of cardiac arrhythmias in the elderly. Med Clin North Am 2001;85:527–50, xii.

236. De Ponti F, Poluzzi E, Cavalli A, et al. Safety of non-antiarrhythmic drugs that prolong the QT interval or induce torsade de pointes: an overview. Drug Saf 2002;25:263–86.
237. De Ponti F, Poluzzi E, Vaccheri A, et al. Non-antiarrhythmic drugs prolonging the QT interval: considerable use in seven countries. Br J Clin Pharmacol 2002;54:171–7.
238. Haddad PM, Anderson IM. Antipsychotic-related QTc prolongation, torsade de pointes and sudden death. Drugs 2002;62:1649–71.
239. Haverkamp W, Monnig G, Schulze-Bahr E, et al. Physician-induced torsade de pointes—therapeutic implications. Cardiovasc Drugs Ther 2002;16:101–9.
240. Vaughan Williams EM. A classification of antiarrhythmic actions reassessed after a decade of new drugs. J Clin Pharmacol 1984;24:129–47.
241. The Sicilian Gambit. A new approach to the classification of antiarrhythmic drugs based on their actions on arrhythmogenic mechanisms. Task Force of the Working Group on Arrhythmias of the European Society of Cardiology. Circulation 1991;84:1831–51.
242. Reiter MJ, Reiffel JA. Importance of beta blockade in the therapy of serious ventricular arrhythmias. Am J Cardiol 1998;82:9I–19I.
243. Ellison KE, Hafley GE, Hickey K, et al. Effect of beta-blocking therapy on outcome in the Multicenter UnSustained Tachycardia Trial (MUSTT). Circulation 2002;106:2694–9.
244. Reiken S, Wehrens XH, Vest JA, et al. Beta-blockers restore calcium release channel function and improve cardiac muscle performance in human heart failure. Circulation 2003;107:2459–66.
245. Connolly SJ. Meta-analysis of antiarrhythmic drug trials. Am J Cardiol 1999;84:90R–3R.
246. Steinberg JS, Martins J, Sadanandan S, et al. Antiarrhythmic drug use in the implantable defibrillator arm of the Antiarrhythmics Versus Implantable Defibrillators (AVID) study. Am Heart J 2001;142:520–9.
247. Farre J, Romero J, Rubio JM, et al. Amiodarone and "primary" prevention of sudden death: critical review of a decade of clinical trials. Am J Cardiol 1999;83:55D–63D.
248. Cleland JG, Ghosh J, Freemantle N, et al. Clinical trials update and cumulative meta-analyses from the American College of Cardiology: WATCH, SCD-HeFT, DINAMIT, CASINO, INSPIRE, STRATUS-US, RIO-Lipids and cardiac resynchronisation therapy in heart failure. Eur J Heart Fail 2004;6:501–8.
249. Kuhlkamp V, Mewis C, Mermi J, et al. Suppression of sustained ventricular tachyarrhythmias: a comparison of d,l-sotalol with no antiarrhythmic drug treatment. J Am Coll Cardiol 1999;33:46–52.
250. Janse MJ, Malik M, Camm AJ, et al. Identification of post acute myocardial infarction patients with potential benefit from prophylactic treatment with amiodarone. A substudy of EMIAT (the European Myocardial Infarct Amiodarone Trial). Eur Heart J 1998;19:85–95.
251. Boutitie F, Boissel JP, Connolly SJ, et al. Amiodarone interaction with beta-blockers: analysis of the merged EMIAT (European Myocardial Infarct Amiodarone Trial) and CAMIAT (Canadian Amiodarone Myocardial Infarction Trial) databases. The EMIAT and CAMIAT Investigators. Circulation 1999;99:2268–75.
252. Dorian P, Borggrefe M, Al-Khalidi HR, et al. Placebo-controlled, randomized clinical trial of azimilide for prevention of ventricular tachyarrhythmias in patients with an implantable cardioverter defibrillator. Circulation 2004;110:3646–54.
253. Pacifico A, Hohnloser SH, Williams JH, et al. Prevention of implantable-defibrillator shocks by treatment with sotalol. d,l-Sotalol Implantable Cardioverter-Defibrillator Study Group. N Engl J Med 1999;340:1855–62.
254. Connolly SJ, Dorian P, Roberts RS, et al. Comparison of beta-blockers, amiodarone plus beta-blockers, or sotalol for prevention of shocks from implantable cardioverter defibrillators: the OPTIC Study: a randomized trial. JAMA 2006;295:165–71.
255. Issa ZF, Zhou X, Ujhelyi MR, et al. Thoracic spinal cord stimulation reduces the risk of ischemic ventricular arrhythmias in a postinfarction heart failure canine model. Circulation 2005;111:3217–20.
256. Issa ZF, Ujhelyi MR, Hildebrand KR, et al. Intrathecal clonidine reduces the incidence of ischemia-provoked ventricular arrhythmias in a canine postinfarction heart failure model. Heart Rhythm 2005;2:1122–7.
257. Mahajan A, Moore J, Cesario DA, et al. Use of thoracic epidural anesthesia for management of electrical storm: a case report. Heart Rhythm 2005;2:1359–62.
258. Pitt B, Remme W, Zannad F, et al. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. N Engl J Med 2003;348:1309–21.
259. Dries DL, Domanski MJ, Waclawiw MA, et al. Effect of antithrombotic therapy on risk of sudden coronary death in patients with congestive heart failure. Am J Cardiol 1997;79:909–13.
260. Billman GE, Kang JX, Leaf A. Prevention of ischemia-induced cardiac sudden death by n-3 polyunsaturated fatty acids in dogs. Lipids 1997;32:1161–8.
261. Leaf A, Kang JX, Xiao YF, et al. Clinical prevention of sudden cardiac death by n-3 polyunsaturated fatty acids and mechanism of prevention of arrhythmias by n-3 fish oils. Circulation 2003;107:2646–52.
262. Raitt MH, Connor WE, Morris C, et al. Fish oil supplementation and risk of ventricular tachycardia and ventricular fibrillation in patients with implantable defibrillators: a randomized controlled trial. JAMA 2005;293:2884–91.
263. Leaf A, Albert CM, Josephson M, et al. Prevention of fatal arrhythmias in high-risk subjects by fish oil n-3 fatty acid intake. Circulation 2005;112:2762–8.
264. Mitchell LB, Powell JL, Gillis AM, et al. Are lipid-lowering drugs also antiarrhythmic drugs? An analysis of the Antiarrhythmics versus Implantable Defibrillators (AVID) trial. J Am Coll Cardiol 2003;42:81–7.
265. Bigger JT Jr. Prophylactic use of implanted cardiac defibrillators in patients at high risk for ventricular arrhythmias after coronary-artery bypass graft surgery. Coronary Artery Bypass Graft (CABG) Patch Trial Investigators. N Engl J Med 1997;337:1569–75.
266. The Antiarrhythmics versus Implantable Defibrillators (AVID) Investigators. A comparison of antiarrhythmic-drug therapy with implantable defibrillators in patients resuscitated from near-fatal ventricular arrhythmias. N Engl J Med 1997;337:1576–83.
267. Buxton AE, Lee KL, Fisher JD, et al. A randomized study of the prevention of sudden death in patients with coronary artery disease. Multicenter Unsustained Tachycardia Trial Investigators. N Engl J Med 1999;341:1882–90.
268. Moss AJ, Zareba W, Hall WJ, et al. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. N Engl J Med 2002;346:877–83.
269. Lee DS, Green LD, Liu PP, et al. Effectiveness of implantable defibrillators for preventing arrhythmic events and death: a meta-analysis. J Am Coll Cardiol 2003;41:1573–82.
270. Ezekowitz JA, Armstrong PW, McAlister FA. Implantable cardioverter defibrillators in primary and secondary prevention: a systematic review of randomized, controlled trials. Ann Intern Med 2003;138:445–52.
271. Wilkoff BL, Cook Jr., Epstein AE, et al. Dual-chamber pacing or ventricular backup pacing in patients with an implantable defibrillator: the Dual Chamber and VVI Implantable Defibrillator (DAVID) trial. JAMA 2002;288:3115–23.
272. Marenco JP, Wang PJ, Link MS, et al. Improving survival from sudden cardiac arrest: the role of the automated external defibrillator. JAMA 2001;285:1193–200.
273. Priori SG, Bossaert LL, Chamberlain DA, et al. ESC-ERC recommendations for the use of automated external defibrillators (AEDs) in Europe. Eur Heart J 2004;25:437–45.
274. Koster RW. Automatic external defibrillator: key link in the chain of survival. J Cardiovasc Electrophysiol 2002;13:S92–S95.
275. Valenzuela TD, Roe DJ, Nichol G, et al. Outcomes of rapid defibrillation by security officers after cardiac arrest in casinos. N Engl J Med 2000;343:1206–9.
276. Caffrey SL, Willoughby PJ, Pepe PE, et al. Public use of automated external defibrillators. N Engl J Med 2002;347:1242–7.
277. Page RL, Joglar JA, Kowal RC, et al. Use of automated external defibrillators by a U.S. airline. N Engl J Med 2000;343:1210–6.
278. Silva RM, Mont L, Nava S, et al. Radiofrequency catheter ablation for arrhythmic storm in patients with an implantable cardioverter defibrillator. Pacing Clin Electrophysiol 2004;27:971–5.
279. Pappone C, Santinelli V, Manguso F, et al. A randomized study of prophylactic catheter ablation in asymptomatic patients with

the Wolff-Parkinson-White syndrome. N Engl J Med 2003;349:1803–11.
280. Haissaguerre M, Shoda M, Jais P, et al. Mapping and ablation of idiopathic ventricular fibrillation. Circulation 2002;106:962–7.
281. Takemoto M, Yoshimura H, Ohba Y, et al. Radiofrequency catheter ablation of premature ventricular complexes from right ventricular outflow tract improves left ventricular dilation and clinical status in patients without structural heart disease. J Am Coll Cardiol 2005;45:1259–65.
282. Scheinman MM. NASPE survey on catheter ablation. Pacing Clin Electrophysiol 1995;18:1474–8.
283. Twidale N, Hazlitt HA, Berbari EJ, et al. Late potentials are unaffected by radiofrequency catheter ablation in patients with ventricular tachycardia. Pacing Clin Electrophysiol 1994;17: 157–65.
284. SippensGroenewegen A, Spekhorst H, van Hemel NM, et al. Localization of the site of origin of postinfarction ventricular tachycardia by endocardial pace mapping. Body surface mapping compared with the 12-lead electrocardiogram. Circulation 1993;88: 2290–306.
285. Morady F, Harvey M, Kalbfleisch SJ, et al. Radiofrequency catheter ablation of ventricular tachycardia in patients with coronary artery disease. Circulation 1993;87:363–72.
286. Stevenson WG, Khan H, Sager P, et al. Identification of reentry circuit sites during catheter mapping and radiofrequency ablation of ventricular tachycardia late after myocardial infarction. Circulation 1993;88:1647–70.
287. Cohen TJ, Chien WW, Lurie KG, et al. Radiofrequency catheter ablation for treatment of bundle branch reentrant ventricular tachycardia: results and long-term follow-up. J Am Coll Cardiol 1991; 18:1767–73.
288. Tchou P, Jazayeri M, Denker S, et al. Transcatheter electrical ablation of right bundle branch. A method of treating macroreentrant ventricular tachycardia attributed to bundle branch reentry. Circulation 1988;78:246–57.
289. Nakagawa H, Beckman KJ, McClelland JH, et al. Radiofrequency catheter ablation of idiopathic left ventricular tachycardia guided by a Purkinje potential. Circulation 1993;88:2607–17.
290. Page RL, Shenasa H, Evans JJ, et al. Radiofrequency catheter ablation of idiopathic recurrent ventricular tachycardia with right bundle branch block, left axis morphology. Pacing Clin Electrophysiol 1993;16:327–36.
291. Klein LS, Shih HT, Hackett FK, et al. Radiofrequency catheter ablation of ventricular tachycardia in patients without structural heart disease. Circulation 1992;85:1666–74.
292. Calkins H, Kalbfleisch SJ, el-Atassi R, et al. Relation between efficacy of radiofrequency catheter ablation and site of origin of idiopathic ventricular tachycardia. Am J Cardiol 1993;71:827–33.
293. Kim YH, Sosa-Suarez G, Trouton TG, et al. Treatment of ventricular tachycardia by transcatheter radiofrequency ablation in patients with ischemic heart disease. Circulation 1994;89:1094–102.
294. Coggins DL, Lee RJ, Sweeney J, et al. Radiofrequency catheter ablation as a cure for idiopathic tachycardia of both left and right ventricular origin. J Am Coll Cardiol 1994;23:1333–41.
295. Brooks R, Burgess JH. Idiopathic ventricular tachycardia. A review. Medicine (Baltimore) 1988;67:271–94.
296. Belhassen B, Viskin S. Idiopathic ventricular tachycardia and fibrillation. J Cardiovasc Electrophysiol 1993;4:356–68.
297. Buxton AE, Waxman HL, Marchlinski FE, et al. Right ventricular tachycardia: clinical and electrophysiologic characteristics. Circulation 1983;68:917–27.
298. Vohra J, Shah A, Hua W, et al. Radiofrequency ablation of idiopathic ventricular tachycardia. Aust N Z J Med 1996;26: 186–94.
299. Talwar KK, Singh B, Goel P, et al. Radiofrequency ablation of idiopathic ventricular tachycardia. Indian Heart J 1996;48:49–52.
300. Rodriguez LM, Smeets JL, Timmermans C, et al. Predictors for successful ablation of right- and left-sided idiopathic ventricular tachycardia. Am J Cardiol 1997;79:309–14.
301. Blanck Z, Dhala A, Deshpande S, et al. Bundle branch reentrant ventricular tachycardia: cumulative experience in 48 patients. J Cardiovasc Electrophysiol 1993;4:253–62.
302. Scheinman MM, Huang S. The 1998 NASPE prospective catheter ablation registry. Pacing Clin Electrophysiol 2000;23:1020–8.
303. O'Donnell D, Bourke JP, Anilkumar R, et al. Radiofrequency ablation for post infarction ventricular tachycardia. Report of a single centre experience of 112 cases. Eur Heart J 2002;23: 1699–705.
304. O'Callaghan PA, Poloniecki J, Sosa-Suarez G, et al. Long-term clinical outcome of patients with prior myocardial infarction after palliative radiofrequency catheter ablation for frequent ventricular tachycardia. Am J Cardiol 2001;87:975–9.
305. El-Shalakany A, Hadjis T, Papageorgiou P, et al. Entrainment/mapping criteria for the prediction of termination of ventricular tachycardia by single radiofrequency lesion in patients with coronary artery disease. Circulation 1999;99:2283–9.
306. Kuck KH, Schluter M, Geiger M, et al. Successful catheter ablation of human ventricular tachycardia with radiofrequency current guided by an endocardial map of the area of slow conduction. Pacing Clin Electrophysiol 1991;14:1060–71.
307. Stevenson WG, Weiss JN, Wiener I, et al. Resetting of ventricular tachycardia: implications for localizing the area of slow conduction. J Am Coll Cardiol 1988;11:522–9.
308. de Bakker JM, van Capelle FJ, Janse MJ, et al. Macroreentry in the infarcted human heart: the mechanism of ventricular tachycardias with a "focal" activation pattern. J Am Coll Cardiol 1991;18:1005–14.
309. Harada T, Stevenson WG, Kocovic DZ, et al. Catheter ablation of ventricular tachycardia after myocardial infarction: relation of endocardial sinus rhythm late potentials to the reentry circuit. J Am Coll Cardiol 1997;30:1015–23.
310. Soejima K, Suzuki M, Maisel WH, et al. Catheter ablation in patients with multiple and unstable ventricular tachycardias after myocardial infarction: short ablation lines guided by reentry circuit isthmuses and sinus rhythm mapping. Circulation 2001;104:664–9.
311. Marchlinski FE, Callans DJ, Gottlieb CD, et al. Linear ablation lesions for control of unmappable ventricular tachycardia in patients with ischemic and nonischemic cardiomyopathy. Circulation 2000; 101:1288–96.
312. Stevenson WG, Sager PT, Natterson PD, et al. Relation of pace mapping QRS configuration and conduction delay to ventricular tachycardia reentry circuits in human infarct scars. J Am Coll Cardiol 1995;26:481–8.
313. Swarup V, Morton JB, Arruda M, et al. Ablation of epicardial macroreentrant ventricular tachycardia associated with idiopathic nonischemic dilated cardiomyopathy by a percutaneous transthoracic approach. J Cardiovasc Electrophysiol 2002;13:1164–8.
314. Friedman RA, Walsh EP, Silka MJ, et al. NASPE Expert Consensus Conference: Radiofrequency catheter ablation in children with and without congenital heart disease. Report of the Writing Committee. North American Society of Pacing and Electrophysiology. Pacing Clin Electrophysiol 2002;25:1000–17.
315. Sosa E, Scanavacca M, d'Avila A, et al. A new technique to perform epicardial mapping in the electrophysiology laboratory. J Cardiovasc Electrophysiol 1996;7:531–6.
316. Lustgarten DL, Keane D, Ruskin J. Cryothermal ablation: mechanism of tissue injury and current experience in the treatment of tachyarrhythmias. Prog Cardiovasc Dis 1999;41:481–98.
317. Haissaguerre M, Extramiana F, Hocini M, et al. Mapping and ablation of ventricular fibrillation associated with long-QT and Brugada syndromes. Circulation 2003;108:925–8.
318. Saliba W, Abul KA, Tchou P, et al. Ventricular fibrillation: ablation of a trigger? J Cardiovasc Electrophysiol 2002;13:1296–9.
319. Nellens P, Gursoy S, Andries E, et al. Transcoronary chemical ablation of arrhythmias. Pacing Clin Electrophysiol 1992;15:1368–73.
320. Inoue H, Waller BF, Zipes DP. Intracoronary ethyl alcohol or phenol injection ablates aconitine-induced ventricular tachycardia in dogs. J Am Coll Cardiol 1987;10:1342–9.
321. Weerasooriya R, Hsu LF, Scavee C, et al. Catheter Ablation of Ventricular Fibrillation in Structurally Normal Hearts Targeting the RVOT and Purkinje Ectopy. Herz 2003;28:598–606.
322. Eagle KA, Guyton RA, Davidoff R, et al. ACC/AHA 2004 guideline update for coronary artery bypass graft surgery: summary article. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1999 Guidelines for Coronary Artery Bypass Graft Surgery). J Am Coll Cardiol 2004;44:1146–310.

