

Sudden Cardiac Death Compendium

Circulation Research Compendium on Sudden Cardiac Death

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Gordon Tomaselli, Editor

Clinical Management and Prevention of Sudden Cardiac Death

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Abstract: Despite the revolutionary advancements in the past 3 decades in the treatment of ventricular tachyarrhythmias with device-based therapy, sudden cardiac death (SCD) remains an enormous public health burden. Survivors of SCD are generally at high risk for recurrent events. The clinical management of such patients requires a multidisciplinary approach from postresuscitative care to a thorough cardiovascular investigation in an attempt to identify the underlying substrate, with potential to eliminate or modify the triggers through catheter ablation and ultimately an implantable cardioverter-defibrillator (ICD) for prompt treatment of recurrences in those at risk. Early recognition of low left ventricular ejection fraction as a strong predictor of death and association of ventricular arrhythmias with sudden death led to significant investigation with antiarrhythmic drugs. The lack of efficacy and the proarrhythmic effects of drugs catalyzed the development and investigation of the ICD through several major clinical trials that proved the efficacy of ICD as a bedrock tool to detect and promptly treat life-threatening arrhythmias. The ICD therapy is routinely used for primary prevention of SCD in patients with cardiomyopathy and high risk inherited arrhythmic conditions and secondary prevention in survivors of sudden cardiac arrest. This compendium will review the clinical management of those surviving SCD and discuss landmark studies of antiarrhythmic drugs, ICD, and cardiac resynchronization therapy in the primary and secondary prevention of SCD. (*Circ Res.* 2015;116:2020-2040. DOI: 10.1161/CIRCRESAHA.116.304555.)

Key Words: cardiac resynchronization therapy ■ cardiomyopathies ■ death, sudden, cardiac ■ defibrillators ■ defibrillators, implantable ■ heart arrest ■ tachycardia, ventricular ■ ventricular fibrillation

Sudden cardiac death (SCD) is defined as an unexpected, nontraumatic death from a cardiovascular cause that occurs within a short period in those with or without antecedent heart disease. Accounting for >50% of all deaths from

cardiovascular disease, it is the most common cause of death in the United States and hence, an enormous public health hazard.¹⁻³ Although there has been a decline in the incidence of SCD paralleling the overall reduction in cardiovascular

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Nonstandard Abbreviations and Acronyms

AAD	antiarrhythmic drug
ACE	angiotensin-converting enzyme
ALIVE	Azimilide Post Infarct Survival
ARVD/c	arrhythmogenic right ventricular dysplasia/cardiomyopathy
AVID	Antiarrhythmics Versus Implantable Defibrillators
BASIS	Basel Antiarrhythmic Study of Infarct Survival
BEST	Beta-Blocker Bucindolol in Patients with Advance Chronic Heart Failure
BHAT	Beta-blocker Heart Attack Trial
CAD	coronary artery disease
CABG-Patch	Coronary Artery Bypass Graft-Patch
CARE-HF	Cardiac Resynchronization-Heart Failure
CASCADE	Cardiac Arrest in Seattle: Conventional Versus Amiodarone Drug Evaluation
CASH	Cardiac Arrest Study Hamburg
CAST	Cardiac Arrhythmia Suppression Trial
CHD	coronary heart disease
CHF-STAT	Survival Trial of Antiarrhythmic Therapy in Congestive Heart Failure
CIBIS-II	Cardiac Insufficiency Bisoprolol Study II
CIDS	Canadian Implantable Defibrillator Study
CLARIDI	Cholesterol Lowering and Arrhythmia Recurrences after Internal Defibrillator Implantation
COMMIT	Clopidogrel and Metoprolol in Myocardial Infarction Trial
COMPANION	Comparison of Medical Therapy, Pacing, and Defibrillation in Chronic Heart Failure
CPVT	catecholaminergic polymorphic ventricular tachycardia
CRT	cardiac resynchronization therapy
DEFINITE	Defibrillators In Non-Ischemic Cardiomyopathy Treatment Evaluation
DIAMOND	Danish Investigations of Arrhythmia and Mortality on Dofetilide
DINAMIT	Defibrillator in Acute Myocardial Infarction Trial
EMIAT	European Myocardial Infarct Amiodarone Trial
EPHESUS	Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study
EPS	electrophysiology study
GESICA	Grupo de Estudio de la Sobrevida en la Insuficiencia Cardiaca en Argentina
GISSI-2	Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico
HCM	hypertrophic cardiomyopathy
ICD	implantable cardioverter-defibrillator
IDE	Investigational Drug Exemption
IRIS	Immediate Risk Stratification Improves Survival
ISIS	First International Study of Infarct Survival Collaborative Group study (ISIS-1)
LBBS	left bundle branch
LQTS	long QT syndrome
LV	left ventricular
LVEF	left ventricular ejection fraction
MADIT	Multicenter Automatic Defibrillator Implantation Trial
MERIT-HF	Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure
MI	myocardial infarction
MIAMI	Metoprolol in Acute Myocardial Infarction

MIRACLE	Multicenter InSync Randomized Clinical Evaluation-ICD
MUSTT	Multicenter Unsustained Tachycardia Trial
NSVT	nonsustained ventricular tachycardia
NYHA	New York Heart Association
OPTIC	Optimal Pharmacological Therapy in Cardioverter Defibrillator Patients
PMVT	polymorphic ventricular tachycardia
PVC	premature ventricular complex
QRSd	QRS duration
RAFT	Resynchronization-Defibrillation for Ambulatory Heart Failure Trial
RALES	Randomized Aldactone Evaluation Study
RRR	relative risk reduction
RV	right ventricular
S-ICD	subcutaneous ICD
SCA	sudden cardiac arrest
SCD	sudden cardiac death
SCD-HeFT	Sudden Cardiac Death in Heart Failure Trial
SMASH-VT	Substrate Mapping and Ablation in Sinus Rhythm to Halt Ventricular Tachycardia
SWORD	Survival with Oral d-Sotalol
VEST	Vest Prevention of Early Sudden Death Trial
VF	ventricular fibrillation
VTACH	Multicenter Catheter Ablation of Stable Ventricular Tachycardia Before Defibrillator Implantation in Patients With Coronary Artery Disease
WCD	wearable cardioverter-defibrillator

mortality, largely because of primary and secondary prevention of coronary heart disease (CHD) and tremendous advancement in resuscitative and postresuscitative care, the burden of SCD is substantial.¹⁻⁴ The annual incidence estimates vary widely from just under 200 000 to ≈500 000 in the United States. Death certificate adjudications overestimate the incidence,⁵ and multisource prospective data provide a more reliable estimate of between 200 000 and 250 000 per year.^{4,6,7} Importantly, only 8% of patients who are resuscitated from an out-of-hospital cardiac arrest survive to hospital discharge.⁴ SCD prevention remains a major conundrum because most episodes occur at home in patients without pre-existing heart disease and warning signs.

Pathophysiology

SCD is defined by the duration of symptoms preceding the terminal event. According to the World Health Organization, SCD is an unexpected death that occurs within 1 hour from symptom onset in witnessed circumstances or within 24 hours from last observed alive and without symptoms in unwitnessed circumstances.⁶ Sudden cardiac arrest (SCA) is distinct from SCD, which by definition is a fatal event. SCA is defined as circulatory collapse with cessation of cardiac function that is reversed by cardiopulmonary resuscitation or defibrillation. SCD occurs when a triggering factor serves as the catalyst in an anatomic or electrophysiological substrate, either genetically determined or acquired, resulting in the final common pathway of ventricular fibrillation (VF) or ventricular tachycardia (VT) degenerating into VF and resultant hemodynamic

Table 1. Causes of Sudden Cardiac Death

Coronary artery disease	Ischemia secondary to atherosclerotic heart disease
	Anomalous coronary
	Coronary vasospasm
Cardiomyopathies	Ischemic cardiomyopathy
	Nonischemic/idiopathic dilated cardiomyopathy
	Hypertrophic cardiomyopathy
	Takotsubo cardiomyopathy
	Infiltrative sarcoid heart disease
	Infiltrative amyloid heart disease
	Arrhythmogenic right ventricular dysplasia/cardiomyopathy
	Left ventricular noncompaction
	Myocarditis
Electrophysiological	Valvular heart disease
	Congenital heart disease
	Long QT syndrome
	Short QT syndrome
	Brugada syndrome
	Catecholaminergic polymorphic ventricular tachycardia
	Idiopathic ventricular fibrillation
	Ventricular pre-excitation
Metabolic	Hyper/hypokalemia
	Hypomagnesemia
	Hypocalcemia
	Severe acidosis
Noncardiac	Intracranial hemorrhage
	Pulmonary embolus
	Epileptic seizure

collapse with cessation of cardiac mechanical activity. It is not uncommon for asystole or pulseless electric activity to follow VF. On the other hand, asystole or pulseless electric activity is often the primary event responsible for out-of-hospital SCD.⁸ Polymorphic VT or torsades de pointes may be observed in patients with genetically inherited long QT syndrome (LQTS) or drug-induced long QT. Although noncardiac causes of SCD, such as stroke, aortic rupture, pulmonary embolus, and drugs, may result in circulatory collapse and cardiac arrest, the emphasis of this review will be on cardiac arrhythmic causes of SCD (Table 1), of which >70% are associated with CHD.⁹

VT or VF may occur in patients with and without cardiovascular disease. Ventricular tachyarrhythmias can present differently depending on hemodynamic stability. When presenting as SCA, VT/VF is hemodynamically compromising and sustained resulting in circulatory collapse and loss of cerebral perfusion. Irreversible anoxic neurological injury or death may ensue if defibrillation and cardiopulmonary resuscitation are not performed in a timely manner. Hemodynamically well-tolerated VT may present as palpitations, irregular or skipped heart beats, lightheadedness, dizziness, or a warm sensation felt throughout the body. Rapid VT is usually hemodynamically unstable and not well tolerated. Patients may experience a

prodrome of presyncopal symptoms before syncope or present with only syncope depending on the duration of tachycardia. Nonsustained VT (NSVT) is defined as ≥ 3 beats and terminates spontaneously in <30 s. Sustained VT lasts >30 s in duration or requires defibrillation because of hemodynamic compromise in <30 s.³