323. von Oppell UO, Milne D, Okreglicki A, et al. Surgery for ventricular tachycardia of left ventricular origin: risk factors for success and long-term outcome. Eur J Cardiothorac Surg 2002;22: 762–70.
324. Moss AJ, McDonald J. Unilateral cervicothoracic sympathetic ganglionectomy for the treatment of long QT interval syndrome. N Engl J Med 1971;285:903–4.
325. Ouriel K, Moss AJ. Long QT syndrome: an indication for cervicothoracic sympathectomy. Cardiovasc Surg 1995;3:475–8.
326. Schwartz PJ, Priori SG, Cerrone M, et al. Left cardiac sympathetic denervation in the management of high-risk patients affected by the long-QT syndrome. Circulation 2004;109:1826–33.
327. Josephson ME, Spear JF, Harken AH, et al. Surgical excision of automatic atrial tachycardia: anatomic and electrophysiologic correlates. Am Heart J 1982;104:1076–85.
328. Carnendran L, Steinberg JS. Does an open infarct-related artery after myocardial infarction improve electrical stability? Prog Cardiovasc Dis 2000;42:439–54.
329. Hillis LD, Cigarroa JE, Lange RA. Late revascularization reduces mortality in survivors of myocardial infarction. Cardiol Rev 1999; 7:144–8.
330. Brugada J, Aguinaga L, Mont L, et al. Coronary artery revascularization in patients with sustained ventricular arrhythmias in the chronic phase of a myocardial infarction: effects on the electrophysiologic substrate and outcome. J Am Coll Cardiol 2001;37:529–33.
331. Natale A, Sra J, Axtell K, et al. Ventricular fibrillation and polymorphic ventricular tachycardia with critical coronary artery stenosis: does bypass surgery suffice? J Cardiovasc Electrophysiol 1994;5:988–94.
332. Brockes C, Rahn-Schonbeck M, Duru F, et al. ICD implantation with and without combined myocardial revascularization—incidence of ICD therapy and late survival. Thorac Cardiovasc Surg 2002;50:333–6.
333. Mittal S, Lomnitz DJ, Mirchandani S, et al. Prognostic significance of nonsustained ventricular tachycardia after revascularization. J Cardiovasc Electrophysiol 2002;13:342–6.
334. 2005 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation 2005;112:IV1–203.
335. Nolan JP, Deakin CD, Soar J, et al. European Resuscitation Council Guidelines for Resuscitation 2005 Section 4. Adult advanced life support. Resuscitation 2005;67 Suppl 1:S39–86.
336. Myerburg RJ, Velez M, Fenster J, et al. Community-based responses to impending or actual cardiac arrest and advances in post-cardiac arrest care. J Interv Card Electrophysiol 2003;9:189–202.
337. Cobb LA, Weaver WD, Fahrenbruch CE, et al. Community-based interventions for sudden cardiac death. Impact, limitations, and changes. Circulation 1992;85:I98–102.
338. Cobb LA, Fahrenbruch CE, Walsh TR, et al. Influence of cardiopulmonary resuscitation prior to defibrillation in patients with out-of-hospital ventricular fibrillation. JAMA 1999;281:1182–8.
339. Wik L, Hansen TB, Fylling F, et al. Delaying defibrillation to give basic cardiopulmonary resuscitation to patients with out-of-hospital ventricular fibrillation: a randomized trial. JAMA 2003;289:1389–95.
340. Weisfeldt ML, Becker LB. Resuscitation after cardiac arrest: a 3-phase time-sensitive model. JAMA 2002;288:3035–8.
341. The American Heart Association in Collaboration With the International Liaison Committee on Resuscitation. Guidelines 2000 for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Part 6: advanced cardiovascular life support: section 7: algorithm approach to ACLS emergencies: section 7A: principles and practice of ACLS. Circulation 2000;102:I136–I139.
342. Gueugniaud PY, Mols P, Goldstein P, et al. A comparison of repeated high doses and repeated standard doses of epinephrine for cardiac arrest outside the hospital. European Epinephrine Study Group. N Engl J Med 1998;339:1595–601.
343. Dorian P, Cass D, Schwartz B, et al. Amiodarone as compared with lidocaine for shock-resistant ventricular fibrillation. N Engl J Med 2002;346:884–90.
344. Wenzel V, Lindner KH. Arginine vasopressin during cardiopulmonary resuscitation: laboratory evidence, clinical experience and recommendations, and a view to the future. Crit Care Med 2002;30: S157–S161.
345. Cummins RO, Graves Jr., Larsen MP, et al. Out-of-hospital transcutaneous pacing by emergency medical technicians in patients with asystolic cardiac arrest. N Engl J Med 1993;328:1377–82.
346. Behar S, Goldbourt U, Reicher-Reiss H, et al. Prognosis of acute myocardial infarction complicated by primary ventricular fibrillation. Principal Investigators of the SPRINT Study. Am J Cardiol 1990;66:1208–11.
347. Newby KH, Thompson T, Stebbins A, et al. Sustained ventricular arrhythmias in patients receiving thrombolytic therapy: incidence and outcomes. The GUSTO Investigators. Circulation 1998; 98:2567–73.
348. Antman EM, Berlin JA. Declining incidence of ventricular fibrillation in myocardial infarction. Implications for the prophylactic use of lidocaine. Circulation 1992;86:764–73.
349. MacMahon S, Collins R, Peto R, et al. Effects of prophylactic lidocaine in suspected acute myocardial infarction. An overview of results from the randomized, controlled trials. JAMA 1988;260: 1910–6.
350. Higham PD, Adams PC, Murray A, et al. Plasma potassium, serum magnesium and ventricular fibrillation: a prospective study. Q J Med 1993;86:609–17.
351. Pitt B, White H, Nicolau J, et al. Eplerenone reduces mortality 30 days after randomization following acute myocardial infarction in patients with left ventricular systolic dysfunction and heart failure. J Am Coll Cardiol 2005;46:425–31.
352. Solomon SD, Ridker PM, Antman EM. Ventricular arrhythmias in trials of thrombolytic therapy for acute myocardial infarction. A meta-analysis. Circulation 1993;88:2575–81.
353. Berger PB, Ruocco NA Jr., Ryan TJ, et al. Incidence and prognostic implications of heart block complicating inferior myocardial infarction treated with thrombolytic therapy: results from TIMI II. J Am Coll Cardiol 1992;20:533–40.
354. Wellens HJ. Electrophysiology: Ventricular tachycardia: diagnosis of broad QRS complex tachycardia. Heart 2001;86:579–85.
355. Buxton AE, Marchlinski FE, Doherty JU, et al. Hazards of intravenous verapamil for sustained ventricular tachycardia. Am J Cardiol 1987;59:1107–10.
356. Stewart RB, Bardy GH, Greene HL. Wide complex tachycardia: misdiagnosis and outcome after emergent therapy. Ann Intern Med 1986;104:766–71.
357. Belhassen B, Horowitz LN. Use of intravenous verapamil for ventricular tachycardia. Am J Cardiol 1984;54:1131–3.
358. Griffith MJ, Garratt CJ, Rowland E, et al. Effects of intravenous adenosine on verapamil-sensitive "idiopathic" ventricular tachycardia. Am J Cardiol 1994;73:759–64.
359. van der Watt MJ, Aboo AA, Millar RN. A prospective study of electrical cardioversion for sustained tachycardias by emergency unit personnel. S Afr Med J 1995;85:508–11.
360. Atkins DL, Dorian P, Gonzalez ER, et al. Treatment of tachyarrhythmias. Ann Emerg Med 2001;37:S91–109.
361. Fuster V, Ryden LE, Cannon DS, et al. ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 Guidelines for the Management of Patients With Atrial Fibrillation): developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. J Am Coll Cardiol 2006;18:e149–246.
362. Ochi RP, Goldenberg IF, Almquist A, et al. Intravenous amiodarone for the rapid treatment of life-threatening ventricular arrhythmias in critically ill patients with coronary artery disease. Am J Cardiol 1989;64:599–603.
363. Mooss AN, Mohiuddin SM, Hee TT, et al. Efficacy and tolerance of high-dose intravenous amiodarone for recurrent, refractory ventricular tachycardia. Am J Cardiol 1990;65:609–14.
364. Levine JH, Massumi A, Scheinman MM, et al. Intravenous amiodarone for recurrent sustained hypotensive ventricular tachyarrhythmias. Intravenous Amiodarone Multicenter Trial Group. J Am Coll Cardiol 1996;27:67–75.
365. Hamaad A, Lip GY. Intravenous water-soluble amiodarone improved 24–hour survival in incessant ventricular tachycardia. ACP J Club 2003;138:62.

366. Hohnloser SH, Meinertz T, Dammbacher T, et al. Electrocardiographic and antiarrhythmic effects of intravenous amiodarone: results of a prospective, placebo-controlled study. Am Heart J 1991;121:89–95.
367. Kulakowski P, Karczmarewicz S, Karpinski G, et al. Effects of intravenous amiodarone on ventricular refractoriness, intraventricular conduction, and ventricular tachycardia induction. Europace 2000;2:207–15.
368. Kowey PR, Marinchak RA, Rials SJ, et al. Intravenous amiodarone. J Am Coll Cardiol 1997;29:1190–8.
369. Mitchell LB, Wyse DG, Gillis AM, et al. Electropharmacology of amiodarone therapy initiation. Time courses of onset of electrophysiologic and antiarrhythmic effects. Circulation 1989;80:34–42.
370. Gorgels AP, van den Dool A, Hofs A, et al. Comparison of procainamide and lidocaine in terminating sustained monomorphic ventricular tachycardia. Am J Cardiol 1996;78:43–6.
371. Callans DJ, Marchlinski FE. Dissociation of termination and prevention of inducibility of sustained ventricular tachycardia with infusion of procainamide: evidence for distinct mechanisms. J Am Coll Cardiol 1992;19:111–7.
372. Sharma AD, Purves P, Yee R, et al. Hemodynamic effects of intravenous procainamide during ventricular tachycardia. Am Heart J 1990;119:1034–41.
373. Nasir N Jr., Taylor A, Doyle TK, et al. Evaluation of intravenous lidocaine for the termination of sustained monomorphic ventricular tachycardia in patients with coronary artery disease with or without healed myocardial infarction. Am J Cardiol 1994;74:1183–6.
374. Lie KI, Wellens HJ, van Capelle FJ, et al. Lidocaine in the prevention of primary ventricular fibrillation. A double-blind, randomized study of 212 consecutive patients. N Engl J Med 1974; 291:1324–6.
375. Buxton AE, Marchlinski FE, Doherty JU, et al. Repetitive, monomorphic ventricular tachycardia: clinical and electrophysiologic characteristics in patients with and patients without organic heart disease. Am J Cardiol 1984;54:997–1002.
376. Rahilly GT, Prystowsky EN, Zipes DP, et al. Clinical and electrophysiologic findings in patients with repetitive monomorphic ventricular tachycardia and otherwise normal electrocardiogram. Am J Cardiol 1982;50:459–68.
377. Lerman BB, Stein K, Engelstein ED, et al. Mechanism of repetitive monomorphic ventricular tachycardia. Circulation 1995;92:421–9.
378. Ouyang F, Fotuhi P, Ho SY, et al. Repetitive monomorphic ventricular tachycardia originating from the aortic sinus cusp: electrocardiographic characterization for guiding catheter ablation. J Am Coll Cardiol 2002;39:500–8.
379. Sadanaga T, Saeki K, Yoshimoto T, et al. Repetitive monomorphic ventricular tachycardia of left coronary cusp origin. Pacing Clin Electrophysiol 1999;22:1553–6.
380. Grimm W, Menz V, Hoffmann J, et al. Reversal of tachycardia induced cardiomyopathy following ablation of repetitive monomorphic right ventricular outflow tract tachycardia. Pacing Clin Electrophysiol 2001;24:166–71.
381. Fung JW, Chan HC, Chan JY, et al. Ablation of nonsustained or hemodynamically unstable ventricular arrhythmia originating from the right ventricular outflow tract guided by noncontact mapping. Pacing Clin Electrophysiol 2003;26:1699–705.
382. Sumitomo N, Harada K, Nagashima M, et al. Catecholaminergic polymorphic ventricular tachycardia: electrocardiographic characteristics and optimal therapeutic strategies to prevent sudden death. Heart 2003;89:66–70.
383. Takeuchi T, Sato N, Kawamura Y, et al. A case of a short-coupled variant of torsades de pointes with electrical storm. Pacing Clin Electrophysiol 2003;26:632–6.
384. Nademanee K, Taylor R, Bailey WE, et al. Treating electrical storm: sympathetic blockade versus advanced cardiac life support-guided therapy. Circulation 2000;102:742–7.
385. Kowey PR, Marinchak RA, Rials SJ, et al. Intravenous antiarrhythmic therapy in the acute control of in-hospital destabilizing ventricular tachycardia and fibrillation. Am J Cardiol 1999;84:46R–51R.
386. The American Heart Association in Collaboration With the International Liaison Committee on Resuscitation. Guidelines 2000 for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Part 6: advanced cardiovascular life support: section 5: pharmacology I: agents for arrhythmias. Circulation 2000;102:I112–28.
387. Dorian P, Cass D. An overview of the management of electrical storm. Can J Cardiol 1997;13 Suppl A:13A–7A.
388. Viskin S, Fish R, Zeltser D, et al. Arrhythmias in the congenital long QT syndrome: how often is torsade de pointes pause dependent? Heart 2000;83:661–6.
389. Exner DV, Pinski SL, Wyse DG, et al. Electrical storm presages nonsudden death: the Antiarrhythmics Versus Implantable Defibrillators (AVID) trial. Circulation 2001;103:2066–71.
390. Credner SC, Klingenheben T, Mauss O, et al. Electrical storm in patients with transvenous implantable cardioverter-defibrillators: incidence, management and prognostic implications. J Am Coll Cardiol 1998;32:1909–15.
391. Halkin A, Roth A, Lurie I, et al. Pause-dependent torsade de pointes following acute myocardial infarction: a variant of the acquired long QT syndrome. J Am Coll Cardiol 2001;38:1168–74.
392. Greene M, Newman D, Geist M, et al. Is electrical storm in ICD patients the sign of a dying heart? Outcome of patients with clusters of ventricular tachyarrhythmias. Europace 2000;2:263–9.
393. Jaoude SA, Salame E, Azar R, et al. T wave pacing inducing electrical storm and multiple shocks in an ICD-recipient: a novel complication of the automatic gain control function. J Interv Card Electrophysiol 2003;9:401–3.
394. Olatidoye AG, Verroneau J, Kluger J. Mechanisms of syncope in implantable cardioverter-defibrillator recipients who receive device therapies. Am J Cardiol 1998;82:1372–6.
395. Mok NS, Chan NY, Chiu AC. Successful use of quinidine in treatment of electrical storm in Brugada syndrome. Pacing Clin Electrophysiol 2004;27:821–3.
396. Wolfe CL, Nibley C, Bhandari A, et al. Polymorphous ventricular tachycardia associated with acute myocardial infarction. Circulation 1991;84:1543–51.
397. Bansch D, Oyang F, Antz M, et al. Successful catheter ablation of electrical storm after myocardial infarction. Circulation 2003;108: 3011–6.
398. Burjorjee JE, Milne B. Propofol for electrical storm; a case report of cardioversion and suppression of ventricular tachycardia by propofol. Can J Anaesth 2002;49:973–7.
399. Sarter BH, Finkle JK, Gerszten RE, et al. What is the risk of sudden cardiac death in patients presenting with hemodynamically stable sustained ventricular tachycardia after myocardial infarction? J Am Coll Cardiol 1996;28:122–9.
400. Brugada P, Talajic M, Smeets J, et al. The value of the clinical history to assess prognosis of patients with ventricular tachycardia or ventricular fibrillation after myocardial infarction. Eur Heart J 1989;10:747–52.
401. Moss AJ. MADIT-II and its implications. Eur Heart J 2003;24: 16–8.
402. Moss AJ. MADIT-II: substudies and their implications. Card Electrophysiol Rev 2003;7:430–3.
403. Wilber DJ, Zareba W, Hall WJ, et al. Time dependence of mortality risk and defibrillator benefit after myocardial infarction. Circulation 2004;109:1082–4.
404. Cairns JA, Connolly SJ, Roberts R, et al. Randomised trial of outcome after myocardial infarction in patients with frequent or repetitive ventricular premature depolarisations: CAMIAT. Canadian Amiodarone Myocardial Infarction Arrhythmia Trial Investigators. Lancet 1997;349:675–82.
405. Julian DG, Camm AJ, Frangin G, et al. Randomised trial of effect of amiodarone on mortality in patients with left-ventricular dysfunction after recent myocardial infarction: EMIAT. European Myocardial Infarct Amiodarone Trial Investigators. Lancet 1997; 349:667–74.
406. Bonow RO, Carabello B, Chatterjee K, et al. ACC/AHA 2006 Guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Management of Patients with Valvular Heart Disease). J Am Coll Cardiol 1998;48:e1–e148.
407. Olesen KH. The natural history of 271 patients with mitral stenosis under medical treatment. Br Heart J 1962;24:349–57.

408. Avierinos JF, Gersh BJ, Melton LJ III, et al. Natural history of asymptomatic mitral valve prolapse in the community. Circulation 2002;106:1355–61.
409. Grigioni F, Enriquez-Sarano M, Ling LH, et al. Sudden death in mitral regurgitation due to flail leaflet. J Am Coll Cardiol 1999;34: 2078–85.
410. Chambers JB, Ward DE. The QT and QS2 intervals in patients with mitral leaflet prolapse. Am Heart J 1987;114:355–61.
411. Trends in infant mortality attributable to birth defects—United States, 1980–1995. MMWR Morb Mortal Wkly Rep 1998;47: 773–8.
412. Perloff JK, Warnes CA. Challenges posed by adults with repaired congenital heart disease. Circulation 2001;103:2637–43.
413. Silka MJ, Hardy BG, Menashe VD, et al. A population-based prospective evaluation of risk of sudden cardiac death after operation for common congenital heart defects. J Am Coll Cardiol 1998;32: 245–51.
414. State-specific mortality from sudden cardiac death—United States, 1999. MMWR Morb Mortal Wkly Rep 2002;51:123–6.
415. Deanfield J, Thaulow E, Warnes C, et al. Management of grown up congenital heart disease. Eur Heart J 2003;24:1035–84.
416. Oechslin EN, Harrison DA, Connelly MS, et al. Mode of death in adults with congenital heart disease. Am J Cardiol 2000;86:1111–6.
417. Graham TP Jr., Bernard YD, Mellen BG, et al. Long-term outcome in congenitally corrected transposition of the great arteries: a multi-institutional study. J Am Coll Cardiol 2000;36:255–61.
418. Garson A Jr.. Ventricular arrhythmias after repair of congenital heart disease: who needs treatment? Cardiol Young 1991;1:177–81.
419. Bricker JT. Sudden death and tetralogy of Fallot. Risks, markers, and causes. Circulation 1995;92:158–9.
420. Gatzoulis MA, Balaji S, Webber SA, et al. Risk factors for arrhythmia and sudden cardiac death late after repair of tetralogy of Fallot: a multicentre study. Lancet 2000;356:975–81.
421. Gatzoulis MA, Till JA, Somerville J, et al. Mechanoelectrical interaction in tetralogy of Fallot. QRS prolongation relates to right ventricular size and predicts malignant ventricular arrhythmias and sudden death. Circulation 1995;92:231–7.
422. Chandar JS, Wolff GS, Garson A Jr., et al. Ventricular arrhythmias in postoperative tetralogy of Fallot. Am J Cardiol 1990;65:655–61.
423. Alexander ME, Walsh EP, Saul JP, et al. Value of programmed ventricular stimulation in patients with congenital heart disease. J Cardiovasc Electrophysiol 1999;10:1033–44.
424. Silka MJ, Kron J, Cutler JE, et al. Analysis of programmed stimulation methods in the evaluation of ventricular arrhythmias in patients 20 years old and younger. Am J Cardiol 1990;66:826–30.
425. Gelatt M, Hamilton RM, McCrindle BW, et al. Arrhythmia and mortality after the Mustard procedure: a 30-year single-center experience. J Am Coll Cardiol 1997;29:194–201.
426. Helbing WA, Hansen B, Ottenkamp J, et al. Long-term results of atrial correction for transposition of the great arteries. Comparison of Mustard and Senning operations. J Thorac Cardiovasc Surg 1994;108:363–72.
427. Rhodes LA, Walsh EP, Gamble WJ, et al. Benefits and potential risks of atrial antitachycardia pacing after repair of congenital heart disease. Pacing Clin Electrophysiol 1995;18:1005–16.
428. Lundstrom U, Bull C, Wyse RK, et al. The natural and "unnatural" history of congenitally corrected transposition. Am J Cardiol 1990; 65:1222–9.
429. Seliem MA, Benson DW Jr., Strasburger JF, et al. Complex ventricular ectopic activity in patients less than 20 years of age with or without syncope, and the role of ventricular extrastimulus testing. Am J Cardiol 1991;68:745–50.
430. Paul T, Marchal C, Garson A Jr.. Ventricular couplets in the young: prognosis related to underlying substrate. Am Heart J 1990;119: 577–82.
431. Fish FA, Gillette PC, Benson DW Jr.. Proarrhythmia, cardiac arrest and death in young patients receiving encainide and flecainide. The Pediatric Electrophysiology Group. J Am Coll Cardiol 1991;18: 356–65.
432. Saul JP, Alexander ME. Preventing sudden death after repair of tetralogy of Fallot: complex therapy for complex patients. J Cardiovasc Electrophysiol 1999;10:1271–87.
433. Liberthson RR. Sudden death from cardiac causes in children and young adults. N Engl J Med 1996;334:1039–44.
434. Silka MJ, Kron J, Walance CG, et al. Assessment and follow-up of pediatric survivors of sudden cardiac death. Circulation 1990;82: 341–9.
435. Hufnagel G, Pankuweit S, Richter A, et al. The European Study of Epidemiology and Treatment of Cardiac Inflammatory Diseases (ESETCID). First epidemiological results. Herz 2000;25:279–85.
436. Friman G, Wesslen L, Fohlman J, et al. The epidemiology of infectious myocarditis, lymphocytic myocarditis and dilated cardiomyopathy. Eur Heart J 1995;16 Suppl O:36–41.
437. Frishman W, Kraus ME, Zabkar J, et al. Infectious mononucleosis and fatal myocarditis. Chest 1977;72:535–8.
438. Vikerfors T, Stjerna A, Olcen P, et al. Acute myocarditis. Serologic diagnosis, clinical findings and follow-up. Acta Med Scand 1988; 223:45–52.
439. Karjalainen J, Viitasalo M. Fever and cardiac rhythm. Arch Intern Med 1986;146:1169–71.
440. Pfammatter JP, Paul T, Flik J, et al. [Q-fever associated myocarditis in a 14-year-old boy]. Z Kardiol 1995;84:947–50.
441. Barraclough D, Popert AJ. Q fever presenting with paroxysmal ventricular tachycardia. Br Med J 1975;2:423–4.
442. Marin-Garcia J, Gooch WM III, Coury DL. Cardiac manifestations of Rocky Mountain spotted fever. Pediatrics 1981;67:358–61.
443. Devriendt J, Staroukine M, Schils E, et al. Legionellosis and "torsades de pointes." Acta Cardiol 1990;45:329–33.
444. Etherington J, Salmon J, Ratcliffe G. Atrio-ventricular dissociation in meningococcal meningitis. J R Army Med Corps 1995;141: 169–71.
445. Dhar KL, Adlakha A, Phillip PJ. Recurrent seizures and syncope, ventricular arrhythmias with reversible prolonged Q-Tc interval in typhoid myocarditis. J Indian Med Assoc 1987;85:336–7.
446. Aziz I, Kastelik JA, Meigh RE, et al. Collapse with a streptococcal infection. Lancet 1999;354:738.
447. Leak D, Meghji M. Toxoplasmic infection in cardiac disease. Am J Cardiol 1979;43:841–9.
448. Reznick JW, Braunstein DB, Walsh RL, et al. Lyme carditis. Electrophysiologic and histopathologic study. Am J Med 1986;81: 923–7.
449. Steere AC, Batsford WP, Weinberg M, et al. Lyme carditis: cardiac abnormalities of Lyme disease. Ann Intern Med 1980;93:8–16.
450. Klein RM, Jiang H, Du M, et al. Detection of enteroviral RNA (poliovirus types 1 and 3) in endomyocardial biopsies from patients with ventricular tachycardia and survivors of sudden cardiac death. Scand J Infect Dis 2002;34:746–52.
451. Bowles NE, Ni J, Marcus F, et al. The detection of cardiotropic viruses in the myocardium of patients with arrhythmogenic right ventricular dysplasia/cardiomyopathy. J Am Coll Cardiol 2002;39: 892–5.
452. Calabrese F, Angelini A, Thiene G, et al. No detection of enteroviral genome in the myocardium of patients with arrhythmogenic right ventricular cardiomyopathy. J Clin Pathol 2000;53: 382–7.
453. Maisch B, Herzum M, Schonian U. Immunomodulating factors and immunosuppressive drugs in the therapy of myocarditis. Scand J Infect Dis Suppl 1993;88:149–62.
454. Wagner A, Schulz-Menger J, Dietz R, et al. Long-term follow-up of patients paragraph sign with acute myocarditis by magnetic paragraph sign resonance imaging. MAGMA 2003;16:17–20.
455. Kawai C. From myocarditis to cardiomyopathy: mechanisms of inflammation and cell death: learning from the past for the future. Circulation 1999;99:1091–100.
456. Jonas M, Hod H. Is immunosuppressive treatment an option for myocarditis? Isr J Med Sci 1997;33:762–6.
457. Tai YT, Lau CP, Fong PC, et al. Incessant automatic ventricular tachycardia complicating acute coxsackie B myocarditis. Cardiology 1992;80:339–44.
458. Tubman TR, Craig B, Mulholland HC. Ventricular tachycardia associated with Coxsackie B4 virus infection. Acta Paediatr Scand 1990;79:572–5.
459. Gowrishankar K, Rajajee S. Varied manifestations of viral myocarditis. Indian J Pediatr 1994;61:75–80.
460. Mary AS, Hamilton M. Ventricular tachycardia in a patient with toxoplasmosis. Br Heart J 1973;35:349–52.
461. Winkel E, Parrillo J. Myocarditis. Curr Treat Options Cardiovasc Med 2002;4:455–66.