SCD and fatal arrhythmias may have a diurnal, circadian pattern with peaks in the early morning and a nadir during evening sleep. In a review of 2203 death certificates from cases of SCD in Massachusetts, there was an increased incidence between the hours of 7 and 11 AM with a trough between 12 to 4 AM.¹⁰ Similar findings were seen in the Framingham Heart cohort, in which a 70% increased risk of SCD was observed between 7 and 9 AM.¹¹ Increased tachyarrhythmia therapy by implantable cardioverter-defibrillator (ICDs) has also been observed in the early morning hours in patients with cardiomyopathy.^{12,13} However, these reports are not consistent.¹⁴ Although the pathophysiological basis of this diurnal variation has not been readily elucidated, increased sympathetic tone because of physical activity in the early morning hours may be implicated. Molecular experiments have shown that cardiac ion-channel expression and QT-interval duration express circadian rhythmicity via the *kruppel*-like factor (Klf15) that also plays a role in cardiac remodeling and fibrosis. Impaired levels of Klf15 may cause abnormal repolarization and susceptibility to ventricular arrhythmias.¹⁵ Furthermore, mutations in the *SCN5A* gene, which is implicated in inherited arrhythmias, such as LQTS and Brugada syndrome similarly, was shown to be expressed in a circadian pattern.¹⁶ It has been suggested that disruption of the circadian clock in patients with advanced heart failure (HF) may increase the risk of SCD.^{16,17}

Cause of SCA and Death

It is important to determine the pathophysiological cause of SCA to mitigate recurrence of VT or VF, establish prognosis, direct appropriate therapies, and identify family members if the condition is inherited.

Among all the causes of SCA, CHD is responsible for $\leq 75\%$ of SCA in the Western world.¹⁸ However, the incidence is far less under the age of 40. In the Framingham Study, antecedent CHD was associated with ≤ 5.3 -fold increase in SCD risk.¹⁹ Men who have an acute myocardial infarction (MI) have up to a 10-fold higher risk of SCD. CHD predisposes to SCD because of a vulnerable substrate in the setting of an acute MI and structural alterations with ventricular dilation and scar formation in those with previous MI or chronic ischemia.

Beyond ischemic cardiomyopathy and CHD, SCA occurs in 10% to 15% of patients with structural heart disease and other types of cardiomyopathies, such as dilated cardiomyopathy, arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVD/c), sarcoidosis, hypertrophic cardiomyopathy (HCM), myocarditis, or congenital coronary artery anomalies.^{18,20}

Approximately 5% to 10% of SCA victims do not have any structural abnormalities or CHD and are attributed to manifest or latent primary electric disease.²⁰ Among several causes, 5 important causes should be considered: (1) acquired (drugs) or inherited LQTS can result in torsades de pointe form of polymorphic VT (PMVT), (2) Brugada syndrome, (3)

catecholaminergic polymorphic VT (CPVT), (4) early repolarization syndrome, and (5) idiopathic VF (Table 1).

Clinical Evaluation After SCA

History and Laboratory

Survivors of SCA require a comprehensive evaluation that should start with a detailed history obtained from the patient (if awake) and family members of antecedent symptoms, family, and drug history. Family history should not only include sudden death but also other profound events, such as syncope, history of drowning, sudden infant death syndrome, frequent miscarriages, and fatal automobile accidents, which may represent an inherited predilection to SCD.²⁰ Unfortunately, most out-of-hospital arrests are not witnessed, and the patient often has retrograde amnesia and is unable to provide a meaningful history. Laboratory testing for myocardial injury, electrolytes, and metabolic derangements should be performed. However, electrolyte abnormalities periresuscitation are often secondary to organ hypoperfusion. Furthermore, electrolyte or metabolic derangements alone in the absence of a pre-existing vulnerable substrate are often an innocent bystander and should not be ascribed to the cardiac arrest.²¹ Further immunologic and biochemical testing should be undertaken if there is clinical suspicion for a systemic disease with myocardial involvement, such as amyloidosis, sarcoidosis, or myocarditis.

Electrocardiogram

A 12-lead ECG should be thoroughly reviewed and compared with a historical ECG if one is available. The ECG should be evaluated for on-going myocardial ischemia and injury, previous MI, ventricular ectopy, pre-excitation, conduction system disease, including the presence of bundle branch block, and second or third degree heart block, all which may potentially have an etiologic role. Although far less common, clinicians should be vigilant for signature ECG patterns in rare but well-defined causes of SCD (Table 1).

- Coronary artery disease (CAD) may present with ST-segment elevation in a territory subtended by the culprit vessel or ST-segment depression with T-wave inversion in the setting of ischemia.
- Brugada syndrome is associated with one of the several ECG patterns characterized by varying degrees of right bundle branch block pattern and ≥ 2 -mV coved ST-segment elevation with T-wave inversion in the precordial leads, usually V_1 - V_3 .²²
- ARVD/c is suggested by VT or premature ventricular complexes (PVCs) with a left bundle branch (LBBB) configuration and an inferior axis (positive QRS in leads II, III, and aVF and negative in aVL), although a variable axis can be observed. Right bundle branch block and inverted T waves in the right precordial leads may also be present. A specific but less common finding is the presence of epsilon waves (low-amplitude signals at end of the QRS) in leads V_1 - V_3 .²²
- Torsade de pointes is a form of PMVT that is a hallmark of acquired or inherited LQTS that often self terminates but will rarely degenerate into VF resulting in SCD. Acquired LQTS can occur from many QT-prolonging medications. Although the duration of pathological QT

interval is widely debated, >440 ms and >460 ms in men and women, respectively, are considered prolonged. Furthermore, QT prolongation is not always manifested on a baseline ECG even in patients with a LQTS-causing mutation. Morphological differences between T-wave patterns exist between the 3 most common forms of LQTS (LQT1-LQT3).^{22,23} QT prolongation may also be transiently observed after SCA.

- Short QT syndrome is associated with a corrected QT interval of <360 ms in symptomatic patients and <320 ms in asymptomatic patients. Tall or peaked T waves are commonly observed.²²
- Early repolarization syndrome is found in $\leq 31\%$ of patients with idiopathic VF and is associated with J-point ST-segment elevation with notching of the QRS-ST junction (Osborne wave) of at least 0.1 mV in the inferior or lateral leads.^{22,24}
- Wolff Parkinson White syndrome is characterized by pre-excitation of the ventricles over an accessory pathway producing a δ wave or slurred upstroke in the QRS complex and is associated with a short PR interval.

Management in SCA

Early postresuscitative management should be focused on determining and treating the cause of SCA, maximizing neurological recovery, management of cardiac dysfunction, and multiorgan failure that may arise from global hypoperfusion and reperfusion injury.

Imaging

Coronary angiography is performed urgently when ST-segment elevation is noted on the 12-lead ECG or there is heightened clinical concern for on-going ischemia as the cause of SCA. It should be routinely performed once a full recovery is made if there are significant underlying risk factors for CAD or ischemia is suspected.

An echocardiogram is routinely performed to evaluate left ventricular (LV) and RV systolic function, chamber hypertrophy, and dilation, as well as an assessment of the endocardial borders to evaluate for noncompaction channels. In the absence of clear pathology at this juncture, exercise treadmill testing should be performed as a provocation test for CPVT and idiopathic outflow tract VT. It may also aid in uncovering subtle findings associated with LQTS, such as inadequate or excessive QT shortening, exercise-induced T-wave notching, and postural changes in T-wave morphology.²⁰ Cardiac MRI should be strongly considered when the clinical suspicion is heightened for ARVD/c, sarcoidosis, and myocarditis.

Other Diagnostic Considerations

Signal-averaged ECG uses computational averaging of ECG complexes to facilitate detection of late potentials that occur beyond the normal activation sequence of myocardial depolarization because of slow conduction that is disrupted by inflammation, edema, or scar. These late potentials are found in high-risk substrates, particularly in ARVD/c, HCM, and Brugada Syndrome, where they have been shown to have prognostic significance.²⁰

An electrophysiology study (EPS) is not routinely performed when there is an established cause of SCA. However,

in those an identifiable cause has not been established, EPS can be valuable in identifying abnormalities in atrioventricular conduction, presence of an accessory pathway, and inducible ventricular tachyarrhythmias. Inducible VF with nonaggressive stimuli in the absence of structural heart disease may suggest the diagnosis or idiopathic VF and predict recurrent events.^{25,26} However, inducible ventricular arrhythmias should be cautiously defined as aggressive stimulation can induce PMVT or VF in individuals without cardiac disease. The absence of inducibility does not necessarily predict a low-risk substrate in whom ICD therapy may be withheld. Although Multicenter Automatic Defibrillator Implantation Trial (MADIT II) was a primary prevention study, 82% of the randomized patients to the ICD arm underwent electrophysiological testing. Patients received an ICD irrespective of inducibility. Remarkably, >25% of patients who were noninducible by EPS had VT or VF.²⁷

Drug provocation in the EP laboratory has a pivotal role in unmasking some primary electric causes of SCA, particularly when the diagnosis remains elusive or, for risk stratification of phenotypically suggestive ECG patterns. Epinephrine is used to unmask concealed LQT1 and possibly LQT2 syndrome. Epinephrine or isoproterenol administration resulting in increasing ventricular ectopy that degenerates into PMVT or bidirectional VT is characteristic of CPVT. Sodium channel-blocking agents, including flecainide, ajmaline, and procainamide are widely used to unmask Brugada syndrome when the ECG pattern is not diagnostic at rest.²⁰

Prevention of SCD

The current paradigm of understanding SCD and SCA is based on the presence of abnormal, susceptible structural or electrophysiological substrate that interacts with a functional trigger. These triggers may be autonomic changes, electrolyte imbalances, ischemia, drugs, hypoxia, or physical or emotional exertion. This complex interaction between anatomic and functional substrates differs widely based on the underlying cardiac cause. As such, the confluence of events that must occur at the right time to result in SCA and our incomplete understanding of the pathophysiology of the SCD syndrome make precise and individualized preventive therapies an enormous challenge.