462. Cooper LT, Okura Y. Idiopathic giant cell myocarditis. Curr Treat Options Cardiovasc Med 2001;3:463–7.
463. Cooper LT Jr. Giant cell myocarditis: diagnosis and treatment. Herz 2000;25:291–8.
464. Cooper LT Jr., Berry GJ, Shabetai R. Idiopathic giant-cell myocarditis—natural history and treatment. Multicenter Giant Cell Myocarditis Study Group Investigators. N Engl J Med 1997;336:1860–6.
465. Marelli D, Kermani R, Bresson J, et al. Support with the BVS 5000 assist device during treatment of acute giant-cell myocarditis. Tex Heart Inst J 2003;30:50–6.
466. Brilakis ES, Olson LJ, Berry GJ, et al. Survival outcomes of patients with giant cell myocarditis bridged by ventricular assist devices. ASAIO J 2000;46:569–72.
467. Hanawa H, Izumi T, Saito Y, et al. Recovery from complete atrioventricular block caused by idiopathic giant cell myocarditis after corticosteroid therapy. Jpn Circ J 1998;62:211–4.
468. Lo R, Menzies DJ, Archer H, et al. Complete heart block due to Lyme carditis. J Invasive Cardiol 2003;15:367–9.
469. Mayer W, Kleber FX, Wilske B, et al. Persistent atrioventricular block in Lyme borreliosis. Klin Wochenschr 1990;68:431–5.
470. Nagi KS, Joshi R, Thakur RK. Cardiac manifestations of Lyme disease: a review. Can J Cardiol 1996;12:503–6.
471. Mason JW, O'Connell JB, Herskowitz A, et al. A clinical trial of immunosuppressive therapy for myocarditis. The Myocarditis Treatment Trial Investigators. N Engl J Med 1995;333:269–75.
472. Nagi KS, Thakur RK. Lyme carditis: indications for cardiac pacing. Can J Cardiol 1995;11:335–8.
473. Midttun M, Lebech AM, Hansen K, et al. Lyme carditis: a clinical presentation and long time follow-up. Scand J Infect Dis 1997;29: 153–7.
474. Midttun M, Videbaek J. [Serious arrhythmias in Borrelia infections]. Ugeskr Laeger 1993;155:2147–50.
475. Vlay SC, Dervan JP, Elias J, et al. Ventricular tachycardia associated with Lyme carditis. Am Heart J 1991;121:1558–60.
476. Mirri A, Rapezzi C, Iacopi F, et al. [Cardiac involvement in HIV infection: a prospective, multicenter clinical and echocardiographic study]. Cardiologia 1990;35:203–9.
477. Yunis NA, Stone VE. Cardiac manifestations of HIV/AIDS: a review of disease spectrum and clinical management. J Acquir Immune Defic Syndr Hum Retrovirol 1998;18:145–54.
478. Milei J, Grana D, Fernandez AG, et al. Cardiac involvement in acquired immunodeficiency syndrome—a review to push action. The Committee for the Study of Cardiac Involvement in AIDS. Clin Cardiol 1998;21:465–72.
479. Cecchi E, Parrini I, Chinaglia A, et al. [Cardiac complications in HIV infections]. G Ital Cardiol 1997;27:917–24.
480. Kovacs A, Hinton DR, Wright D, et al. Human immunodeficiency virus type 1 infection of the heart in three infants with acquired immunodeficiency syndrome and sudden death. Pediatr Infect Dis J 1996;15:819–24.
481. Kocheril AG, Bokhari SA, Batsford WP, et al. Long QTc and torsades de pointes in human immunodeficiency virus disease. Pacing Clin Electrophysiol 1997;20:2810–6.
482. Cortese LM, Gasser RA Jr., Bjornson DC, et al. Prolonged recurrence of pentamidine-induced torsades de pointes. Ann Pharmacother 1992;26:1365–9.
483. Otsuka M, Kanamori H, Sasaki S, et al. Torsades de pointes complicating pentamidine therapy of Pneumocystis carinii pneumonia in acute myelogenous leukemia. Intern Med 1997;36:705–8.
484. Quadrel MA, Atkin SH, Jaker MA. Delayed cardiotoxicity during treatment with intravenous pentamidine: two case reports and a review of the literature. Am Heart J 1992;123:1377–9.
485. Rassi A Jr., Rassi A, Little WC. Chagas' heart disease. Clin Cardiol 2000;23:883–9.
486. Muratore C, Rabinovich R, Iglesias R, et al. Implantable cardioverter defibrillators in patients with Chagas' disease: are they different from patients with coronary disease? Pacing Clin Electrophysiol 1997;20:194–7.
487. d'Avila A, Splinter R, Svenson RH, et al. New perspectives on catheter-based ablation of ventricular tachycardia complicating Chagas' disease: experimental evidence of the efficacy of near infrared lasers for catheter ablation of Chagas' VT. J Interv Card Electrophysiol 2002;7:23–38.
488. Malik JA, Hassan C, Khan GQ. Transient complete heart block complicating acute rheumatic fever. Indian Heart J 2002;54:91–2.
489. Liberman L, Hordof AJ, Alfayyadh M, et al. Torsade de pointes in a child with acute rheumatic fever. J Pediatr 2001;138:280–2.
490. Freed MS, Sacks P, Ellman MH. Ventricular tachycardia in acute rheumatic fever. Arch Intern Med 1985;145:1904–5.
491. Nunley DL, Perlman PE. Endocarditis. Changing trends in epidemiology, clinical and microbiologic spectrum. Postgrad Med 1993; 93:235–4, 247.
492. Mylonakis E, Calderwood SB. Infective endocarditis in adults. N Engl J Med 2001;345:1318–30.
493. Schmitt M, Puri S, Dalal NR. Aortic valve endocarditis causing fatal myocardial infarction caused by ostial coronary artery obliteration. Heart 2004;90:303.
494. Anguera I, Quaglio G, Ferrer B, et al. Sudden death in Staphylococcus aureus-associated infective endocarditis due to perforation of a free-wall myocardial abscess. Scand J Infect Dis 2001;33:622–5.
495. Bussani R, Sinagra G, Poletti A, Pinamonti B, Silvestri F. Cardiac tamponade: an unusual, fatal complication of infective endocarditis. G Ital Cardiol 1999;29:1512–6.
496. Wallace SM, Walton BI, Kharbanda RK, et al. Mortality from infective endocarditis: clinical predictors of outcome. Heart 2002; 88:53–60.
497. Weinstein L. Life-threatening complications of infective endocarditis and their management. Arch Intern Med 1986;146:953–7.
498. Aguado JM, Gonzalez-Vilchez F, Martin-Duran R, et al. Perivalvular abscesses associated with endocarditis. Clinical features and diagnostic accuracy of two-dimensional echocardiography. Chest 1993;104:88–93.
499. Heinle SK, Kisslo J. The clinical utility of transesophageal echocardiography in patients with left-sided infective endocarditis. Am J Card Imaging 1995;9:199–202.
500. Bansal RC. Infective endocarditis. Med Clin North Am 1995;79: 1205–40.
501. Glazier JJ, Verwilghen J, Donaldson RM, et al. Treatment of complicated prosthetic aortic valve endocarditis with annular abscess formation by homograft aortic root replacement. J Am Coll Cardiol 1991;17:1177–82.
502. Watanabe G, Haverich A, Speier R, et al. Surgical treatment of active infective endocarditis with paravalvular involvement. J Thorac Cardiovasc Surg 1994;107:171–7.
503. Aranki SF, Santini F, Adams DH, et al. Aortic valve endocarditis. Determinants of early survival and late morbidity. Circulation 1994;90:II175–82.
504. Horstkotte D, Follath F, Gutschik E, et al. Guidelines on prevention, diagnosis and treatment of infective endocarditis executive summary: the Task Force on Infective Endocarditis of the European Society of Cardiology. Eur Heart J 2004;25:267–76.
505. Mitchell DN, du Bois RM, Oldershaw PJ. Cardiac sarcoidosis. BMJ 1997;314:320–1.
506. Fleming HA, Bailey SM. Sarcoid heart disease. J R Coll Physicians Lond 1981;15:245–53.
507. Winters SL, Cohen M, Greenberg S, et al. Sustained ventricular tachycardia associated with sarcoidosis: assessment of the underlying cardiac anatomy and the prospective utility of programmed ventricular stimulation, drug therapy and an implantable antitachycardia device. J Am Coll Cardiol 1991;18:937–43.
508. Kyle RA, Gertz MA. Primary systemic amyloidosis: clinical and laboratory features in 474 cases. Semin Hematol 1995;32:45–59.
509. Kyle RA, Gertz MA, Greipp PR, et al. A trial of three regimens for primary amyloidosis: colchicine alone, melphalan and prednisone, and melphalan, prednisone, and colchicine. N Engl J Med 1997; 336:1202–7.
510. Palladini G, Malamani G, Co F, et al. Holter monitoring in AL amyloidosis: prognostic implications. Pacing Clin Electrophysiol 2001;24:1228–33.
511. Dispenzieri A, Kyle RA, Gertz MA, et al.Survival in patients with primary systemic amyloidosis and raised serum cardiac troponins. Lancet 2003;361:1787–9., et al. , Edwards WD, Wood DL, Seward JB. Echocardiographic features of amyloid ischemic heart disease. Am J Cardiol 1985;55:606–7.
513. Dubrey S, Falk RH. QT interval in cardiac amyloidosis. Clin Cardiol 1996;19:A22, 442.

514. Reisinger J, Dubrey SW, Lavalley M, et al. Electrophysiologic abnormalities in AL (primary) amyloidosis with cardiac involvement. J Am Coll Cardiol 1997;30:1046–51.
515. Parthenakis FI, Vardas PE, Ralidis L, et al. QT interval in cardiac amyloidosis. Clin Cardiol 1996;19:51–4.
516. Mathew V, Chaliki H, Nishimura RA. Atrioventricular sequential pacing in cardiac amyloidosis: an acute Doppler echocardiographic and catheterization hemodynamic study. Clin Cardiol 1997;20: 723–5.
517. Nakao S, Takenaka T, Maeda M, et al. An atypical variant of Fabry's disease in men with left ventricular hypertrophy. N Engl J Med 1995;333:288–93.
518. Sachdev B, Takenaka T, Teraguchi H, et al. Prevalence of Anderson-Fabry disease in male patients with late onset hypertrophic cardiomyopathy. Circulation 2002;105:1407–11.
519. Whybra C, Kampmann C, Willers I, et al. Anderson-Fabry disease: clinical manifestations of disease in female heterozygotes. J Inherit Metab Dis 2001;24:715–24.
520. Becker AE, Schoorl R, Balk AG, et al. Cardiac manifestations of Fabry's disease. Report of a case with mitral insufficiency and electrocardiographic evidence of myocardial infarction. Am J Cardiol 1975;36:829–35.
521. Sheth KJ, Thomas JP Jr.. Electrocardiograms in Fabry's disease. J Electrocardiol 1982;15:153–6.
522. Mehta J, Tuna N, Moller JH, Desnick RJ. Electrocardiographic and vectorcardiographic abnormalities in Fabry's disease. Am Heart J 1977;93:699–705.
523. Yokoyama A, Yamazoe M, Shibata A. A case of heterozygous Fabry's disease with a short PR interval and giant negative T waves. Br Heart J 1987;57:296–9.
524. Yanagawa Y, Sakuraba H. Cardiovascular manifestations in Fabry's disease—age-related changes in hemizygotes and heterozygotes. Acta Paediatr Jpn 1988;30:38–48.
525. Ikari Y, Kuwako K, Yamaguchi T. Fabry's disease with complete atrioventricular block: histological evidence of involvement of the conduction system. Br Heart J 1992;68:323–5.
526. Schiffmann R, Kopp JB, Austin HA III, et al. Enzyme replacement therapy in Fabry disease: a randomized controlled trial. JAMA 2001;285:2743–9.
527. Yalcinkaya S, Kumbasar SD, Semiz E, et al. Sustained ventricular tachycardia in cardiac hemochromatosis treated with amiodarone. J Electrocardiol 1997;30:147–9.
528. Strobel JS, Fuisz AR, Epstein AE, et al. Syncope and inducible ventricular fibrillation in a woman with hemochromatosis. J Interv Card Electrophysiol 1999;3:225–9.
529. Short EM, Winkle RA, Billingham ME. Myocardial involvement in idiopathic hemochromatosis. Morphologic and clinical improvement following venesection. Am J Med 1981;70:1275–9.
530. Davison ET, Davison MJ. Triiodothyronine (T3) toxicosis with hypokalemic periodic paralysis and ventricular tachycardia. J Electrocardiol 1995;28:161–4.
531. Nesher G, Zion MM. Recurrent ventricular tachycardia in hypothyroidism report of a case and review of the literature. Cardiology 1988;75:301–6.
532. Osborn LA, Skipper B, Arellano I, et al. Results of resting and ambulatory electrocardiograms in patients with hypothyroidism and after return to euthyroid status. Heart Dis 1999;1:8–11.
533. Aragona M, Aragona F. [Pheochromocytoma and catecholamine cardiomyopathy]. Pathologica 1992;84:197–203.
534. Singh AK, Nguyen PN. Refractory ventricular tachycardia following aortic valve replacement complicated by unsuspected pheochromocytoma. Thorac Cardiovasc Surg 1993;41:372–3.
535. Michaels RD, Hays JH, O'Brian JT, et al. Pheochromocytoma associated ventricular tachycardia blocked with atenolol. J Endocrinol Invest 1990;13:943–7.
536. Shimizu K, Miura Y, Meguro Y, et al. QT prolongation with torsade de pointes in pheochromocytoma. Am Heart J 1992;124: 235–9.
537. Viskin S, Fish R, Roth A, et al. Clinical problem-solving. QT or not QT? N Engl J Med 2000;343:352–6.
538. Colao A. Are patients with acromegaly at high risk for dysrhythmias? Clin Endocrinol (Oxf) 2001;55:305–6.
539. Kahaly G, Olshausen KV, Mohr-Kahaly S, et al. Arrhythmia profile in acromegaly. Eur Heart J 1992;13:51–6.
540. Colao A, Ferone D, Marzullo P, et al. Long-term effects of depot long-acting somatostatin analog octreotide on hormone levels and tumor mass in acromegaly. J Clin Endocrinol Metab 2001;86:2779–86.
541. Minniti G, Moroni C, Jaffrain-Rea ML, et al. Marked improvement in cardiovascular function after successful transsphenoidal surgery in acromegalic patients. Clin Endocrinol (Oxf) 2001; 55:307–13.
542. Suyama K, Uchida D, Tanaka T, et al. Octreotide improved ventricular arrhythmia in an acromegalic patient. Endocr J 2000;47 Suppl:S73–5.
543. Lombardi G, Colao A, Marzullo P, et al. Improvement of left ventricular hypertrophy and arrhythmias after lanreotide-induced GH and IGF-I decrease in acromegaly. A prospective multi-center study. J Endocrinol Invest 2002;25:971–6.
544. Colao A, Marzullo P, Cuocolo A, et al. Reversal of acromegalic cardiomyopathy in young but not in middle-aged patients after 12 months of treatment with the depot long-acting somatostatin analogue octreotide. Clin Endocrinol (Oxf) 2003;58:169–76.
545. Izumi C, Inoko M, Kitaguchi S, et al. Polymorphic ventricular tachycardia in a patient with adrenal insufficiency and hypothyroidism. Jpn Circ J 1998;62:543–5.
546. Abdo A, Bebb RA, Wilkins GE. Ventricular fibrillation: an extreme presentation of primary hyperaldosteronism. Can J Cardiol 1999; 15:347–8.
547. Sade E, Oto A, Oto A, et al. Adrenal adenoma presenting with torsade de pointes—a case report. Angiology 2002;53:471–4.
548. Geist M, Dorian P, Davies T, Greene M, Newman D. Hyperaldosteronism and sudden cardiac death. Am J Cardiol 1996;78: 605–6.
549. Chang CJ, Chen SA, Tai CT, et al. Ventricular tachycardia in a patient with primary hyperparathyroidism. Pacing Clin Electrophysiol 2000;23:534–7.
550. Whang W, Bigger JT Jr.. Diabetes and outcomes of coronary artery bypass graft surgery in patients with severe left ventricular dysfunction: results from the CABG Patch Trial database. The CABG Patch Trial Investigators and Coordinators. J Am Coll Cardiol 2000;36:1166–72.
551. Marques JL, George E, Peacey SR, et al. Altered ventricular repolarization during hypoglycaemia in patients with diabetes. Diabet Med 1997;14:648–54.
552. Heller SR. Abnormalities of the electrocardiogram during hypoglycaemia: the cause of the dead in bed syndrome? Int J Clin Pract Suppl 2002;27–32.
553. Jassal SV, Coulshed SJ, Douglas JF, et al. Autonomic neuropathy predisposing to arrhythmias in hemodialysis patients. Am J Kidney Dis 1997;30:219–23.
554. Burger AJ, Aronson D. Effect of diabetes mellitus on heart rate variability in patients with congestive heart failure. Pacing Clin Electrophysiol 2001;24:53–9.
555. Athyros VG, Didangelos TP, Karamitsos DT, et al. Long-term effect of converting enzyme inhibition on circadian sympathetic and parasympathetic modulation in patients with diabetic autonomic neuropathy. Acta Cardiol 1998;53:201–9.
556. Weston PJ, Gill GV. Is undetected autonomic dysfunction responsible for sudden death in Type 1 diabetes mellitus? The 'dead in bed' syndrome revisited. Diabet Med 1999;16:626–31.
557. Kontopoulos AG, Athyros VG, Didangelos TP, et al. Effect of chronic quinapril administration on heart rate variability in patients with diabetic autonomic neuropathy. Diabetes Care 1997;20:355–61.
558. Landray MJ, Toescu V, Kendall MJ. The cardioprotective role of beta-blockers in patients with diabetes mellitus. J Clin Pharm Ther 2002;27:233–42.
559. Sawicki PT, Siebenhofer A. Beta blocker treatment in diabetes mellitus. J Intern Med 2001;250:11–7.
560. Lindholm LH, Dahlof B, Edelman JM, et al. Effect of losartan on sudden cardiac death in people with diabetes: data from the LIFE study. Lancet 2003;362:619–20.
561. Singh JP, Sleight P, Kardos A, Hart G. QT interval dynamics and heart rate variability preceding a case of cardiac arrest. Heart 1997;77:375–7.

562. Meier P, Vogt P, Blanc E. Ventricular arrhythmias and sudden cardiac death in end-stage renal disease patients on chronic hemodialysis. Nephron 2001;87:199–214.
563. de Lima JJ, Vieira ML, Lopes HF, et al. Blood pressure and the risk of complex arrhythmia in renal insufficiency, hemodialysis, and renal transplant patients. Am J Hypertens 1999;12:204–8.
564. Drenick EJ, Fisler JS. Sudden cardiac arrest in morbidly obese surgical patients unexplained after autopsy. Am J Surg 1988;155: 720–6.
565. Sjostrom LV. Mortality of severely obese subjects. Am J Clin Nutr 1992;55:516S–23S.
566. Bharati S, Lev M. Cardiac conduction system involvement in sudden death of obese young people. Am Heart J 1995;129:273–81.
567. Alpert MA, Terry BE, Cohen MV, et al. The electrocardiogram in morbid obesity. Am J Cardiol 2000;85:908–10.
568. Frank S, Colliver JA, Frank A. The electrocardiogram in obesity: statistical analysis of 1,029 patients. J Am Coll Cardiol 1986;7: 295–9.
569. Mshui ME, Saikawa T, Ito K, et al. QT interval and QT dispersion before and after diet therapy in patients with simple obesity. Proc Soc Exp Biol Med 1999;220:133–8.
570. Palmieri V, de Simone G, Roman MJ, Schwartz JE, Pickering TG, Devereux RB. Ambulatory blood pressure and metabolic abnormalities in hypertensive subjects with inappropriately high left ventricular mass. Hypertension 1999;34:1032–40.
571. Messerli FH, Nunez BD, Ventura HO, et al. Overweight and sudden death. Increased ventricular ectopy in cardiopathy of obesity. Arch Intern Med 1987;147:1725–8.
572. Lattimore JD, Celermajer DS, Wilcox I. Obstructive sleep apnea and cardiovascular disease. J Am Coll Cardiol 2003;41:1429–37.
573. MacMahon SW, Wilcken DE, Macdonald GJ. The effect of weight reduction on left ventricular mass. A randomized controlled trial in young, overweight hypertensive patients. N Engl J Med 1986;314: 334–9.
574. Alpert MA, Lambert CR, Terry BE, et al. Effect of weight loss on left ventricular mass in nonhypertensive morbidly obese patients. Am J Cardiol 1994;73:918–21.
575. Carella MJ, Mantz SL, Rovner DR, et al. Obesity, adiposity, and lengthening of the QT interval: improvement after weight loss. Int J Obes Relat Metab Disord 1996;20:938–42.
576. Singh BN, Gaarder TD, Kanegae T, et al. Liquid protein diets and torsade de pointes. JAMA 1978;240:115–9.
577. Doherty JU, Wadden TA, Zuk L, et al. Long-term evaluation of cardiac function in obese patients treated with a very-low-calorie diet: a controlled clinical study of patients without underlying cardiac disease. Am J Clin Nutr 1991;53:854–8.
578. Fisler JS. Cardiac effects of starvation and semistarvation diets: safety and mechanisms of action. Am J Clin Nutr 1992;56:230S–4S.
579. Surawicz B, Waller BF. The enigma of sudden cardiac death related to dieting. Can J Cardiol 1995;11:228–31.
580. Ahmed W, Flynn MA, Alpert MA. Cardiovascular complications of weight reduction diets. Am J Med Sci 2001;321:280–4.
581. Neumarker KJ. Mortality and sudden death in anorexia nervosa. Int J Eat Disord 1997;21:205–12.
582. Lupoglazoff JM, Berkane N, Denjoy I, et al. [Cardiac consequences of adolescent anorexia nervosa]. Arch Mal Coeur Vaiss 2001;94: 494–8.
583. Isner JM, Roberts WC, Heymsfield SB, et al. Anorexia nervosa and sudden death. Ann Intern Med 1985;102:49–52.
584. Swenne I, Larsson PT. Heart risk associated with weight loss in anorexia nervosa and eating disorders: risk factors for QTc interval prolongation and dispersion. Acta Paediatr 1999;88:304–9.
585. Brooks MJ, Melnik G. The refeeding syndrome: an approach to understanding its complications and preventing its occurrence. Pharmacotherapy 1995;15:713–26.
586. Schocken DD, Holloway JD, Powers PS. Weight loss and the heart. Effects of anorexia nervosa and starvation. Arch Intern Med 1989;149:877–81.
587. Solomon SM, Kirby DF. The refeeding syndrome: a review. JPEN J Parenter Enteral Nutr 1990;14:90–7.
588. Weinsier RL, Krumdieck CL. Death resulting from overzealous total parenteral nutrition: the refeeding syndrome revisited. Am J Clin Nutr 1981;34:393–9.
589. Maisch B, Seferovic PM, Ristic AD, et al. Guidelines on the diagnosis and management of pericardial diseases executive summary: the Task Force on the Diagnosis and Management of Pericardial Diseases of the European Society of Cardiology. Eur Heart J 2004;25:587–610.
590. Laurain AR, Inoshita T. Sudden death from pericardial tamponade. Unusual complication of nonbacterial thrombotic endocarditis. Arch Pathol Lab Med 1985;109:171–2.
591. Glass JD, McQuillen EN, Hardin NJ. Iatrogenic cardiac herniation: post mortem case. J Trauma 1984;24:632–3.
592. Norell MS, Sarvasvaran R, Sutton GC. Solitary tumour metastasis: a rare cause of right ventricular outflow tract obstruction and sudden death. Eur Heart J 1984;5:684–8.
593. Bjornsson J, Edwards WD. Primary pulmonary hypertension: a histopathologic study of 80 cases. Mayo Clin Proc 1985;60:16–25.
594. Kanemoto N. Natural history of pulmonary hemodynamics in primary pulmonary hypertension. Am Heart J 1987;114:407–13.
595. Walley VM, Virmani R, Silver MD. Pulmonary arterial dissections and ruptures: to be considered in patients with pulmonary arterial hypertension presenting with cardiogenic shock or sudden death. Pathology 1990;22:1–4.
596. Yamamoto ME, Jones JW, McManus BM. Fatal dissection of the pulmonary trunk. An obscure consequence of chronic pulmonary hypertension. Am J Cardiovasc Pathol 1988;1:353–9.
597. Patrat JF, Jondeau G, Dubourg O, et al. Left main coronary artery compression during primary pulmonary hypertension. Chest 1997; 112:842–3.
598. Robalino BD, Moodie DS. Primary pulmonary hypertension, then and now: 28 years of experience. Cleve Clin J Med 1992;59:411–7.
599. Shiomi T, Guilleminault C, Sasanabe R, et al. Primary pulmonary hypertension with central sleep apnea: sudden death after bilevel positive airway pressure therapy. Jpn Circ J 2000;64:723–6.
600. Rubin LJ. Diagnosis and management of pulmonary arterial hypertension: ACCP evidence-based clinical practice guidelines. Chest 2004;126:7S–10S.
601. The Task Force on Diagnosis and Treatment of Pulmonary Arterial Hypertension of the European Society of Cardiology. Guidelines on diagnosis and treatment of pulmonary arterial hypertension. Eur Heart J 2004;25:2243–78.
602. Kliegel A, Eisenburger P, Sterz F, et al. Survivors of ventricular tachyarrhythmias due to a transient or reversible disorder have a high recurrence rate of lethal cardiac events. Resuscitation 2002;54: 237–43.
603. Ray WA, Murray KT, Meredith S, et al. Oral erythromycin and the risk of sudden death from cardiac causes. N Engl J Med 2004;351: 1089–96.
604. Kelly P, Ruskin JN, Vlahakes GJ, et al. Surgical coronary revascularization in survivors of prehospital cardiac arrest: its effect on inducible ventricular arrhythmias and long-term survival. J Am Coll Cardiol 1990;15:267–73.
605. Volpi A, Cavalli A, Santoro L, et al. Incidence and prognosis of early primary ventricular fibrillation in acute myocardial infarction—results of the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI-2) database. Am J Cardiol 1998;82: 265–71.
606. Schaffer WA, Cobb LA. Recurrent ventricular fibrillation and modes of death in survivors of out-of-hospital ventricular fibrillation. N Engl J Med 1975;293:259–62.
607. Goldstein S, Landis Jr., Leighton R, et al. Characteristics of the resuscitated out-of-hospital cardiac arrest victim with coronary heart disease. Circulation 1981;64:977–84.
608. Myerburg RJ, Kessler KM, Mallon SM, et al. Life-threatening ventricular arrhythmias in patients with silent myocardial ischemia due to coronary-artery spasm. N Engl J Med 1992;326:1451–5.
609. Buxton AE, Goldberg S, Harken A, et al. Coronary-artery spasm immediately after myocardial revascularization: recognition and management. N Engl J Med 1981;304:1249–53.
610. Buxton AE, Hirshfeld JW Jr., Untereker WJ, et al. Perioperative coronary arterial spasm: long-term follow-up. Am J Cardiol 1982; 50:444–51.
611. Salerno DM, Asinger RW, Elsperger J, et al. Frequency of hypokalemia after successfully resuscitated out-of-hospital cardiac arrest compared with that in transmural acute myocardial infarction. Am J Cardiol 1987;59:84–8.

612. Kudenchuk PJ, Kron J, Walance C, et al. Spontaneous sustained ventricular tachyarrhythmias during treatment with type IA antiarrhythmic agents. Am J Cardiol 1990;65:446–52.
613. Buxton AE, Rosenthal ME, Marchlinski FE, et al. Usefulness of the electrophysiology laboratory for evaluation of proarrhythmic drug response in coronary artery disease. Am J Cardiol 1991;67:835–42.
614. Dec GW, Fuster V. Idiopathic dilated cardiomyopathy. N Engl J Med 1994;331:1564–75.
615. Di LA, Secoli G, Perkan A, et al. Changing mortality in dilated cardiomyopathy. The Heart Muscle Disease Study Group. Br Heart J 1994;72:S46–S51.
616. Sugrue DD, Rodeheffer RJ, Codd MB, Ballard DJ, Fuster V, Gersh BJ. The clinical course of idiopathic dilated cardiomyopathy. A population-based study. Ann Intern Med 1992;117:117–23.
617. Komajda M, Jais JP, Reeves F, et al. Factors predicting mortality in idiopathic dilated cardiomyopathy. Eur Heart J 1990;11:824–31.
618. Kelly P, Coats A. Variation in mode of sudden cardiac death in patients with dilated cardiomyopathy. Eur Heart J 1997;18:879–80.
619. Tamburro P, Wilber D. Sudden death in idiopathic dilated cardiomyopathy. Am Heart J 1992;124:1035–45.
620. Stewart RA, McKenna WJ, Oakley CM. Good prognosis for dilated cardiomyopathy without severe heart failure or arrhythmia. Q J Med 1990;74:309–18.
621. Gradman A, Deedwania P, Cody R, et al. Predictors of total mortality and sudden death in mild to moderate heart failure. Captopril-Digoxin Study Group. J Am Coll Cardiol 1989;14:564–70.
622. Keogh AM, Baron DW, Hickie JB. Prognostic guides in patients with idiopathic or ischemic dilated cardiomyopathy assessed for cardiac transplantation. Am J Cardiol 1990;65:903–8.
623. Hofmann T, Meinertz T, Kasper W, et al. Mode of death in idiopathic dilated cardiomyopathy: a multivariate analysis of prognostic determinants. Am Heart J 1988;116:1455–63.
624. Romeo F, Pelliccia F, Cianfrocca C, et al. Predictors of sudden death in idiopathic dilated cardiomyopathy. Am J Cardiol 1989;63:138–40.
625. Brembilla-Perrot B, Donetti J, de la Chaise AT, et al. Diagnostic value of ventricular stimulation in patients with idiopathic dilated cardiomyopathy. Am Heart J 1991;121:1124–31.
626. Knight BP, Goyal R, Pelosi F, et al. Outcome of patients with nonischemic dilated cardiomyopathy and unexplained syncope treated with an implantable defibrillator. J Am Coll Cardiol 1999;33:1964–70.
627. Kron J, Hart M, Schual-Berke S, et al. Idiopathic dilated cardiomyopathy. Role of programmed electrical stimulation and Holter monitoring in predicting those at risk of sudden death. Chest 1988;93:85–90.
628. Meinertz T, Treese N, Kasper W, et al. Determinants of prognosis in idiopathic dilated cardiomyopathy as determined by programmed electrical stimulation. Am J Cardiol 1985;56:337–41.
629. Das SK, Morady F, DiCarlo L Jr., et al. Prognostic usefulness of programmed ventricular stimulation in idiopathic dilated cardiomyopathy without symptomatic ventricular arrhythmias 1. Am J Cardiol 1986;58:998–1000.
630. Poll DS, Marchlinski FE, Buxton AE, et al. Usefulness of programmed stimulation in idiopathic dilated cardiomyopathy. Am J Cardiol 1986;58:992–7.
631. Fatkin D, Graham RM. Molecular mechanisms of inherited cardiomyopathies. Physiol Rev 2002;82:945–80.
632. Fatkin D, MacRae C, Sasaki T, et al. Missense mutations in the rod domain of the lamin A/C gene as causes of dilated cardiomyopathy and conduction-system disease. N Engl J Med 1999;341:1715–24.
633. Tsubata S, Bowles KR, Vatta M, et al. Mutations in the human delta-sarcoglycan gene in familial and sporadic dilated cardiomyopathy. J Clin Invest 2000;106:655–62.
634. Michels VV, Moll PP, Miller FA, et al. The frequency of familial dilated cardiomyopathy in a series of patients with idiopathic dilated cardiomyopathy. N Engl J Med 1992;326:77–82.
635. Bansch D, Antz M, Boczor S, et al. Primary prevention of sudden cardiac death in idiopathic dilated cardiomyopathy: the Cardiomyopathy Trial (CAT). Circulation 2002;105:1453–8.
636. Caceres J, Jazayeri M, McKinnie J, et al. Sustained bundle branch reentry as a mechanism of clinical tachycardia. Circulation 1989;79:256–70.
637. Doval HC, Nul DR, Grancelli HO, et al. Randomised trial of low-dose amiodarone in severe congestive heart failure. Grupo de Estudio de la Sobrevida en la Insuficiencia Cardiaca en Argentina (GESICA). Lancet 1994;344:493–8.
638. Singh SN, Fletcher RD, Fisher SG, et al. Amiodarone in patients with congestive heart failure and asymptomatic ventricular arrhythmia. Survival Trial of Antiarrhythmic Therapy in Congestive Heart Failure. N Engl J Med 1995;333:77–82.
639. The SOLVD Investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. N Engl J Med 1991;325:293–302.
640. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial. Lancet 1999;353:9–13.
641. Neri R, Mestroni L, Salvi A, et al. Ventricular arrhythmias in dilated cardiomyopathy: efficacy of amiodarone. Am Heart J 1987;113:707–15.
642. Connolly SJ, Gent M, Roberts RS, et al. Canadian Implantable Defibrillator Study (CIDS): a randomized trial of the implantable cardioverter defibrillator against amiodarone. Circulation 2000;101:1297–302.
643. Kuck KH, Cappato R, Siebels J, et al. Randomized comparison of antiarrhythmic drug therapy with implantable defibrillators in patients resuscitated from cardiac arrest: the Cardiac Arrest Study Hamburg (CASH). Circulation 2000;102:748–54.
644. Connolly SJ, Hallstrom AP, Cappato R, et al. Meta-analysis of the implantable cardioverter defibrillator secondary prevention trials. AVID, CASH and CIDS studies. Antiarrhythmics vs Implantable Defibrillator study. Cardiac Arrest Study Hamburg. Canadian Implantable Defibrillator Study. Eur Heart J 2000;21:2071–8.
645. Strickberger SA, Hummel JD, Bartlett TG, et al. Amiodarone versus implantable cardioverter-defibrillator:randomized trial in patients with nonischemic dilated cardiomyopathy and asymptomatic nonsustained ventricular tachycardia—AMIOVIRT. J Am Coll Cardiol 2003;41:1707–12.
646. Kadish A, Quigg R, Schaechter A, et al. Defibrillators in nonischemic cardiomyopathy treatment evaluation. Pacing Clin Electrophysiol 2000;23:338–43.
647. Grimm W, Alter P, Maisch B. Arrhythmia risk stratification with regard to prophylactic implantable defibrillator therapy in patients with dilated cardiomyopathy. Results of MACAS, DEFINITE, and SCD-HeFT. Herz 2004;29:348–52.
648. Kadish A, Dyer A, Daubert JP, et al. Prophylactic defibrillator implantation in patients with nonischemic dilated cardiomyopathy. N Engl J Med 2004;350:2151–8.
649. Nanthakumar K, Epstein AE, Kay GN, et al. Prophylactic implantable cardioverter-defibrillator therapy in patients with left ventricular systolic dysfunction: a pooled analysis of 10 primary prevention trials. J Am Coll Cardiol 2004;44:2166–72.
650. Desai AS, Fang JC, Maisel WH, et al. Implantable defibrillators for the prevention of mortality in patients with nonischemic cardiomyopathy: a meta-analysis of randomized controlled trials. JAMA 2004;292:2874–9.
651. Spirito P, Bellone P. Natural history of hypertrophic cardiomyopathy. Br Heart J 1994;72:S10–S12.
652. Louie EK, Edwards LC III. Hypertrophic cardiomyopathy. Prog Cardiovasc Dis 1994;36:275–308.
653. Wigle ED, Rakowski H, Kimball BP, et al. Hypertrophic cardiomyopathy. Clinical spectrum and treatment. Circulation 1995;92:1680–92.
654. DeRose JJ Jr., Banas JS Jr., Winters SL. Current perspectives on sudden cardiac death in hypertrophic cardiomyopathy. Prog Cardiovasc Dis 1994;36:475–84.
655. Maron BJ, Bonow RO, Cannon RO III, et al. Hypertrophic cardiomyopathy. Interrelations of clinical manifestations, pathophysiology, and therapy (2). N Engl J Med 1987;316:844–52.
656. Maron BJ, Bonow RO, Cannon RO III, et al. Hypertrophic cardiomyopathy. Interrelations of clinical manifestations, pathophysiology, and therapy (1). N Engl J Med 1987;316:780–9.
657. Maron BJ, Roberts WC, Epstein SE. Sudden death in hypertrophic cardiomyopathy: a profile of 78 patients. Circulation 1982;65:1388–94.