Studies as far back as the 1980s identified low LV ejection fraction (LVEF) as a strong predictor of death after a MI.^{28,29} This coupled with a strong association of ambient ventricular arrhythmias with increased risk of sudden death paved the road for investigation with antiarrhythmic drugs (AADs) for efficacy in preventing SCD.³⁰ However, large randomized trials of AAD therapy, as will be discussed below, demonstrated increased mortality or no survival benefit after a MI.^{31–34} This lack of efficacy led to the widespread deployment and investigation of ICDs³⁵ as a tool to detect life-threatening arrhythmias and deliver appropriate electric therapy to terminate arrhythmias and catheter ablation as a strategy to eliminate triggers or modify the substrate. Nonetheless, AAD therapy continues to be used as adjunctive therapy for ventricular arrhythmias. Randomized clinical trials have investigated the use of ICDs in primary and secondary prevention of SCD.^{36–42}

Primary prevention therapy targets patients who are at high risk of SCD but have not had any life-threatening sustained ventricular tachyarrhythmias (Table 3). Secondary prevention is aimed at preventing SCD in those who have survived a life-threatening ventricular arrhythmia and selected high-risk groups with unexplained syncope (Table 4).

Secondary Prevention of SCD

Drug Therapy for Secondary Prevention

Survivors of SCD are at increased risk of recurrent VT or VF. In a study of survivors of SCA or sustained VT, there was a 19%, 33%, and 43% recurrence of VT or SCD at 1, 3, and 5 years, respectively.⁴³ Previous management of secondary prevention of SCD predominantly occurred with AAD therapy that was guided by Holter monitoring or programmed stimulation of the ventricle to try to induce VT or VF. The Cardiac Arrest in Seattle: Conventional Versus Amiodarone Drug Evaluation (CASCADE) study assessed the efficacy of amiodarone for secondary prevention.⁴⁴ The study randomized 228 survivors of an out-of-hospital cardiac arrest, not secondary to MI, to empirical therapy with amiodarone versus other AADs (most commonly quinidine or procainamide) guided by EPS, Holter recording, or both. In this mostly male population (89%) with a history of CAD (82%), survival free of cardiac death or resuscitated VF was improved in the amiodarone arm at 2 years (82% versus 69%), and this difference persisted after 6 years of follow-up.⁴⁴

The Optimal Pharmacological Therapy in Cardioverter Defibrillator Patients (OPTIC) investigators randomized 412 patients with an LVEF of <40%, a dual chamber ICD, and a history of sustained VT, VF, SCA, or inducible VT or VF to β -blocker therapy (metoprolol, carvedilol, or bisoprolol), amiodarone+ β -blocker, or sotalol. The primary outcome was ICD firing for any cause, a surrogate for true SCD. The amiodarone+ β -blocker arm decreased the number of shocks when compared with β -blocker or sotalol therapy alone. There was increased pulmonary and thyroid toxicity along with symptomatic bradycardia in the amiodarone+ β -blocker arm that resulted in 18.2% of the patients in the study to discontinue amiodarone at 1 year.⁴⁵

ICD Therapy for Secondary Prevention

Evidence from 3 randomized clinical trials (Table 2)—Antiarrhythmics Versus Implantable Defibrillators (AVID),⁴⁰ Cardiac Arrest Study Hamburg (CASH),³⁷ and Canadian Implantable Defibrillator Study (CIDS)³⁶—demonstrated the efficacy of ICD therapy in reducing sudden death and total mortality compared with AAD therapy. The AVID trial, which was the largest of the 3 with the longest follow-up, randomized 1016 patients who had survived near fatal VT or VF to ICD implantation or class III AADs (predominantly amiodarone). At 2 years, there was a 27% relative risk reduction (RRR) in survival in the ICD arm.⁴⁰ A meta-analysis of the 3 trials demonstrated a robust 50% RRR for arrhythmic death and a 28% RRR for all-cause mortality with ICD therapy.⁴⁶

On the basis of these findings, ICD therapy is the well-established first-line treatment for survivors of SCA from VF

Table 2. Clinical Trials of Primary and Secondary Prevention ICD

Trials	Follow-Up Analysis (Mean)	Inclusion Criteria	No. of Patients	LVEF	All-Cause Mortality		Relative Risk Reduction	NNT
					Control	ICD		
Primary prevention; ischemic cardiomyopathy								
MADIT (1996)	27 mo	Previous MI w/LVEF≤35%; NYHA classes I, II, III	196	26%	39%	16%	−54% (<i>P</i> =0.009)	4
CABG-Patch (1997)	32 mo	LVEF≤35% with abnormal SAEKG undergoing CABG	900	27%	21%	23%	+7% (<i>P</i> =0.64)	...
MUSTT (1999)	39 mo	LVEF≤40%; CAD; NSVT; inducible VT	704	30%	55%	24%	−58% (<i>P</i> <0.001)	3
MADIT-II (2002)	20 mo	LVEF≤30%, previous MI >1 mo	1232	23%	20%	14%	−31% (<i>P</i> =0.016)	18
DINAMIT (2004)	30 mo	LVEF<35%, MI in the past 6–40 days	674	28%	17%	19%	+8% (<i>P</i> =0.66)	...
Primary prevention; nonischemic cardiomyopathy								
DEFINITE (2004)	29 mo	NICM w/LVEF ≤36%, NYHA classes I–III, NSVT or PVC	458	21%	18%	12%	−35% (<i>P</i> =0.08)	...
Primary prevention; ischemic and nonischemic cardiomyopathy								
SCD-HeFT (2005)	46 mo	LVEF<35% with NYHA class II or III	2521	25%	29%	22%	−23% (<i>P</i> =0.0007)	14
Secondary prevention								
AVID (1997)	18 mo	VF or VT with Syncope VT with LVEF </= 40%	1016	32%	24%	16%	−27% (<i>P</i> <0.02)	12
CIDS (2000)	36 mo	VF, resuscitated out of hospital cardiac arrest secondary to VF or VT, symptomatic VT with LVEF≤35% Unwitnessed syncope with subsequent or inducible VT	659	34%	10%/y	8%/y	−20% (<i>P</i> =0.142)	...
CASH (2000)	57 mo	VF and VT	288	46%	44%	36%	−23% (<i>P</i> =0.081)	...
Connolly et al, ⁴⁶ Meta- Analysis (2000)	...	Eligible patients from AVID, CIDS, CASH database	1866	34%	12%/y	9%/y	−28% (<i>P</i> =0.0006)	29

AVID, Antiarrhythmics versus Implantable Defibrillator; CABG-PATCH, Coronary Artery Bypass Graft Patch Trial; CAD, coronary artery disease; CIDS, Canadian Implantable Defibrillator Study; CASH, Cardiac Arrest Study Hamburg; DINAMIT, Defibrillator in Acute Myocardial Infarction Trial; DEFINITE, Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation; ICD, implantable cardioverter-defibrillator; LVEF, left ventricular ejection fraction; MADIT, Multicenter Automatic Defibrillator Implantation Trial; MADIT-II, Multicenter Automatic Defibrillator Implantation Trial II; MI, myocardial infarction; MUSTT, Multicenter Unsustained Tachycardia Trial; NICM, nonischemic cardiomyopathy; NNT, number needed to treat; NSVT, nonsustained ventricular tachycardia; NYHA, New York Heart Association; ; PVC, premature ventricular complex; SAEKG, signaled average ECG; SCD-HEFT, Sudden Cardiac Death in Heart Failure Trial; VF, ventricular fibrillation; and VT, ventricular tachycardia.

and VT (Tables 2–4). Individualized decisions should be made about ICD therapy in those with transient or reversible causes. Unless electrolyte abnormalities or drugs are identified as the sole cause of SCA, these patients should be evaluated and treated similarly to those who have survived VT or VF from other causes.⁴⁷

Most patients enrolled in the secondary prevention trials had CAD (73%–83%).^{36,37,40} The mean LVEF ranged between 32% and 45%. Multiple analyses have suggested that patients with impaired LV function achieve the greatest benefit with ICD therapy.^{46,48,49} A subgroup analysis of the AVID trial demonstrated improved survival with ICD when compared with AADs in those with an LVEF of ≤35%;⁴⁸ however, in the absence of any prospective data, a threshold for LVEF reduction is not used for recommendations about ICD therapy for secondary prevention.^{3,47}

Secondary Prevention of SCA in Acute Coronary Syndrome

An ICD should not be implanted for secondary prevention if SCA occurs in the setting of an acute MI. Complete coronary revascularization is the treatment of choice in patients in whom ischemia has been implicated as the immediate cause of VF or PMVT and do not have a history of previous MI.⁴⁷ β -Blockers improve outcomes and reduce the incidence of VF in the setting of an acute MI. Patients experiencing VF beyond 48 hours from an acute MI, however, are at risk for

recurrent arrhythmias. If coronary revascularization is not feasible and there is evidence of previous MI with significant LV dysfunction, the primary treatment in those resuscitated from VF and on chronic optimal medical therapy is ICD implantation for secondary prevention.^{3,47} ICD therapy is also indicated in patients with sustained VT or VF occurring 48 hours after a ST-segment-elevation MI that is not because of transient or reversible ischemia or infarction.⁵⁰

Sustained monomorphic VT in patients with previous MI is usually not affected by revascularization. ICD therapy is reasonable in patients with sustained VT with normal LV function.^{3,47}

Primary Prevention of SCD

Drug Therapy in Primary Prevention of SCD

Ruberman et al⁵¹ in 1977 recognized that the presence of complex premature ventricular beats (R on T, couplets or greater, and bigeminy) was an independent risk factor for mortality with a 4-fold increase in death among patients with post-MI before the reperfusion era. During the fibrinolytic testing era, the Gruppo Italiano per lo Studio della Soprawivenza nell'Infarto Miocardico (GISSI-2) investigators found that frequent (>10 per hour) PVCs based on 24-hour Holter monitoring were associated with both an increase in arrhythmic and total mortality for a 6-month period.⁵² On the basis of these findings, it was hypothesized that suppression of PVCs would prevent SCD in this high-risk cohort.

Many studies have demonstrated that systolic HF is associated with an increased risk of SCD associated with extensive electric remodeling. The substrate in the failing heart includes areas of scar and deranged tissue architecture with altered conduction because of remodeling of intercellular ion channels or connexins.⁵³ Active membrane properties are altered in cells in failing hearts, and a hallmark is prolongation of action potential duration with exaggerated physiological heterogeneity of the action potential duration, in essence, a form of acquired long QT replete with arrhythmogenic early afterdepolarizations. The situation in the failing heart is complicated by defects in calcium homeostasis, which will affect contraction and increase arrhythmic risk.⁵³ Pharmacological modification of autonomic imbalance is a pivotal focus in preventing SCD in the patient with HF.

Class I AADs

Class I agents in the Vaughan Williams classification are so-called membrane-stabilizing drugs that block Na⁺ channels and reduce conduction velocity and increase the refractory period, as mechanisms for arrhythmia suppression.