658. Sadoul N, Prasad K, Elliott PM, et al. Prospective prognostic assessment of blood pressure response during exercise in patients with hypertrophic cardiomyopathy. Circulation 1997;96:2987–91.
659. Gilligan DM, Nihoyannopoulos P, Chan WL, et al. Investigation of a hemodynamic basis for syncope in hypertrophic cardiomyopathy. Use of a head-up tilt test. Circulation 1992;85:2140–8.
660. Spirito P, Seidman CE, McKenna WJ, et al. The management of hypertrophic cardiomyopathy. N Engl J Med 1997;336:775–85.
661. McKenna WJ, Behr ER. Hypertrophic cardiomyopathy: management, risk stratification, and prevention of sudden death. Heart 2002;87:169–76.
662. Kofflard MJ, Ten Cate FJ, van der Lee C, et al. Hypertrophic cardiomyopathy in a large community-based population: clinical outcome and identification of risk factors for sudden cardiac death and clinical deterioration. J Am Coll Cardiol 2003;41:987–93.
663. Maron BJ, Peterson EE, Maron MS, et al. Prevalence of hypertrophic cardiomyopathy in an outpatient population referred for echocardiographic study. Am J Cardiol 1994;73:577–80.
664. Maron BJ, Spirito P. Impact of patient selection biases on the perception of hypertrophic cardiomyopathy and its natural history. Am J Cardiol 1993;72:970–2.
665. Spirito P, Rapezzi C, Autore C, et al. Prognosis of asymptomatic patients with hypertrophic cardiomyopathy and nonsustained ventricular tachycardia. Circulation 1994;90:2743–7.
666. Cecchi F, Olivotto I, Montereggi A, et al. Hypertrophic cardiomyopathy in Tuscany: clinical course and outcome in an unselected regional population. J Am Coll Cardiol 1995;26:1529–36.
667. Cannan CR, Reeder GS, Bailey KR, et al. Natural history of hypertrophic cardiomyopathy. A population-based study, 1976 through 1990. Circulation 1995;92:2488–95.
668. Mittal SR. Sudden cardiac death in hypertrophic cardiomyopathy: risk evaluation. Int J Cardiol 1995;52:1–4.
669. Fatkin D, Graham RM. Prognostic value of left ventricular hypertrophy in hypertrophic cardiomyopathy. N Engl J Med 2001;344: 63–5.
670. Ikeda H, Maki S, Yoshida N, et al. Predictors of death from congestive heart failure in hypertrophic cardiomyopathy. Am J Cardiol 1999;83:1280–3.
671. Kyriakidis M, Triposkiadis F, Anastasakis A, et al. Hypertrophic cardiomyopathy in Greece: clinical course and outcome. Chest 1998;114:1091–6.
672. Maki S, Ikeda H, Muro A, et al. Predictors of sudden cardiac death in hypertrophic cardiomyopathy. Am J Cardiol 1998;82:774–8.
673. Marian AJ, Mares A Jr., Kelly DP, et al. Sudden cardiac death in hypertrophic cardiomyopathy. Variability in phenotypic expression of beta-myosin heavy chain mutations. Eur Heart J 1995; 16:368–76.
674. Maron BJ, Casey SA, Poliac LC, et al. Clinical course of hypertrophic cardiomyopathy in a regional United States cohort. JAMA 1999;281:650–5.
675. Maron BJ. Hypertrophic cardiomyopathy and sudden death: new perspectives on risk stratification and prevention with the implantable cardioverter-defibrillator. Eur Heart J 2000;21:1979–83.
676. Takagi E, Yamakado T, Nakano T. Prognosis of completely asymptomatic adult patients with hypertrophic cardiomyopathy. J Am Coll Cardiol 1999;33:206–11.
677. Takagi E, Yamakado T. Prognosis of patients with hypertrophic cardiomyopathy in Japan. Card Electrophysiol Rev 2002;6:34–5.
678. Spirito P, Bellone P, Harris KM, et al. Magnitude of left ventricular hypertrophy and risk of sudden death in hypertrophic cardiomyopathy. N Engl J Med 2000;342:1778–85.
679. Elliott PM, Gimeno B Jr., Mahon NG, et al. Relation between severity of left-ventricular hypertrophy and prognosis in patients with hypertrophic cardiomyopathy. Lancet 2001;357:420–4.
680. Maron BJ, Chaitman BR, Ackerman MJ, et al. Recommendations for physical activity and recreational sports participation for young patients with genetic cardiovascular diseases. Circulation 2004;109: 2807–16.
681. Hipp AA, Heitkamp HC, Rocker K, et al. Hypertrophic cardiomyopathy—sports-related aspects of diagnosis, therapy, and sports eligibility. Int J Sports Med 2004;25:20–6.
682. Maron BJ, Zipes DP. Introduction: eligibility recommendations for competitive athletes with cardiovascular abnormalities-general considerations. J Am Coll Cardiol 2005;45:1318–21.
683. Rizvi AA, Thompson PD. Hypertrophic cardiomyopathy: who plays and who sits. Curr Sports Med Rep 2002;1:93–9.
684. Moon JC, McKenna WJ, McCrohon JA, et al. Toward clinical risk assessment in hypertrophic cardiomyopathy with gadolinium cardiovascular magnetic resonance. J Am Coll Cardiol 2003;41: 1561–7.
685. Nishimura T, Nagata S, Uehara T, et al. Prognosis of hypertrophic cardiomyopathy: assessment by 123I-BMIPP (beta-methyl-p-(123I)iodophenyl pentadecanoic acid) myocardial single photon emission computed tomography. Ann Nucl Med 1996;10:71–8.
686. Maron BJ. Hypertrophic cardiomyopathy. Lancet 1997;350: 127–33.
687. Roberts R, Sigwart U. New concepts in hypertrophic cardiomyopathies, part I. Circulation 2001;104:2113–6.
688. Watkins H, McKenna WJ, Thierfelder L, et al. Mutations in the genes for cardiac troponin T and alpha-tropomyosin in hypertrophic cardiomyopathy. N Engl J Med 1995;332:1058–64.
689. Brugada R, Kelsey W, Lechin M, et al. Role of candidate modifier genes on the phenotypic expression of hypertrophy in patients with hypertrophic cardiomyopathy. J Investig Med 1997;45:542–51.
690. Redwood CS, Moolman-Smook JC, Watkins H. Properties of mutant contractile proteins that cause hypertrophic cardiomyopathy. Cardiovasc Res 1999;44:20–36.
691. Varnava A, Baboonian C, Davison F, et al. A new mutation of the cardiac troponin T gene causing familial hypertrophic cardiomyopathy without left ventricular hypertrophy. Heart 1999;82:621–4.
692. McKenna WJ, Camm AJ. Sudden death in hypertrophic cardiomyopathy. Assessment of patients at high risk. Circulation 1989;80: 1489–92.
693. Maron BJ, Estes NA III, Maron MS, et al. Primary prevention of sudden death as a novel treatment strategy in hypertrophic cardiomyopathy. Circulation 2003;107:2872–5.
694. McKenna W, Deanfield J, Faruqui A, et al. Prognosis in hypertrophic cardiomyopathy: role of age and clinical, electrocardiographic and hemodynamic features. Am J Cardiol 1981;47:532–8.
695. McKenna WJ, Franklin RC, Nihoyannopoulos P, et al. Arrhythmia and prognosis in infants, children and adolescents with hypertrophic cardiomyopathy. J Am Coll Cardiol 1988;11:147–53.
696. McKenna WJ, England D, Doi YL, et al. Arrhythmia in hypertrophic cardiomyopathy. I: Influence on prognosis. Br Heart J 1981; 46:168–72.
697. Frenneaux MP, Counihan PJ, Caforio AL, et al. Abnormal blood pressure response during exercise in hypertrophic cardiomyopathy. Circulation 1990;82:1995–2002.
698. Olivotto I, Montereggi A, Mazzuoli F, et al. Clinical utility and safety of exercise testing in patients with hypertrophic cardiomyopathy. G Ital Cardiol 1999;29:11–9.
699. Counihan PJ, Frenneaux MP, Webb DJ, et al. Abnormal vascular responses to supine exercise in hypertrophic cardiomyopathy. Circulation 1991;84:686–96.
700. Maron BJ, Savage DD, Wolfson JK, et al. Prognostic significance of 24 hour ambulatory electrocardiographic monitoring in patients with hypertrophic cardiomyopathy: a prospective study. Am J Cardiol 1981;48:252–7.
701. McKenna WJ, Sadoul N, Slade AK, et al. The prognostic significance of nonsustained ventricular tachycardia in hypertrophic cardiomyopathy. Circulation 1994;90:3115–7.
702. Monserrat L, Elliott PM, Gimeno Jr., et al. Non-sustained ventricular tachycardia in hypertrophic cardiomyopathy: an independent marker of sudden death risk in young patients 1. J Am Coll Cardiol 2003;42:873–9.
703. Kuck KH, Kunze KP, Schluter M, et al. Programmed electrical stimulation in hypertrophic cardiomyopathy. Results in patients with and without cardiac arrest or syncope. Eur Heart J 1988;9: 177–85.
704. Saumarez RC, Slade AK, Grace AA, et al. The significance of paced electrogram fractionation in hypertrophic cardiomyopathy. A prospective study 1. Circulation 1995;91:2762–8.
705. Maron BJ, McKenna WJ, Danielson GK, et al. American College of Cardiology/European Society of Cardiology clinical expert consensus document on hypertrophic cardiomyopathy. A report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents and the European Society of Cardi-

ology Committee for Practice Guidelines. J Am Coll Cardiol 2003;42:1687–713.
706. Behr ER, Elliott P, McKenna WJ. Role of invasive EP testing in the evaluation and management of hypertrophic cardiomyopathy. Card Electrophysiol Rev 2002;6:482–6.
707. Fananapazir L, Tracy CM, Leon MB, et al. Electrophysiologic abnormalities in patients with hypertrophic cardiomyopathy. A consecutive analysis in 155 patients. Circulation 1989;80:1259–68.
708. Maron BJ, Shen WK, Link MS, et al. Efficacy of implantable cardioverter-defibrillators for the prevention of sudden death in patients with hypertrophic cardiomyopathy. N Engl J Med 2000; 342:365–73.
709. Pollick C. Muscular subaortic stenosis: hemodynamic and clinical improvement after disopyramide. N Engl J Med 1982;307:997–9.
710. Robinson K, Frenneaux MP, Stockins B, et al. Atrial fibrillation in hypertrophic cardiomyopathy: a longitudinal study. J Am Coll Cardiol 1990;15:1279–85.
711. Spirito P, Lakatos E, Maron BJ. Degree of left ventricular hypertrophy in patients with hypertrophic cardiomyopathy and chronic atrial fibrillation. Am J Cardiol 1992;69:1217–22.
712. McKenna WJ, Harris L, Rowland E, et al. Amiodarone for long-term management of patients with hypertrophic cardiomyopathy. Am J Cardiol 1984;54:802–10.
713. McKenna WJ, Oakley CM, Krikler DM, et al. Improved survival with amiodarone in patients with hypertrophic cardiomyopathy and ventricular tachycardia. Br Heart J 1985;53:412–6.
714. Fananapazir L, Leon MB, Bonow RO, et al. Sudden death during empiric amiodarone therapy in symptomatic hypertrophic cardiomyopathy. Am J Cardiol 1991;67:169–74.
715. Gilligan DM, Missouris CG, Boyd MJ, et al. Sudden death due to ventricular tachycardia during amiodarone therapy in familial hypertrophic cardiomyopathy. Am J Cardiol 1991;68:971–3.
716. Exner DV, Klein GJ, Prystowsky EN. Primary prevention of sudden death with implantable defibrillator therapy in patients with cardiac disease: can we afford to do it? (Can we afford not to?). Circulation 2001;104:1564–70.
717. Chatrath R, Porter CB, Ackerman MJ. Role of transvenous implantable cardioverter-defibrillators in preventing sudden cardiac death in children, adolescents, and young adults. Mayo Clin Proc 2002;77:226–31.
718. Hauer RN, Aliot E, Block M, et al. Indications for implantable cardioverter defibrillator (ICD) therapy. Study Group on Guidelines on ICDs of the Working Group on Arrhythmias and the Working Group on Cardiac Pacing of the European Society of Cardiology. Eur Heart J 2001;22:1074–81.
719. Peters S, Peters H, Thierfelder L. Heart failure in arrhythmogenic right ventricular dysplasia-cardiomyopathy. Int J Cardiol 1999;71: 251–6.
720. Gemayel C, Pelliccia A, Thompson PD. Arrhythmogenic right ventricular cardiomyopathy. J Am Coll Cardiol 2001;38:1773–81.
721. Marcus FI, Fontaine G. Arrhythmogenic right ventricular dysplasia/cardiomyopathy: a review. Pacing Clin Electrophysiol 1995; 18:1298–314.
722. Niroomand F, Carbucicchio C, Tondo C, et al. Electrophysiological characteristics and outcome in patients with idiopathic right ventricular arrhythmia compared with arrhythmogenic right ventricular dysplasia. Heart 2002;87:41–7.
723. Kinoshita O, Fontaine G, Rosas F, et al. Time- and frequency-domain analyses of the signal-averaged ECG in patients with arrhythmogenic right ventricular dysplasia. Circulation 1995;91: 715–21.
724. Turrini P, Angelini A, Thiene G, et al. Late potentials and ventricular arrhythmias in arrhythmogenic right ventricular cardiomyopathy. Am J Cardiol 1999;83:1214–9.
725. Schionning JD, Frederiksen P, Kristensen IB. Arrhythmogenic right ventricular dysplasia as a cause of sudden death. Am J Forensic Med Pathol 1997;18:345–8.
726. Munclinger MJ, Patel JJ, Mitha AS. Follow-up of patients with arrhythmogenic right ventricular cardiomyopathy dysplasia. S Afr Med J 2000;90:61–8.
727. McKenna WJ, Thiene G, Nava A, et al. Diagnosis of arrhythmogenic right ventricular dysplasia/cardiomyopathy. Task Force of the Working Group Myocardial and Pericardial Disease of the European Society of Cardiology and of the Scientific Council on Cardiomyopathies of the International Society and Federation of Cardiology. Br Heart J 1994;71:215–8.
728. Nava A, Bauce B, Basso C, et al. Clinical profile and long-term follow-up of 37 families with arrhythmogenic right ventricular cardiomyopathy. J Am Coll Cardiol 2000;36:2226–33.
729. Fung WH, Sanderson JE. Clinical profile of arrhythmogenic right ventricular cardiomyopathy in Chinese patients. Int J Cardiol 2001;81:9–18.
730. Peters S, Peters H, Thierfelder L. Risk stratification of sudden cardiac death and malignant ventricular arrhythmias in right ventricular dysplasia-cardiomyopathy. Int J Cardiol 1999;71:243–50.
731. Basso C, Thiene G, Corrado D, et al. Arrhythmogenic right ventricular cardiomyopathy. Dysplasia, dystrophy, or myocarditis? Circulation 1996;94:983–91.
732. Fornes P, Ratel S, Lecomte D. Pathology of arrhythmogenic right ventricular cardiomyopathy/dysplasia—an autopsy study of 20 forensic cases. J Forensic Sci 1998;43:777–83.
733. Furlanello F, Bertoldi A, Dallago M, et al. Cardiac arrest and sudden death in competitive athletes with arrhythmogenic right ventricular dysplasia. Pacing Clin Electrophysiol 1998;21:331–5.
734. Burke AP, Robinson S, Radentz S, et al. Sudden death in right ventricular dysplasia with minimal gross abnormalities. J Forensic Sci 1999;44:438–43.
735. Peters S. Left ventricular impairment in arrhythmogenic right ventricular dysplasia: what we can learn from angiography. Cardiology 1995;86:473–6.
736. Peters S, Reil GH. Risk factors of cardiac arrest in arrhythmogenic right ventricular dysplasia. Eur Heart J 1995;16:77–80.
737. Bauce B, Nava A, Rampazzo A, et al. Familial effort polymorphic ventricular arrhythmias in arrhythmogenic right ventricular cardiomyopathy map to chromosome 1q42-43. Am J Cardiol 2000;85: 573–9.
738. Di Biase M, Favale S, Massari V, et al. Programmed stimulation in patients with minor forms of right ventricular dysplasia. Eur Heart J 1989;10 Suppl D:49–53.
739. Lemery R, Brugada P, Janssen J, et al. Nonischemic sustained ventricular tachycardia: clinical outcome in 12 patients with arrhythmogenic right ventricular dysplasia. J Am Coll Cardiol 1989;14:96–105.
740. Wichter T, Paul M, Wollmann C, et al. Implantable cardioverter/defibrillator therapy in arrhythmogenic right ventricular cardiomyopathy: single-center experience of long-term follow-up and complications in 60 patients. Circulation 2004;109:1503–8.
741. Corrado D, Leoni L, Link MS, et al. Implantable cardioverter-defibrillator therapy for prevention of sudden death in patients with arrhythmogenic right ventricular cardiomyopathy/dysplasia. Circulation 2003;108:3084–91.
742. Link MS, Wang PJ, Haugh CJ, et al. Arrhythmogenic right ventricular dysplasia: clinical results with implantable cardioverter defibrillators. J Interv Card Electrophysiol 1997;1:41–8.
743. Myerburg RJ, Castellanos A. Clinical trials of implantable defibrillators. N Engl J Med 1997;337:1621–3.
744. Fontaine G, Tonet J, Gallais Y, et al. Ventricular tachycardia catheter ablation in arrhythmogenic right ventricular dysplasia: a 16-year experience. Curr Cardiol Rep 2000;2:498–506.
745. Guiraudon GM, Klein GJ, Gulamhusein SS, et al. Total disconnection of the right ventricular free wall: surgical treatment of right ventricular tachycardia associated with right ventricular dysplasia. Circulation 1983;67:463–70.
746. DeSilva RA. Central nervous system risk factors for sudden cardiac death. Ann N Y Acad Sci 1982;382:143–61.
747. Cox GF, Kunkel LM. Dystrophies and heart disease. Curr Opin Cardiol 1997;12:329–43.
748. Pelargonio G, Dello RA, Sanna T, et al. Myotonic dystrophy and the heart. Heart 2002;88:665–70.
749. Munoz J, Sanjuan R, Morell JS, et al. Ventricular tachycardia in Duchenne's muscular dystrophy. Int J Cardiol 1996;54:259–62.
750. Samuels MA. Neurally induced cardiac damage. Definition of the problem. Neurol Clin 1993;11:273–92.
751. Merino JL, Peinado R. Arrhythmias associated with neuromuscular disorders. Card Electrophysiol Rev 2002;6:132–5.
752. Becane HM, Bonne G, Varnous S, et al. High incidence of sudden death with conduction system and myocardial disease due to lamins