The Cardiac Arrhythmia Suppression Trial (CAST) was the first randomized clinical trial to assess whether suppression of PVCs in patients with post-MI resulted in a decrease in mortality.⁵⁴ One thousand seven hundred twenty-seven patients with asymptomatic or mildly symptomatic ventricular ectopy (defined as >5 PVCs per hour) were randomized to encainide, flecainide, moricizine, or placebo. After a mean follow-up of 10 months, there was an increase in the both arrhythmic and nonarrhythmic deaths in the AAD arm. This was followed by CAST II, which randomized participants to moricizine or placebo and found a significant increase in arrhythmias in the moricizine arm, leading to early termination of the study.⁵⁵ The study was well conceived and planned; patients in the treatment arm had suppression of their PVCs in a run-in phase of the study, and both groups had ischemic event rates that were similar; thus, the exact mechanism of the proarrhythmic death in the CAST trial was unclear. Animal data suggest that class I AADs bind with greater affinity in the setting of ischemia leading to QRS prolongation and increasing susceptibility to ventricular tachyarrhythmias.^{56,57} On the basis of these findings, the use of class I agents in patients with post-MI is generally contraindicated.

Class II AADs

Class II AADs are comprised of β -adrenergic receptor blockers. Their primary pharmacological property is competitive antagonism of endogenous catecholamines at the β -adrenergic receptor. Increased sympathetic tone decreases the threshold for VF by increasing automaticity, shortens the ventricular action potential duration, decreases the refractory period, and increases the dispersion of the myocardial refractory period.^{58–60} β -Blockers have been suggested to blunt the early morning, circadian variation, increase in SCD.^{61,62} In a series of patients with ICDs, the number of tachyarrhythmia episodes were homogeneously distributed throughout the day in those on β -blocker therapy, compared with those who were not, in whom there was a distinct peak of arrhythmic events between 6 AM and 12 PM.⁶²

The Norwegian Multicentric Study Group trial was a randomized, double-blind trial that enrolled 1884 patients ≤ 28 days after MI to receive timolol or placebo.⁶³ During a 33-month follow-up period, there was a 44.9% reduction in SCD in the timolol arm. This was followed by the Beta-blocker Heart Attack Trial (BHAT), which randomized patients 5 to 21 days after an MI to propranolol or placebo.⁶⁴ This resulted in a 28% RRR in SCD in the propranolol arm. The Metoprolol in Acute Myocardial Infarction (MIAMI)⁶⁵ and First International Study of Infarct Survival Collaborative Group study (ISIS-1)⁶⁶ trials replicated similar findings with metoprolol and atenolol, respectively.

These trials were conducted before the reperfusion era, and thus, the effect of β -blockers on SCD after revascularization was unclear. The Carvedilol Post-Infarct Survival Control in Left Ventricular Dysfunction (CAPRICORN) trial randomized 1959 patients with reduced LVEF post MI to carvedilol or placebo.⁶⁷ There was a 76% decrease in the risk of VF and VT in the carvedilol arm. The risk of SCD was reduced by 26%, although it did not reach statistical significance. Finally, the Clopidogrel and Metoprolol in Myocardial Infarction Trial (COMMIT) randomized 45 852 patients with acute MI who underwent thrombolysis to IV metoprolol followed by oral metoprolol or placebo.⁶⁸ The metoprolol arm had a 17% reduction of VF compared with placebo.

β -Blockers have consistently decreased mortality and arrhythmic deaths in the HF population. The Cardiac Insufficiency

Table 3. Guideline Recommendations for ICD Implantation: Indications for Primary Prevention ICD

	LVEF \leq 30%	LVEF \leq 35%	LVEF \leq 40%	No LVEF Requirement
NYHA class I	Patients at least 40 days post-MI while receiving guideline directed medical therapy	...	Patients with nonsustained VT because of previous MI and inducible VF or sustained VT at electrophysiological study	HCM who have ≥ 1 major risk factors for SCD (Table 7) ² Patients with ARVD/C who have ≥ 1 risk factors for SCD (Table 7) ² Patients with cardiac sarcoidosis, giant cell myocarditis, or Chagas disease ²
NYHA class II/III	...	Patients with ischemic heart disease at least 40 days post-MI on chronic guideline directed medical therapy Patients with nonischemic dilated cardiomyopathy

ARVD/c indicates arrhythmogenic right ventricular dysplasia/cardiomyopathy; HCM, hypertrophic cardiomyopathy; ICD, implantable cardioverter-defibrillator; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NYHA, New York Heart Association; SCD, sudden cardiac death; VF, ventricular fibrillation; and VT, ventricular tachycardia.

Table 4. Guideline Recommendations for ICD Implantation: Indications for Secondary Prevention ICD

Survivors of cardiac arrest because of VF or hemodynamically unstable sustained VT not because of completely reversible causes
Patients with structural heart disease and spontaneous sustained VT
Patients with sustained VT and normal or near-normal LV function
Patients with syncope of undetermined origin with clinically relevant, hemodynamically significant sustained VT/VF induced at electrophysiological study
Patients who develop sustained VT/VF >48 h after a myocardial infarction, provided the arrhythmia is not because of a reversible cause.
Patients with unexplained syncope, significant LV dysfunction, and nonischemic DCM

DCM indicates dilated cardiomyopathy; ICD, implantable cardioverter-defibrillator; LV, left ventricular; VT, ventricular tachycardia; and VF, ventricular fibrillation.