A and C gene mutation. Pacing Clin Electrophysiol 2000;23:1661–6.
753. Colleran JA, Hawley RJ, Pinnow EE, et al. Value of the electrocardiogram in determining cardiac events and mortality in myotonic dystrophy. Am J Cardiol 1997;80:1494–7.
754. Corrado G, Lissoni A, Beretta S, et al. Prognostic value of electrocardiograms, ventricular late potentials, ventricular arrhythmias, and left ventricular systolic dysfunction in patients with Duchenne muscular dystrophy. Am J Cardiol 2002;89:838–41.
755. Ducceschi V, Nigro G, Sarubbi B, et al. Autonomic nervous system imbalance and left ventricular systolic dysfunction as potential candidates for arrhythmogenesis in Becker muscular dystrophy. Int J Cardiol 1997;59:275–9.
756. Perloff JK, Stevenson WG, Roberts NK, et al. Cardiac involvement in myotonic muscular dystrophy (Steinert's disease): a prospective study of 25 patients. Am J Cardiol 1984;54:1074–81.
757. Hiromasa S, Ikeda T, Kubota K, et al. Myotonic dystrophy: ambulatory electrocardiogram, electrophysiologic study, and echocardiographic evaluation. Am Heart J 1987;113:1482–8.
758. Stevenson WG, Perloff JK, Weiss JN, et al. Facioscapulohumeral muscular dystrophy: evidence for selective, genetic electrophysiologic cardiac involvement. J Am Coll Cardiol 1990;15:292–9.
759. James TN, Fisch C. Observations on the cardiovascular involvement in Friedreich's ataxia. Am Heart J 1963;66:164–75.
760. Roberts NK, Perloff JK, Kark RA. Cardiac conduction in the Kearns-Sayre syndrome (a neuromuscular disorder associated with progressive external ophthalmoplegia and pigmentary retinopathy). Report of 2 cases and review of 17 published cases. Am J Cardiol 1979;44:1396–400.
761. Charles R, Holt S, Kay JM, et al. Myocardial ultrastructure and the development of atrioventricular block in Kearns-Sayre syndrome. Circulation 1981;63:214–9.
762. James TN. Observations on the cardiovascular involvement, including the cardiac conduction system, in progressive muscular dystrophy. Am Heart J 1962;63:48–56.
763. Weinfeld MS, Drazner MH, Stevenson WG, et al. Early outcome of initiating amiodarone for atrial fibrillation in advanced heart failure. J Heart Lung Transplant 2000;19:638–43.
764. Khand AU, Rankin AC, Kaye GC, et al. Systematic review of the management of atrial fibrillation in patients with heart failure. Eur Heart J 2000;21:614–32.
765. Remme WJ, Kruyssen HA, Look MP, et al. Hemodynamic effects and tolerability of intravenous amiodarone in patients with impaired left ventricular function. Am Heart J 1991;122:96–103.
766. Singh SN, Fisher SG, Carson PE, et al. Prevalence and significance of nonsustained ventricular tachycardia in patients with premature ventricular contractions and heart failure treated with vasodilator therapy. Department of Veterans Affairs CHF STAT Investigators. J Am Coll Cardiol 1998;32:942–7.
767. Doval HC, Nul DR, Grancelli HO, et al. Nonsustained ventricular tachycardia in severe heart failure. Independent marker of increased mortality due to sudden death. GESICA-GEMA Investigators. Circulation 1996;94:3198–203.
768. Packer M. Lack of relation between ventricular arrhythmias and sudden death in patients with chronic heart failure. Circulation 1992;85:I50–6.
769. Linde C, Braunschweig F, Gadler F, et al. Long-term improvements in quality of life by biventricular pacing in patients with chronic heart failure: results from the Multisite Stimulation in Cardiomyopathy study (MUSTIC). Am J Cardiol 2003;91:1090–5.
770. Young JB, Abraham WT, Smith AL, et al. Combined cardiac resynchronization and implantable cardioversion defibrillation in advanced chronic heart failure: the MIRACLE ICD trial. JAMA 2003;289:2685–94.
771. Bristow MR, Saxon LA, Boehmer J, et al. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. N Engl J Med 2004;350:2140–50.
772. Cleland JG, Daubert JC, Erdmann E, et al. The effect of cardiac resynchronization on morbidity and mortality in heart failure. N Engl J Med 2005;352:1539–49.
773. Cazeau S, Leclercq C, Lavergne T, et al. Effects of multisite biventricular pacing in patients with heart failure and intraventricular conduction delay. N Engl J Med 2001;344:873–80.
774. Leon AR, Abraham WT, Curtis AB, et al. Safety of transvenous cardiac resynchronization system implantation in patients with chronic heart failure: combined results of over 2,000 patients from a multicenter study program. J Am Coll Cardiol 2005;46:2348–56.
775. McKusick-Nathans Institute for Genetic Medicine. Online Mendelian Inheritance in Man, OMIM (TM). Available at: http://www.ncbi.nlm.nih.gov/omim. Last update 2000.
776. Moss AJ, Schwartz PJ, Crampton RS, et al. The long QT syndrome. Prospective longitudinal study of 328 families. Circulation 1991;84:1136–44.
777. Brugada J, Brugada R, Antzelevitch C, et al. Long-term follow-up of individuals with the electrocardiographic pattern of right bundle-branch block and ST-segment elevation in precordial leads V1 to V3. Circulation 2002;105:73–8.
778. Leenhardt A, Lucet V, Denjoy I, et al. Catecholaminergic polymorphic ventricular tachycardia in children. A 7-year follow-up of 21 patients. Circulation 1995;91:1512–9.
779. Moss AJ, Zareba W, Hall WJ, et al. Effectiveness and limitations of beta-blocker therapy in congenital long-QT syndrome. Circulation 2000;101:616–23.
780. Zareba W, Moss AJ, Schwartz PJ, et al. Influence of genotype on the clinical course of the long-QT syndrome. International Long-QT Syndrome Registry Research Group. N Engl J Med 1998;339:960–5.
781. Schwartz PJ, Priori SG, Napolitano C. The long QT syndrome. In: Zipes DP, Jalife J, editors. From Cell to Bedside. 2000:597–615.
782. Romano C, Gemme G, Pongiglione R. [Rare cardiac arrhythmias of the pediatric age. II. Syncopal attacks due to paroxysmal ventricular fibrillation. (Presentation of 1st case in Italian pediatric literature)]. Clin Pediatr (Bologna) 1963;45:656–83.
783. Ward OC. A new familial cardiac syndrome in children. J Isr Med Assoc 1964;54:103–6.
784. Jervell A, Lange-Nielsen F. Congenital deaf-mutism, functional heart disease with prolongation of the QT interval and sudden death. Am Heart J 1957;54:59–68.
785. Wang Q, Curran ME, Splawski I, et al. Positional cloning of a novel potassium channel gene: KVLQT1 mutations cause cardiac arrhythmias. Nat Genet 1996;12:17–23.
786. Curran ME, Splawski I, Timothy KW, et al. A molecular basis for cardiac arrhythmia: HERG mutations cause long QT syndrome. Cell 1995;80:795–803.
787. Wang Q, Shen J, Splawski I, et al. SCN5A mutations associated with an inherited cardiac arrhythmia, long QT syndrome. Cell 1995;80:805–11.
788. Abbott GW, Sesti F, Splawski I, et al. MiRP1 forms IKr potassium channels with HERG and is associated with cardiac arrhythmia. Cell 1999;97:175–87.
789. Splawski I, Tristani-Firouzi M, Lehmann MH, et al. Mutations in the hminK gene cause long QT syndrome and suppress IKs function. Nat Genet 1997;17:338–40.
790. Splawski I, Timothy KW, Sharpe LM, et al. Ca(V)1.2 calcium channel dysfunction causes a multisystem disorder including arrhythmia and autism. Cell 2004;119:19–31.
791. Mohler PJ, Schott JJ, Gramolini AO, et al. Ankyrin-B mutation causes type 4 long-QT cardiac arrhythmia and sudden cardiac death. Nature 2003;421:634–9.
792. Kimbrough J, Moss AJ, Zareba W, et al. Clinical implications for affected parents and siblings of probands with long-QT syndrome. Circulation 2001;104:557–62.
793. Marks ML, Whisler SL, Clericuzio C, et al. A new form of long QT syndrome associated with syndactyly. J Am Coll Cardiol 1995;25:59–64.
794. Crotti L, Lundquist AL, Insolia R, et al. KCNH2-K897T is a genetic modifier of latent congenital long-QT syndrome. Circulation 2005;112:1251–8.
795. Rashba EJ, Zareba W, Moss AJ, et al. Influence of pregnancy on the risk for cardiac events in patients with hereditary long QT syndrome. LQTS Investigators. Circulation 1998;97:451–6.
796. Moss AJ, Zareba W, Kaufman ES, et al. Increased risk of arrhythmic events in long-QT syndrome with mutations in the pore region of the human ether-a-go-go-related gene potassium channel. Circulation 2002;105:794–9.

797. Priori SG, Napolitano C, Schwartz PJ, et al. Association of long QT syndrome loci and cardiac events among patients treated with beta-blockers. JAMA 2004;292:1341–4.
798. Schwartz PJ, Priori SG, Spazzolini C, et al. Genotype-phenotype correlation in the long-QT syndrome: gene-specific triggers for life-threatening arrhythmias. Circulation 2001;103:89–95.
799. Ackerman MJ, Tester DJ, Porter CJ. Swimming, a gene-specific arrhythmogenic trigger for inherited long QT syndrome. Mayo Clin Proc 1999;74:1088–94.
800. Moss AJ, Robinson JL, Gessman L, et al. Comparison of clinical and genetic variables of cardiac events associated with loud noise versus swimming among subjects with the long QT syndrome. Am J Cardiol 1999;84:876–9.
801. Wilde AA, Jongbloed RJ, Doevendans PA, et al. Auditory stimuli as a trigger for arrhythmic events differentiate HERG-related (LQTS2) patients from KVLQT1-related patients (LQTS1). J Am Coll Cardiol 1999;33:327–32.
802. 26th Bethesda Conference: recommendations for determining eligibility for competition in athletes with cardiovascular abnormalities. January 6–7, 1994. J Am Coll Cardiol 1994;24:845–99.
803. Andersen ED, Krasilnikoff PA, Overvad H. Intermittent muscular weakness, extrasystoles, and multiple developmental anomalies. A new syndrome? Acta Paediatr Scand 1971;60:559–64.
804. Tawil R, Ptacek LJ, Pavlakis SG, et al. Andersen's syndrome: potassium-sensitive periodic paralysis, ventricular ectopy, and dysmorphic features. Ann Neurol 1994;35:326–30.
805. Sansone V, Griggs RC, Meola G, et al. Andersen's syndrome: a distinct periodic paralysis. Ann Neurol 1997;42:305–12.
806. Zhang L, Benson DW, Tristani-Firouzi M, et al. Electrocardiographic features in Andersen-Tawil syndrome patients with KCNJ2 mutations: characteristic T-U-wave patterns predict the KCNJ2 genotype. Circulation 2005;111:2720–6.
807. Levitt LP, Rose LI, Dawson DM. Hypokalemic periodic paralysis with arrhythmia. N Engl J Med 1972;286:253–4.
808. Gutmann L. Periodic paralyses. Neurol Clin 2000;18:195–202.
809. Kannankeril PJ, Roden DM, Fish FA. Suppression of bidirectional ventricular tachycardia and unmasking of prolonged QT interval with verapamil in Andersen's syndrome. J Cardiovasc Electrophysiol 2004;15:119.
810. Napolitano C, Priori SG, Schwartz PJ, et al. Genetic testing in the long QT syndrome: development and validation of an efficient approach to genotyping in clinical practice. JAMA 2005;294:2975–80.
811. Gaita F, Giustetto C, Bianchi F, et al. Short QT syndrome: a familial cause of sudden death. Circulation 2003;108:965–70.
812. Priori SG, Pandit SV, Rivolta I, et al. A novel form of short QT syndrome (SQT3) is caused by a mutation in the KCNJ2 gene. Circ Res 2005;96:800–7.
813. Delise P, Guiducci U, Zeppilli P, et al. [Cardiological protocols on evaluation of fitness for competitive sports]. Ital Heart J Suppl 2005;6:502–46.
814. Brugada R, Hong K, Dumaine R, et al. Sudden death associated with short-QT syndrome linked to mutations in HERG. Circulation 2004;109:30–5.
815. Bellocq C, van Ginneken AC, Bezzina CR, et al. Mutation in the KCNQ1 gene leading to the short QT-interval syndrome. Circulation 2004;109:2394–7.
816. Priori SG, Pandit SV, Rivolta I, et al. A novel form of short QT syndrome (SQT3) is caused by a mutation in the KCNJ2 gene. Circ Res 2005;96:800–7.
817. Wolpert C, Schimpf R, Veltmann C, et al. Clinical characteristics and treatment of short QT syndrome. Expert Rev Cardiovasc Ther 2005;3:611–7.
818. Brugada P, Brugada J. Right bundle branch block, persistent ST segment elevation and sudden cardiac death: a distinct clinical and electrocardiographic syndrome. A multicenter report. J Am Coll Cardiol 1992;20:1391–6.
819. Chen Q, Kirsch GE, Zhang D, et al. Genetic basis and molecular mechanism for idiopathic ventricular fibrillation. Nature 1998;392:293–6.
820. Brugada J, Brugada P, Brugada R. The syndrome of right bundle branch block ST segment elevation in V1 to V3 and sudden death—the Brugada syndrome. Europace 1999;1:156–66.
821. Dumaine R, Towbin JA, Brugada P, et al. Ionic mechanisms responsible for the electrocardiographic phenotype of the Brugada syndrome are temperature dependent. Circ Res 1999;85:803–9.
822. Mok NS, Priori SG, Napolitano C, et al. A newly characterized SCN5A mutation underlying Brugada syndrome unmasked by hyperthermia. J Cardiovasc Electrophysiol 2003;14:407–11.
823. Saura D, Garcia-Alberola A, Carrillo P, et al. Brugada-like electrocardiographic pattern induced by fever. Pacing Clin Electrophysiol 2002;25:856–9.
824. Ortega-Carnicer J, Benezet J, Ceres F. Fever-induced ST-segment elevation and T-wave alternans in a patient with Brugada syndrome. Resuscitation 2003;57:315–7.
825. Brugada R, Brugada J, Antzelevitch C, et al. Sodium channel blockers identify risk for sudden death in patients with ST-segment elevation and right bundle branch block but structurally normal hearts. Circulation 2000;101:510–5.
826. Eckardt L, Probst V, Smits JP, et al. Long-term prognosis of individuals with right precordial ST-segment-elevation Brugada syndrome. Circulation 2005.
827. Belhassen B, Glick A, Viskin S. Efficacy of quinidine in high-risk patients with Brugada syndrome. Circulation 2004;110:1731–7.
828. Hermida JS, Denjoy I, Clerc J, et al. Hydroquinidine therapy in Brugada syndrome. J Am Coll Cardiol 2004;43:1853–60.
829. Alings M, Dekker L, Sadee A, et al. Quinidine induced electrocardiographic normalization in two patients with Brugada syndrome. Pacing Clin Electrophysiol 2001;24:1420–2.
830. Martini B, Buja GF, Canciani B, et al. Bidirectional tachycardia. A sustained form, not related to digitalis intoxication, in an adult without apparent cardiac disease. Jpn Heart J 1988;29:381–7.
831. Priori SG, Napolitano C, Tiso N, et al. Mutations in the cardiac ryanodine receptor gene (hRyR2) underlie catecholaminergic polymorphic ventricular tachycardia. Circulation 2001;103:196–200.
832. Laitinen PJ, Brown KM, Piippo K, et al. Mutations of the cardiac ryanodine receptor (RyR2) gene in familial polymorphic ventricular tachycardia. Circulation 2001;103:485–90.
833. Lahat H, Pras E, Olender T, et al. A missense mutation in a highly conserved region of CASQ2 is associated with autosomal recessive catecholamine-induced polymorphic ventricular tachycardia in Bedouin families from Israel. Am J Hum Genet 2001;69:1378–84.
834. Deal BJ, Miller SM, Scagliotti D, et al. Ventricular tachycardia in a young population without overt heart disease. Circulation 1986;73:1111–8.
835. Proclemer A, Ciani R, Feruglio GA. Right ventricular tachycardia with left bundle branch block and inferior axis morphology: clinical and arrhythmological characteristics in 15 patients. Pacing Clin Electrophysiol 1989;12:977–89.
836. Mehta D, Odawara H, Ward DE, et al. Echocardiographic and histologic evaluation of the right ventricle in ventricular tachycardias of left bundle branch block morphology without overt cardiac abnormality. Am J Cardiol 1989;63:939–44.
837. Morady F, Kadish AH, DiCarlo L, et al. Long-term results of catheter ablation of idiopathic right ventricular tachycardia. Circulation 1990;82:2093–9.
838. O'Connor BK, Case CL, Sokoloski MC, et al. Radiofrequency catheter ablation of right ventricular outflow tachycardia in children and adolescents. J Am Coll Cardiol 1996;27:869–74.
839. Movsowitz C, Schwartzman D, Callans DJ, et al. Idiopathic right ventricular outflow tract tachycardia: narrowing the anatomic location for successful ablation. Am Heart J 1996;131:930–6.
840. Lerman BB, Belardinelli L, West GA, et al. Adenosine-sensitive ventricular tachycardia: evidence suggesting cyclic AMP-mediated triggered activity. Circulation 1986;74:270–80.
841. Lerman BB. Response of nonreentrant catecholamine-mediated ventricular tachycardia to endogenous adenosine and acetylcholine. Evidence for myocardial receptor-mediated effects. Circulation 1993;87:382–90.
842. Wilber DJ, Baerman J, Olshansky B, et al. Adenosine-sensitive ventricular tachycardia. Clinical characteristics and response to catheter ablation. Circulation 1993;87:126–34.
843. Lemery R, Brugada P, Bella PD, et al. Nonischemic ventricular tachycardia. Clinical course and long-term follow-up in patients without clinically overt heart disease. Circulation 1989;79:990–9.

844. Goy JJ, Tauxe F, Fromer M, et al. Ten-years follow-up of 20 patients with idiopathic ventricular tachycardia. Pacing Clin Electrophysiol 1990;13:1142–7.
845. Pietras RJ, Lam W, Bauernfeind R, et al. Chronic recurrent right ventricular tachycardia in patients without ischemic heart disease: clinical, hemodynamic, and angiographic findings. Am Heart J 1983;105:357–66.
846. Morgera T, Salvi A, Alberti E, et al. Morphological findings in apparently idiopathic ventricular tachycardia. An echocardiographic haemodynamic and histologic study. Eur Heart J 1985;6:323–34.
847. Foale RA, Nihoyannopoulos P, Ribeiro P, et al. Right ventricular abnormalities in ventricular tachycardia of right ventricular origin: relation to electrophysiological abnormalities. Br Heart J 1986;56: 45–54.
848. Kanagaratnam L, Tomassoni G, Schweikert R, et al. Ventricular tachycardias arising from the aortic sinus of Valsalva: an under-recognized variant of left outflow tract ventricular tachycardia. J Am Coll Cardiol 2001;37:1408–14.
849. Krittayaphong R, Bhuripanyo K, Punlee K, et al. Effect of atenolol on symptomatic ventricular arrhythmia without structural heart disease: a randomized placebo-controlled study. Am Heart J 2002; 144:e10.
850. Mont L, Seixas T, Brugada P, et al. Clinical and electrophysiologic characteristics of exercise-related idiopathic ventricular tachycardia. Am J Cardiol 1991;68:897–900.
851. Hayashi H, Fujiki A, Tani M, et al. Circadian variation of idiopathic ventricular tachycardia originating from right ventricular outflow tract. Am J Cardiol 1999;84:99–101, A8.
852. Gill JS, Blaszyk K, Ward DE, et al. Verapamil for the suppression of idiopathic ventricular tachycardia of left bundle branch block-like morphology. Am Heart J 1993;126:1126–33.
853. Maron BJ, Carney KP, Lever HM, et al. Relationship of race to sudden cardiac death in competitive athletes with hypertrophic cardiomyopathy. J Am Coll Cardiol 2003;41:974–80.
854. Davidson S, Surawicz B. Ectopic beats and atrioventricular conduction disturbances in patients with hypopotassemia. Arch Intern Med 1967;120:280–5.
855. Hollifield JW. Thiazide treatment of hypertension. Effects of thiazide diuretics on serum potassium, magnesium, and ventricular ectopy. Am J Med 1986;80:8–12.
856. Hollifield JW. Thiazide treatment of systemic hypertension: effects on serum magnesium and ventricular ectopic activity. Am J Cardiol 1989;63:22G–5G.
857. Podrid PJ. Potassium and ventricular arrhythmias. Am J Cardiol 1990;65:33E–44E.
858. Dyckner T, Helmers C, Wester PO. Cardiac dysrhythmias in patients with acute myocardial infarction. Relation to serum potassium level and prior diuretic therapy. Acta Med Scand 1984;216: 127–32.
859. Nordrehaug JE, von der Lippe G. Hypokalaemia and ventricular fibrillation in acute myocardial infarction. Br Heart J 1983;50: 525–9.
860. Nordrehaug JE, Johannessen KA, von der Lippe G. Serum potassium concentration as a risk factor of ventricular arrhythmias early in acute myocardial infarction. Circulation 1985;71:645–9.
861. Kafka H, Langevin L, Armstrong PW. Serum magnesium and potassium in acute myocardial infarction. Influence on ventricular arrhythmias. Arch Intern Med 1987;147:465–9.
862. Hulting J. In-hospital ventricular fibrillation and its relation to serum potassium. Acta Med Scand Suppl 1981;647:109–16.
863. Thompson RG, Cobb LA. Hypokalemia after resuscitation from out-of-hospital ventricular fibrillation. JAMA 1982;248:2860–3.
864. Chadda KD, Lichstein E, Gupta P. Hypomagnesemia and refractory cardiac arrhythmia in a nondigitalized patient. Am J Cardiol 1973;31:98–100.
865. Tzivoni D, Keren A, Cohen AM, et al. Magnesium therapy for torsades de pointes. Am J Cardiol 1984;53:528–30.
866. Solomon RJ. Ventricular arrhythmias in patients with myocardial infarction and ischaemia. Relationship to serum potassium and magnesium. Drugs 1984;28 Suppl 1:66–76.
867. Sjogren A, Edvinsson L, Fallgren B. Magnesium deficiency in coronary artery disease and cardiac arrhythmias. J Intern Med 1989;226:213–22.
868. Rasmussen HS, McNair P, Norregard P, et al. Intravenous magnesium in acute myocardial infarction. Lancet 1986;1:234–6.
869. Abraham AS, Rosenmann D, Kramer M, et al. Magnesium in the prevention of lethal arrhythmias in acute myocardial infarction. Arch Intern Med 1987;147:753–5.
870. Rasmussen HS, Suenson M, McNair P, et al. Magnesium infusion reduces the incidence of arrhythmias in acute myocardial infarction. A double-blind placebo-controlled study. Clin Cardiol 1987;10: 351–6.
871. Smith LF, Heagerty AM, Bing RF, Barnett DB. Intravenous infusion of magnesium sulphate after acute myocardial infarction: effects on arrhythmias and mortality. Int J Cardiol 1986;12:175–83.
872. Hollifield JW. Magnesium depletion, diuretics, and arrhythmias. Am J Med 1987;82:30–7.
873. Rajs J, Rajs E, Lundman T. Unexpected death in patients suffering from eating disorders. A medico-legal study. Acta Psychiatr Scand 1986;74:587–96.
874. Iseri LT, Freed J, Bures AR. Magnesium deficiency and cardiac disorders. Am J Med 1975;58:837–46.
875. Zwerling HK. Does exogenous magnesium suppress myocardial irritability and tachyarrhythmias in the nondigitalized patient? Am Heart J 1987;113:1046–53.
876. Spies CD, Sander M, Stangl K, et al. Effects of alcohol on the heart. Curr Opin Crit Care 2001;7:337–43.
877. Albert CM, Manson JE, Cook NR, et al. Moderate alcohol consumption and the risk of sudden cardiac death among U.S. male physicians. Circulation 1999;100:944–50.
878. Dyer AR, Stamler J, Paul O, et al. Alcohol consumption, cardiovascular risk factors, and mortality in two Chicago epidemiologic studies. Circulation 1977;56:1067–74.
879. Wannamethee G, Shaper AG. Alcohol and sudden cardiac death. Br Heart J 1992;68:443–8.
880. Ettinger PO, Wu CF, De La Cruz C Jr., et al. Arrhythmias and the "Holiday Heart": alcohol-associated cardiac rhythm disorders. Am Heart J 1978;95:555–62.
881. Chenet L, McKee M, Leon D, et al. Alcohol and cardiovascular mortality in Moscow: new evidence of a causal association. J Epidemiol Community Health 1998;52:772–4.
882. Chenet L, Britton A, Kalediene R, et al. Daily variations in deaths in Lithuania: the possible contribution of binge drinking. Int J Epidemiol 2001;30:743–8.
883. Shkolnikov VM, McKee M, Chervyakov VV, et al. Is the link between alcohol and cardiovascular death among young Russian men attributable to misclassification of acute alcohol intoxication? Evidence from the city of Izhevsk. J Epidemiol Community Health 2002;56:171–4.
884. Corrao G, Rubbiati L, Bagnardi V, et al. Alcohol and coronary heart disease: a meta-analysis. Addiction 2000;95:1505–23.
885. Shaper AG, Wannamethee SG. Alcohol intake and mortality in middle aged men with diagnosed coronary heart disease. Heart 2000;83:394–9.
886. Campbell PH, Barker LA, McDonough KH. The effect of acute ethanol exposure on the chronotropic and inotropic function of the rat right atrium. J Pharm Pharmacol 2000;52:1001–10.
887. Greenspon AJ, Stang JM, Lewis R, et al. Provocation of ventricular tachycardia after consumption of alcohol. N Engl J Med 1979;301: 1049–50.
888. Greenspon AJ, Schaal SF. The "holiday heart": electrophysiologic studies of alcohol effects in alcoholics. Ann Intern Med 1983;98: 135–9.
889. Kajander OA, Kupari M, Laippala P, et al. Coronary artery disease modifies left ventricular remodeling due to heavy alcohol consumption. Alcohol Clin Exp Res 2001;25:246–52.
890. Fernandez-Sola J, Nicolas JM, Pare JC, et al. Diastolic function impairment in alcoholics. Alcohol Clin Exp Res 2000;24:1830–5.
891. Fernandez-Sola J, Estruch R, Nicolas JM, et al. Comparison of alcoholic cardiomyopathy in women versus men. Am J Cardiol 1997;80:481–5.
892. Fernandez-Sola J, Estruch R, Grau JM, et al. The relation of alcoholic myopathy to cardiomyopathy. Ann Intern Med 1994;120: 529–36.
893. Day CP, James OF, Butler TJ, et al. QT prolongation and sudden cardiac death in patients with alcoholic liver disease. Lancet 1993; 341:1423–8.

894. Wannamethee G, Shaper AG, Macfarlane PW, et al. Risk factors for sudden cardiac death in middle-aged British men. Circulation 1995;91:1749–56.
895. Sexton PT, Walsh J, Jamrozik K, et al. Risk factors for sudden unexpected cardiac death in Tasmanian men. Aust N Z J Med 1997;27:45–50.
896. Escobedo LG, Caspersen CJ. Risk factors for sudden coronary death in the United States. Epidemiology 1997;8:175–80.
897. Kannel WB, Schatzkin A. Sudden death: lessons from subsets in population studies. J Am Coll Cardiol 1985;5:141B–9B.
898. Cupples LA, Gagnon DR, Kannel WB. Long- and short-term risk of sudden coronary death. Circulation 1992;85:I11–I18.
899. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). Lancet 1994;344:1383–9.
900. The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. N Engl J Med 1998;339: 1349–57.
901. De Sutter J, Tavernier R, De Buyzere M, et al. Lipid lowering drugs and recurrences of life-threatening ventricular arrhythmias in high-risk patients. J Am Coll Cardiol 2000;36:766–72.
902. Shepherd J, Cobbe SM, Ford I, et al. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group. N Engl J Med 1995;333:1301–7.
903. Downs Jr., Clearfield M, Weis S, et al. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS. Air Force/Texas Coronary Atherosclerosis Prevention Study. JAMA 1998;279: 1615–22.
904. Albert CM, Hennekens CH, O'Donnell CJ, et al. Fish consumption and risk of sudden cardiac death. JAMA 1998;279:23–8.
905. Albert CM, Campos H, Stampfer MJ, et al. Blood levels of long-chain n-3 fatty acids and the risk of sudden death. N Engl J Med 2002;346:1113–8.
906. Burr ML, Fehily AM, Rogers S, et al. Diet and Reinfarction Trial (DART): design, recruitment, and compliance. Eur Heart J 1989; 10:558–67.
907. de Lorgeril M, Renaud S, Mamelle N, et al. Mediterranean alpha-linolenic acid-rich diet in secondary prevention of coronary heart disease. Lancet 1994;343:1454–9.
908. de Lorgeril M, Salen P, Martin JL, et al. Mediterranean diet, traditional risk factors, and the rate of cardiovascular complications after myocardial infarction: final report of the Lyon Diet Heart Study. Circulation 1999;99:779–85.
909. Singh RB, Niaz MA, Sharma JP, et al. Randomized, double-blind, placebo-controlled trial of fish oil and mustard oil in patients with suspected acute myocardial infarction: the Indian experiment of infarct survival–4. Cardiovasc Drugs Ther 1997;11:485–91.
910. Siscovick DS, Raghunathan TE, King I, et al. Dietary intake and cell membrane levels of long-chain n-3 polyunsaturated fatty acids and the risk of primary cardiac arrest. JAMA 1995;274:1363–7.
911. Marchioli R, Barzi F, Bomba E, et al. Early protection against sudden death by n-3 polyunsaturated fatty acids after myocardial infarction: time-course analysis of the results of the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI)-Prevenzione. Circulation 2002;105:1897–903.
912. Corrado D, Basso C, Rizzoli G, et al. Does sports activity enhance the risk of sudden death in adolescents and young adults? J Am Coll Cardiol 2003;42:1959–63.
913. Maron BJ, Mitchell JH. Revised eligibility recommendations for competitive athletes with cardiovascular abnormalities. J Am Coll Cardiol 1994;24:848–50.
914. Maron BJ, Araujo CG, Thompson PD, et al. Recommendations for preparticipation screening and the assessment of cardiovascular disease in masters athletes: an advisory for healthcare professionals from the working groups of the World Heart Federation, the International Federation of Sports Medicine, and the American Heart Association Committee on Exercise, Cardiac Rehabilitation, and Prevention. Circulation 2001;103:327–34.
915. Maron BJ, Thompson PD, Puffer JC, et al. Cardiovascular preparticipation screening of competitive athletes. A statement for health professionals from the Sudden Death Committee (clinical cardiology) and Congenital Cardiac Defects Committee (cardiovascular disease in the young), American Heart Association. Circulation 1996;94:850–6.
916. Maron BJ, Zipes DP. Introduction: eligibility recommendations for competitive athletes with cardiovascular abnormalities-general considerations. J Am Coll Cardiol 2005;45:1318–21.
917. Pelliccia A, Maron BJ. Preparticipation cardiovascular evaluation of the competitive athlete: perspectives from the 30-year Italian experience. Am J Cardiol 1995;75:827–9.
918. Lyznicki JM, Nielsen NH, Schneider JF. Cardiovascular screening of student athletes. Am Fam Physician 2000;62:765–74.
919. Maron BJ. Sudden death in young athletes. N Engl J Med 2003;349:1064–75.
920. Franklin BA, Fletcher GF, Gordon NF, et al. Cardiovascular evaluation of the athlete. Issues regarding performance, screening and sudden cardiac death. Sports Med 1997;24:97–119.
921. Fuller CM, McNulty CM, Spring DA, et al. Prospective screening of 5,615 high school athletes for risk of sudden cardiac death. Med Sci Sports Exerc 1997;29:1131–8.
922. Fuller CM. Cost effectiveness analysis of screening of high school athletes for risk of sudden cardiac death. Med Sci Sports Exerc 2000;32:887–90.
923. World Anti-Doping Agency. The World Anti-doping Code: the 2004 Prohibited List, International Standard. June 16, 2004.
924. Zipes DP, Garson A Jr. 26th Bethesda Conference: recommendations for determining eligibility for competition in athletes with cardiovascular abnormalities. Task Force 6: arrhythmias. J Am Coll Cardiol 1994;24:892–9.
925. Rautaharju PM, Zhou SH, Wong S, et al. Sex differences in the evolution of the electrocardiographic QT interval with age. Can J Cardiol 1992;8:690–5.
926. Lehmann MH, Timothy KW, Frankovich D, et al. Age-gender influence on the rate-corrected QT interval and the QT-heart rate relation in families with genotypically characterized long QT syndrome. J Am Coll Cardiol 1997;29:93–9.
927. El-Eraky H, Thomas SH. Effects of sex on the pharmacokinetic and pharmacodynamic properties of quinidine. Br J Clin Pharmacol 2003;56:198–204.
928. Ebert SN, Liu XK, Woosley RL. Female gender as a risk factor for drug-induced cardiac arrhythmias: evaluation of clinical and experimental evidence. J Womens Health 1998;7:547–57.
929. Locati EH, Zareba W, Moss AJ, et al. Age- and sex-related differences in clinical manifestations in patients with congenital long-QT syndrome: findings from the International LQTS Registry. Circulation 1998;97:2237–44.
930. Makkar RR, Fromm BS, Steinman RT, et al. Female gender as a risk factor for torsades de pointes associated with cardiovascular drugs. JAMA 1993;270:2590–7.
931. Lehmann MH, Hardy S, Archibald D, et al. Sex difference in risk of torsade de pointes with d,l-sotalol. Circulation 1996;94:2535–41.
932. Pratt CM, Camm AJ, Cooper W, et al. Mortality in the Survival With ORal D-sotalol (SWORD) trial: why did patients die? Am J Cardiol 1998;81:869–76.
933. Kuhlkamp V, Mermi J, Mewis C, et al. Efficacy and proarrhythmia with the use of d,l-sotalol for sustained ventricular tachyarrhythmias. J Cardiovasc Pharmacol 1997;29:373–81.
934. Expert consensus document on management of cardiovascular diseases during pregnancy. Eur Heart J 2003;24:761–81.
935. Widerhorn J, Widerhorn AL, Rahimtoola SH, et al. WPW syndrome during pregnancy: increased incidence of supraventricular arrhythmias. Am Heart J 1992;123:796–8.
936. Tawam M, Levine J, Mendelson M, et al. Effect of pregnancy on paroxysmal supraventricular tachycardia. Am J Cardiol 1993;72: 838–40.
937. Lee SH, Chen SA, Wu TJ, et al. Effects of pregnancy on first onset and symptoms of paroxysmal supraventricular tachycardia. Am J Cardiol 1995;76:675–8.
938. Brodsky M, Doria R, Allen B, et al. New-onset ventricular tachycardia during pregnancy. Am Heart J 1992;123:933–41.
939. Russell RO Jr.. Paroxysmal ventricular tachycardia associated with pregnancy. Ala J Med Sci 1969;6:111–20.

940. Gowda RM, Khan IA, Mehta NJ, et al. Cardiac arrhythmias in pregnancy: clinical and therapeutic considerations. Int J Cardiol 2003;88:129–33.
941. Trappe HJ, Pfitzner P. [Cardiac arrhythmias in pregnancy]. Z Kardiol 2001;90 Suppl 4:36–44.
942. Siu SC, Sermer M, Colman JM, et al. Prospective multicenter study of pregnancy outcomes in women with heart disease. Circulation 2001;104:515–21.
943. Rodriguez LM, de Chillou C, Schlapfer J, et al. Age at onset and gender of patients with different types of supraventricular tachycardias. Am J Cardiol 1992;70:1213–5.
944. Wolbrette D, Patel H. Arrhythmias and women. Curr Opin Cardiol 1999;14:36–43.
945. Calkins H, Langberg J, Sousa J, et al. Radiofrequency catheter ablation of accessory atrioventricular connections in 250 patients. Abbreviated therapeutic approach to Wolff-Parkinson-White syndrome. Circulation 1992;85:1337–46.
946. Jackman WM, Wang XZ, Friday KJ, et al. Catheter ablation of accessory atrioventricular pathways (Wolff-Parkinson-White syndrome) by radiofrequency current. N Engl J Med 1991;324:1605–11.
947. Swartz JF, Tracy CM, Fletcher RD. Radiofrequency endocardial catheter ablation of accessory atrioventricular pathway atrial insertion sites. Circulation 1993;87:487–99.
948. Lerner DJ, Kannel WB. Patterns of coronary heart disease morbidity and mortality in the sexes: a 26-year follow-up of the Framingham population. Am Heart J 1986;111:383–90.
949. Dittrich H, Gilpin E, Nicod P, et al. Acute myocardial infarction in women: influence of gender on mortality and prognostic variables. Am J Cardiol 1988;62:1–7.
950. Aronow WS. Treatment of ventricular arrhythmias in older adults. J Am Geriatr Soc 1995;43:688–95.
951. Fleg JL, Kennedy HL. Cardiac arrhythmias in a healthy elderly population: detection by 24-hour ambulatory electrocardiography. Chest 1982;81:302–7.
952. Lee KL, Tai YT. Long-term low-dose amiodarone therapy in the management of ventricular and supraventricular tachyarrhythmias: efficacy and safety. Clin Cardiol 1997;20:372–7.
953. Aronow WS, Epstein S, Schwartz KS, et al. Prevalence of arrhythmias detected by ambulatory electrocardiographic monitoring and of abnormal left ventricular ejection fraction in persons older than 62 years in a long-term health care facility. Am J Cardiol 1987;59:368–9.
954. Messerli FH, Ventura HO, Elizardi DJ, et al. Hypertension and sudden death. Increased ventricular ectopic activity in left ventricular hypertrophy. Am J Med 1984;77:18–22.
955. Kannel WB, Gordon T, Offutt D. Left ventricular hypertrophy by electrocardiogram. Prevalence, incidence, and mortality in the Framingham study. Ann Intern Med 1969;71:89–105.
956. Stevenson WG, Stevenson LW, Middlekauff HR, Saxon LA. Sudden death prevention in patients with advanced ventricular dysfunction. Circulation 1993;88:2953–61.
957. Aronow WS, Ahn C, Mercando AD, et al. Prevalence and association of ventricular tachycardia and complex ventricular arrhythmias with new coronary events in older men and women with and without cardiovascular disease. J Gerontol A Biol Sci Med Sci 2002;57:M178–80.
958. Volpi A, Cavalli A, Turato R, et al. Incidence and short-term prognosis of late sustained ventricular tachycardia after myocardial infarction: results of the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI-3) Data Base. Am Heart J 2001;142:87–92.
959. Kannel WB, Cupples LA, D'Agostino RB. Sudden death risk in overt coronary heart disease: the Framingham Study. Am Heart J 1987;113:799–804.
960. Kuller L, Lilienfeld A, Fisher R. Epidemiological study of sudden and unexpected deaths due to arteriosclerotic heart disease. Circulation 1966;34:1056–68.
961. Zabel M, Klingenheben T, Franz MR, et al. Assessment of QT dispersion for prediction of mortality or arrhythmic events after myocardial infarction: results of a prospective, long-term follow-up study. Circulation 1998;97:2543–50.
962. More D, O'Brien K, Shaw J. Arrhythmogenic right ventricular dysplasia in the elderly. Pacing Clin Electrophysiol 2002;25:1266–9.
963. Ghai A, Silversides C, Harris L, et al. Left ventricular dysfunction is a risk factor for sudden cardiac death in adults late after repair of tetralogy of Fallot. J Am Coll Cardiol 2002;40:1675–80.
964. Viskin S, Fish R, Eldar M, et al. Prevalence of the Brugada sign in idiopathic ventricular fibrillation and healthy controls. Heart 2000;84:31–6.
965. Ornato JP, Peberdy MA, Tadler SC, et al. Factors associated with the occurrence of cardiac arrest during hospitalization for acute myocardial infarction in the second national registry of myocardial infarction in the U.S. Resuscitation 2001;48:117–23.
966. Aronow WS, Mercando AD, Epstein S, et al. Effect of quinidine or procainamide versus no antiarrhythmic drug on sudden cardiac death, total cardiac death, and total death in elderly patients with heart disease and complex ventricular arrhythmias. Am J Cardiol 1990;66:423–8.
967. The Cardiac Arrhythmia Suppression Trial (CAST) Investigators. Preliminary report: effect of encainide and flecainide on mortality in a randomized trial of arrhythmia suppression after myocardial infarction. N Engl J Med 1989;321:406–12.
968. The Cardiac Arrhythmia Suppression Trial II Investigators. Effect of the antiarrhythmic agent moricizine on survival after myocardial infarction. N Engl J Med 1992;327:227–33.
969. Velebit V, Podrid P, Lown B, et al. Aggravation and provocation of ventricular arrhythmias by antiarrhythmic drugs. Circulation 1982;65:886–94.
970. Waldo AL, Camm AJ, deRuyter H, et al. Effect of d-sotalol on mortality in patients with left ventricular dysfunction after recent and remote myocardial infarction. The SWORD Investigators. Survival With Oral d-Sotalol. Lancet 1996;348:7–12.
971. Sim I, McDonald KM, Lavori PW, et al. Quantitative overview of randomized trials of amiodarone to prevent sudden cardiac death. Circulation 1997;96:2823–9.
972. The CASCADE Investigators. Randomized antiarrhythmic drug therapy in survivors of cardiac arrest (the CASCADE Study). Am J Cardiol 1993;72:280–7.
973. A randomized trial of propranolol in patients with acute myocardial infarction. II. Morbidity results. JAMA 1983;250:2814–9.
974. Gundersen T, Abrahamsen AM, Kjekshus J, et al. Timolol-related reduction in mortality and reinfarction in patients ages 65–75 years surviving acute myocardial infarction. Prepared for the Norwegian Multicentre Study Group. Circulation 1982;66:1179–84.
975. Olsson G, Rehnqvist N, Sjogren A, et al. Long-term treatment with metoprolol after myocardial infarction: effect on 3 year mortality and morbidity. J Am Coll Cardiol 1985;5:1428–37.
976. Dargie HJ. Effect of carvedilol on outcome after myocardial infarction in patients with left-ventricular dysfunction: the CAPRICORN randomised trial. Lancet 2001;357:1385–90.
977. Kennedy HL, Brooks MM, Barker AH, et al. Beta-blocker therapy in the Cardiac Arrhythmia Suppression Trial. CAST Investigators. Am J Cardiol 1994;74:674–80.
978. Packer M, Coats AJ, Fowler MB, et al. Effect of carvedilol on survival in severe chronic heart failure. N Engl J Med 2001;344:1651–8.
979. Leizorovicz A, Lechat P, Cucherat M, et al. Bisoprolol for the treatment of chronic heart failure: a meta-analysis on individual data of two placebo-controlled studies—CIBIS and CIBIS II. Cardiac Insufficiency Bisoprolol Study. Am Heart J 2002;143:301–7.
980. Soumerai SB, McLaughlin TJ, Spiegelman D, et al. Adverse outcomes of underuse of beta-blockers in elderly survivors of acute myocardial infarction. JAMA 1997;277:115–21.
981. Woods KL, Ketley D, Lowy A, et al. Beta-blockers and antithrombotic treatment for secondary prevention after acute myocardial infarction. Towards an understanding of factors influencing clinical practice. The European Secondary Prevention Study Group. Eur Heart J 1998;19:74–9.
982. Tresch DD, Troup PJ, Thakur RK, et al. Comparison of efficacy of automatic implantable cardioverter defibrillator in patients older and younger than 65 years of age. Am J Med 1991;90:717–24.
983. Trappe HJ, Pfitzner P, Achtelik M, et al. Age dependent efficacy of implantable cardioverter-defibrillator treatment: observations in 450 patients over an 11 year period. Heart 1997;78:364–70.

984. Geelen P, Lorga FA, Primo J, et al. Experience with implantable cardioverter defibrillator therapy in elderly patients. Eur Heart J 1997;18:1339–42.
985. Panotopoulos PT, Axtell K, Anderson AJ, et al. Efficacy of the implantable cardioverter-defibrillator in the elderly. J Am Coll Cardiol 1997;29:556–60.
986. Saksena S, Mathew P, Giorgberidze I, et al. Implantable defibrillator therapy for the elderly. Am J Geriatr Cardiol 1998;7:11–3.
987. McDonald KM, Hlatky MA, Saynina O, et al. Trends in hospital treatment of ventricular arrhythmias among Medicare beneficiaries, 1985 to 1995. Am Heart J 2002;144:413–21.
988. Lunney Jr., Lynn J, Foley DJ, et al. Patterns of functional decline at the end of life. JAMA 2003;289:2387–92.
989. Molander N. Sudden natural death in later childhood and adolescence. Arch Dis Child 1982;57:572–6.
990. Neuspiel DR, Kuller LH. Sudden and unexpected natural death in childhood and adolescence. JAMA 1985;254:1321–5.
991. Driscoll DJ, Edwards WD. Sudden unexpected death in children and adolescents. J Am Coll Cardiol 1985;5:118B–21B.
992. Priori SG, Aliot E, Blomstrom-Lundqvist C, et al. Task Force on Sudden Cardiac Death, European Society of Cardiology. Europace 2002;4:3–18.
993. Silka MJ, Kron J, Dunnigan A, et al. Sudden cardiac death and the use of implantable cardioverter-defibrillators in pediatric patients. The Pediatric Electrophysiology Society. Circulation 1993;87:800–7.
994. Southall DP, Richards J, Mitchell P, et al. Study of cardiac rhythm in healthy newborn infants. Br Heart J 1980;43:14–20.
995. Scott O, Williams GJ, Fiddler GI. Results of 24 hour ambulatory monitoring of electrocardiogram in 131 healthy boys aged 10 to 13 years. Br Heart J 1980;44:304–8.
996. Nagashima M, Matsushima M, Ogawa A, et al. Cardiac arrhythmias in healthy children revealed by 24–hour ambulatory ECG monitoring. Pediatr Cardiol 1987;8:103–8.
997. Friedman RA, Kearney DL, Moak JP, et al. Persistence of ventricular arrhythmia after resolution of occult myocarditis in children and young adults. J Am Coll Cardiol 1994;24:780–3.
998. Van Hare GF, Stanger P. Ventricular tachycardia and accelerated ventricular rhythm presenting in the first month of life. Am J Cardiol 1991;67:42–5.
999. Garson A Jr., Smith RT Jr., Moak JP, et al. Incessant ventricular tachycardia in infants: myocardial hamartomas and surgical cure. J Am Coll Cardiol 1987;10:619–26.
1000. Zeigler VL, Gillette PC, Crawford FA Jr., et al. New approaches to treatment of incessant ventricular tachycardia in the very young. J Am Coll Cardiol 1990;16:681–5.
1001. Sellers TD Jr., Bashore TM, Gallagher JJ. Digitalis in the preexcitation syndrome. Analysis during atrial fibrillation. Circulation 1977;56:260–7.
1002. Garson A Jr., Gillette PC, Titus JL, et al. Surgical treatment of ventricular tachycardia in infants. N Engl J Med 1984;310:1443–5.
1003. Garson A Jr., Dick M, Fournier A, et al. The long QT syndrome in children. An international study of 287 patients. Circulation 1993;87:1866–72.
1004. Virdi VS, Bharti B, Poddar B, et al. Ventricular tachycardia in congenital adrenal hyperplasia. Anaesth Intensive Care 2002;30:380–1.
1005. Schwartz PJ, Stramba-Badiale M, Segantini A, et al. Prolongation of the QT interval and the sudden infant death syndrome. N Engl J Med 1998;338:1709–14.
1006. Towbin JA, Friedman RA. Prolongation of the QT interval and the sudden infant death syndrome. N Engl J Med 1998;338:1760–1.
1007. American Academy of Pediatrics. Task Force on Infant Sleep Position and Sudden Infant Death Syndrome. Changing concepts of sudden infant death syndrome: implications for infant sleeping environment and sleep position. Pediatrics 2000;105:650–6.
1008. Davis AM, Gow RM, McCrindle BW, et al. Clinical spectrum, therapeutic management, and follow-up of ventricular tachycardia in infants and young children. Am Heart J 1996;131:186–91.
1009. Benson DW Jr., Benditt DG, Anderson RW, et al. Cardiac arrest in young, ostensibly healthy patients: clinical, hemodynamic, and electrophysiologic findings. Am J Cardiol 1983;52:65–9.
1010. Ellenbogen KA, Wood MA, Shepard RK, et al. Detection and management of an implantable cardioverter defibrillator lead failure: incidence and clinical implications. J Am Coll Cardiol 2003;41:73–80.
1011. Dubin AM, Berul CI, Bevilacqua LM, et al. The use of implantable cardioverter-defibrillators in pediatric patients awaiting heart transplantation. J Card Fail 2003;9:375–9.
1012. Sinha AM, Stellbrink C, Schuchert A, et al. Clinical experience with a new detection algorithm for differentiation of supraventricular from ventricular tachycardia in a dual-chamber defibrillator. J Cardiovasc Electrophysiol 2004;15:646–52.
1013. Gillis AM, Unterberg-Buchwald C, Schmidinger H, et al. Safety and efficacy of advanced atrial pacing therapies for atrial tachyarrhythmias in patients with a new implantable dual chamber cardioverter-defibrillator. J Am Coll Cardiol 2002;40:1653–9.
1014. Olson WH. Sensing and detection of ventricular tachyarrhythmias by the ICD. In: Allessie MA, Fromer M, editors. Atrial and Ventricular Fibrillation: Mechanisms and Device Therapy. 1997:399–415.
1015. Fromer M, Brachmann J, Block M, et al. Efficacy of automatic multimodal device therapy for ventricular tachyarrhythmias as delivered by a new implantable pacing cardioverter-defibrillator. Results of a European multicenter study of 102 implants. Circulation 1992;86:363–74.
1016. Birgersdotter-Green U, Rosenqvist M, Lindemans FW, et al. Holter documented sudden death in a patient with an implanted defibrillator. Pacing Clin Electrophysiol 1992;15:1008–14.
1017. Wilkoff BL, Kuhlkamp V, Volosin K, et al. Critical analysis of dual-chamber implantable cardioverter-defibrillator arrhythmia detection: results and technical considerations. Circulation 2001;103:381–6.
1018. Saksena S, Prakash A, Mangeon L, et al. Clinical efficacy and safety of atrial defibrillation using biphasic shocks and current nonthoracotomy endocardial lead configurations. Am J Cardiol 1995;76:913–21.
1019. Friedman PA, Dijkman B, Warman EN, et al. Atrial therapies reduce atrial arrhythmia burden in defibrillator patients. Circulation 2001;104:1023–8.
1020. Adler SW, Wolpert C, Warman EN, et al. Efficacy of pacing therapies for treating atrial tachyarrhythmias in patients with ventricular arrhythmias receiving a dual-chamber implantable cardioverter defibrillator. Circulation 2001;104:887–92.
1021. Roden DM, Anderson ME. Proarrhythmia. In: Kass RS, Clancey CE, editors. Handbook of Experimental Pharmacology: vol. 171. Basis and Treatment of Cardiac Arrhythmias. Boston, MA: Springer Verlag, 2006:288–304.
1022. Antman EM, Wenger TL, Butler VP Jr., et al. Treatment of 150 cases of life-threatening digitalis intoxication with digoxin-specific Fab antibody fragments. Final report of a multicenter study. Circulation 1990;81:1744–52.
1023. Yang P, Kanki H, Drolet B, et al. Allelic variants in long-QT disease genes in patients with drug-associated torsades de pointes. Circulation 2002;105:1943–8.
1024. Torp-Pedersen C, Moller M, Bloch-Thomsen PE, et al. Dofetilide in patients with congestive heart failure and left ventricular dysfunction. Danish Investigations of Arrhythmia and Mortality on Dofetilide Study Group. N Engl J Med 1999;341:857–65.
1025. Roden DM. Drug-induced prolongation of the QT interval. N Engl J Med 2004;350:1013–22.
1026. Choy AM, Lang CC, Chomsky DM, et al. Normalization of acquired QT prolongation in humans by intravenous potassium. Circulation 1997;96:2149–54.
1027. Yang T, Roden DM. Extracellular potassium modulation of drug block of IKr. Implications for torsade de pointes and reverse use-dependence. Circulation 1996;93:407–11.
1028. Tzivoni D, Banai S, Schuger C, et al. Treatment of torsade de pointes with magnesium sulfate. Circulation 1988;77:392–7.
1029. Assimes TL, Malcolm I. Torsade de pointes with sotalol overdose treated successfully with lidocaine. Can J Cardiol 1998;14:753–6.
1030. Liao WB, Bullard MJ, Kuo CT, et al. Anticholinergic overdose induced torsade de pointes successfully treated with verapamil. Jpn Heart J 1996;37:925–31.
1031. Rankin AC, Pringle SD, Cobbe SM. Acute treatment of torsades de pointes with amiodarone: proarrhythmic and antiarrhythmic association of QT prolongation. Am Heart J 1990;119:185–6.
1032. Lazzara R. Antiarrhythmic drugs and torsade de pointes. Eur Heart J 1993;14 Suppl H:88–92.

1033. Hondeghem LM. Antiarrhythmic agents: modulated receptor applications. Circulation 1987;75:514–20.
1034. Chamberlain DA, Jewitt DE, Julian DG, et al. Oral mexiletine in high-risk patients after myocardial infarction. Lancet 1980;2:1324–7.
1035. U.K. Rythmodan Multicentre Study Group. Oral disopyramide after admission to hospital with suspected acute myocardial infarction. Postgrad Med J 1984;60:98–107.
1036. Akiyama T, Pawitan Y, Greenberg H, et al. Increased risk of death and cardiac arrest from encainide and flecainide in patients after non-Q-wave acute myocardial infarction in the Cardiac Arrhythmia Suppression Trial. CAST Investigators. Am J Cardiol 1991;68:1551–5.
1037. Hellestrand KJ, Burnett PJ, Milne Jr., et al. Effect of the antiarrhythmic agent flecainide acetate on acute and chronic pacing thresholds. Pacing Clin Electrophysiol 1983;6:892–9.
1038. Echt DS, Black JN, Barbey JT, et al. Evaluation of antiarrhythmic drugs on defibrillation energy requirements in dogs. Sodium channel block and action potential prolongation. Circulation 1989;79:1106–17.
1039. Crijns HJ, van Gelder I, Lie KI. Supraventricular tachycardia mimicking ventricular tachycardia during flecainide treatment. Am J Cardiol 1988;62:1303–6.
1040. Alings M, Wilde A. "Brugada" syndrome: clinical data and suggested pathophysiological mechanism. Circulation 1999;99:666–73.
1041. Tada H, Sticherling C, Oral H, et al. Brugada syndrome mimicked by tricyclic antidepressant overdose. J Cardiovasc Electrophysiol 2001;12:275.
1042. Littmann L, Monroe MH, Svenson RH. Brugada-type electrocardiographic pattern induced by cocaine. Mayo Clin Proc 2000;75:845–9.
1043. Roose SP, Glassman AH. Antidepressant choice in the patient with cardiac disease: lessons from the Cardiac Arrhythmia Suppression Trial (CAST) studies. J Clin Psychiatry 1994;55 Suppl A:83–7.
1044. Huang DT, Monahan KM, Zimetbaum P, et al. Hybrid pharmacologic and ablative therapy: a novel and effective approach for the management of atrial fibrillation. J Cardiovasc Electrophysiol 1998;9:462–9.
1045. Bajaj AK, Woosley RL, Roden DM. Acute electrophysiologic effects of sodium administration in dogs treated with O-desmethyl encainide. Circulation 1989;80:994–1002.
1046. Chouty F, Funck-Brentano C, Landau JM, et al. [Efficacy of high doses of molar lactate by the venous route in flecainide poisoning]. Presse Med 1987;16:808–10.
1047. Myerburg RJ, Kessler KM, Cox MM, et al. Reversal of proarrhythmic effects of flecainide acetate and encainide hydrochloride by propranolol. Circulation 1989;80:1571–9.
1048. Hoffman Jr., Votey SR, Bayer M, et al. Effect of hypertonic sodium bicarbonate in the treatment of moderate-to-severe cyclic antidepressant overdose. Am J Emerg Med 1993;11:336–41.
1049. Walczak T. Do antiepileptic drugs play a role in sudden unexpected death in epilepsy? Drug Saf 2003;26:673–83.
1050. Glassman AH, Bigger JT Jr.. Antipsychotic drugs: prolonged QTc interval, torsade de pointes, and sudden death. Am J Psychiatry 2001;158:1774–82.
1051. Witchel HJ, Hancox JC, Nutt DJ. Psychotropic drugs, cardiac arrhythmia, and sudden death. J Clin Psychopharmacol 2003;23:58–77.
1052. Ames D, Camm J, Cook P, et al. Cardiac risk of psychotropic drugs. Aust N Z J Psychiatry 2002;36:819–20.
1053. Heiman EM. Cardiac toxicity with thioridazine-tricyclic antidepressant combination. J Nerv Ment Dis 1977;165:139–43.
1054. Taylor DM. Antipsychotics and QT prolongation. Acta Psychiatr Scand 2003;107:85–95.
1055. Lipshultz SE, Lipsitz SR, Mone SM, et al. Female sex and drug dose as risk factors for late cardiotoxic effects of doxorubicin therapy for childhood cancer. N Engl J Med 1995;332:1738–43.
1056. Steinherz LJ, Steinherz PG, Tan C. Cardiac failure and dysrhythmias 6–19 years after anthracycline therapy: a series of 15 patients. Med Pediatr Oncol 1995;24:352–61.
1057. Ferrari E, Benhamou M, Baudouy M. [Cardiotoxicity associated with trastuzumab (herceptin). An undesired effect leads towards a model of cardiac insufficiency]. Arch Mal Coeur Vaiss 2004;97:333–7.
1058. Suter TM, Cook-Bruns N, Barton C. Cardiotoxicity associated with trastuzumab (Herceptin) therapy in the treatment of metastatic breast cancer. Breast 2004;13:173–83.
1059. Pichon MF, Cvitkovic F, Hacene K, et al. Drug-induced cardiotoxicity studied by longitudinal B-type natriuretic peptide assays and radionuclide ventriculography. In Vivo 2005;19:567–76.
1060. Bu'Lock FA, Mott MG, Oakhill A, et al. Early identification of anthracycline cardiomyopathy: possibilities and implications. Arch Dis Child 1996;75:416–22.
1061. Li CK, Sung RY, Kwok KL, et al. A longitudinal study of cardiac function in children with cancer over 40 months. Pediatr Hematol Oncol 2000;17:77–83.
1062. De WD, Suys B, Maurus R, et al. Dobutamine stress echocardiography in the evaluation of late anthracycline cardiotoxicity in childhood cancer survivors. Pediatr Res 1996;39:504–12.
1063. Klewer SE, Goldberg SJ, Donnerstein RL, et al. Dobutamine stress echocardiography: a sensitive indicator of diminished myocardial function in asymptomatic doxorubicin-treated long-term survivors of childhood cancer. J Am Coll Cardiol 1992;19:394–401.
1064. Lenk MK, Zeybek C, Okutan V, et al. Detection of early anthracycline-induced cardiotoxicity in childhood cancer with dobutamine stress echocardiography. Turk J Pediatr 1998;40:373–83.
1065. Johnson GL, Moffett CB, Geil JD, et al. Late echocardiographic findings following childhood chemotherapy with normal serial cardiac monitoring. J Pediatr Hematol Oncol 1996;18:72–5.
1066. Postma A, Elzenga NJ, Haaksma J, et al. Cardiac status in bone tumor survivors up to nearly 19 years after treatment with doxorubicin: a longitudinal study 1. Med Pediatr Oncol 2002;39:86–92.
1067. Friess GG, Boyd JF, Geer MR, et al. Effects of first-dose doxorubicin on cardiac rhythm as evaluated by continuous 24–hour monitoring. Cancer 1985;56:2762–4.
1068. Steinberg JS, Cohen AJ, Wasserman AG, et al. Acute arrhythmogenicity of doxorubicin administration. Cancer 1987;60:1213–8.
1069. Mladosievicova B, Foltinova A, Petrasova H, et al. Late effects of anthracycline therapy in childhood on signal-averaged ECG parameters. Int J Mol Med 2000;5:411–4.
1070. Schwartz CL, Hobbie WL, Truesdell S, et al. Corrected QT interval prolongation in anthracycline-treated survivors of childhood cancer. J Clin Oncol 1993;11:1906–10.
1071. Robben NC, Pippas AW, Moore JO. The syndrome of 5-fluorouracil cardiotoxicity. An elusive cardiopathy. Cancer 1993; 71:493–509.
1072. Pinter A, Dorian P, Newman D. Cesium-induced torsades de pointes. N Engl J Med 2002;346:383–4.
1073. Gowda RM, Cohen RA, Khan IA. Toad venom poisoning: resemblance to digoxin toxicity and therapeutic implications. Heart 2003;89:e14.
1074. Bain RJ. Accidental digitalis poisoning due to drinking herbal tea. Br Med J (Clin Res Ed) 1985;290:1624.
1075. Eddleston M, Ariaratnam CA, Sjostrom L, et al. Acute yellow oleander (Thevetia peruviana) poisoning: cardiac arrhythmias, electrolyte disturbances, and serum cardiac glycoside concentrations on presentation to hospital. Heart 2000;83:301–6.
1076. Samenuk D, Link MS, Homoud MK, et al. Adverse cardiovascular events temporally associated with ma huang, an herbal source of ephedrine. Mayo Clin Proc 2002;77:12–6.
1077. Haller CA, Benowitz NL. Adverse cardiovascular and central nervous system events associated with dietary supplements containing ephedra alkaloids. N Engl J Med 2000;343:1833–8.
1078. Gardner SF, Franks AM, Gurley BJ, et al. Effect of a multicomponent, ephedra-containing dietary supplement (Metabolife 356) on Holter monitoring and hemostatic parameters in healthy volunteers. Am J Cardiol 2003;91:1510–3, A9.
1079. Anand AJ. Fluorouracil cardiotoxicity. Ann Pharmacother 1994;28: 374–8.
1080. Gorgulu S, Celik S, Tezel T. A case of coronary spasm induced by 5-fluorouracil. Acta Cardiol 2002;57:381–3.
1081. Mizuno Y, Hokamura Y, Kimura T, et al. A case of 5-fluorouracil cardiotoxicity simulating acute myocardial infarction. Jpn Circ J 1995;59:303–7.
1082. Keefe DL, Roistacher N, Pierri MK. Clinical cardiotoxicity of 5-fluorouracil. J Clin Pharmacol 1993;33:1060–70.
1083. Schnetzler B, Popova N, Collao LC, et al. Coronary spasm induced by capecitabine. Ann Oncol 2001;12:723–4.
1084. Welch KM, Saiers J, Salonen R. Triptans and coronary spasm. Clin Pharmacol Ther 2000;68:337–8.
1085. Qasim A, Townend J, Davies MK. Ecstasy induced acute myocardial infarction. Heart 2001;85:E10.