Bisoprolol Study II (CIBIS-II) enrolled 2647 patients with class III and IV HF with an LVEF of <35% and randomized them to bisoprolol versus placebo.⁶⁹ The study was terminated early because of a significant reduction in all-cause mortality in the bisoprolol arm. Furthermore, there was a 41% reduction in SCD in the bisoprolol arm that was independent of the severity of HF. Similarly, the Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF) trial found a 41% RRR in SCD in this population of New York Heart Association (NYHA) classes II to IV with an LVEF of <40%.⁷⁰ The effects of β -blockers of SCD were substantiated with a meta-analysis by Teerlink et al,⁷¹ which demonstrated a 38% RRR with β -blockers based on 6 large randomized clinical trials.

However, the efficacy of β -blockers in preventing SCD is not a class effect. The Beta-Blocker Bucindolol in Patients with Advance Chronic Heart Failure (BEST) trial showed no difference in all-cause mortality or cardiovascular death in patients with an LVEF of <35% and class III and IV HF receiving bucindolol or placebo.⁷² The lipophilic β -blockers (eg, propranolol, metoprolol, and carvedilol) that cross the blood-brain barrier have been shown to be effective in preventing SCD, potentially by maintaining high vagal tone during stress.⁷³

Class III AADs

Vaughn Williams class III antiarrhythmics predominantly block potassium channels, resulting in an increase in the action potential duration and refractory period and consequently prolongation of the QT interval. The Survival with Oral d-Sotalol (SWORD) study randomized 3121 patients with an LVEF of <40% and history of recent (<42 days) or remote MI and HF to d-Sotalol or placebo.⁷⁴ The trial was terminated early because of an increase in arrhythmic and total death in the d-sotalol arm.

The efficacy of dofetilide was tested in the Danish Investigations of Arrhythmia and Mortality on Dofetilide (DIAMOND) study that randomized 1510 patients with a recent MI (<7 days) and an LVEF of <35% to dofetilide or placebo.⁷⁵ There was no significant difference in total mortality, cardiac mortality, or arrhythmic deaths between the 2 arms. Dofetilide was also assessed in the DIAMOND-Congestive Heart Failure study,⁷⁶ in which 1518 patients with NYHA class III and IV HF with an LVEF of <35% were randomized to dofetilide or placebo. There was no significant difference in all-cause mortality, cardiovascular death, or successful resuscitation; however, there were 25 episodes of torsades de pointes in the dofetilide arm and none in the placebo arm.

Azimilide is a chlorophenylfuran compound that blocks the rapid and slow delayed inward rectifier potassium channel with lesser effects on sodium and calcium channel currents. Of 3717 patients with a recent MI (<21 days) and severely depressed an LVEF of 15% to 35%, the Azimilide Post Infarct Survival (ALIVE) study found no difference in all-cause mortality, arrhythmic deaths, or cardiac mortality between azimilide and placebo.⁷⁷ Notably, azimilide was associated with less atrial fibrillation.

Although classified as a class III antiarrhythmic with effects of blocking both the fast and slow delayed rectifier potassium channels, amiodarone has a complex mechanism of action with all Vaughan Williams classes of action. There have been numerous studies evaluating the efficacy of amiodarone in preventing SCD in patients with post-MI and HF. The Basel Antiarrhythmic Study of Infarct Survival (BASIS)

Table 5. ICD Use Recommendations in the Missing Gap Population From Clinical Trials (A)

	ICD Implantation Recommendations		
	Within 40 d of MI	Within 90 d After Revascularization	Within 9 mo From the Initial Diagnosis of NICM
Pre-existing systolic dysfunction who would have previously qualified for primary prevention ICD	Not recommended	Can be useful†	...
Require nonelective permanent pacing in whom recovery of LVEF is uncertain and otherwise meet criteria for primary prevention	Recommended	Recommended	Recommended
Develop sustained or hemodynamically significant VT	Recommended*	Recommended*	Recommended
Develop sustained or hemodynamically significant VT that can be treated by catheter ablation	Can be useful	Can be useful	...
Present with syncope thought to be secondary to ventricular arrhythmia from clinical history, documented NSVT or EPS	Can be useful	Can be useful	Can be useful
Are listed for heart transplant or implanted with LVAD	Not recommended	Can be useful†	Can be useful
ICD generator exchange with pre-existing ICD	Recommended	Recommended	...

EPS indicates electrophysiology study; ICD, implantable cardioverter-defibrillator; LVAD, left ventricular assist device; LVEF, left ventricular ejection fraction; NICM, nonischemic cardiomyopathy; NSVT, nonsustained ventricular tachycardia; and VT, ventricular tachycardia.

trial randomized 311 patients who survived a MI and developed asymptomatic ventricular ectopy to individualized antiarrhythmic treatment, amiodarone, or placebo.⁷⁸ There was a significant improvement in survival and decrease in ventricular arrhythmias in the amiodarone arm compared with placebo at 10-month follow-up.

This led to 2 large studies of amiodarone: European Myocardial Infarct Amiodarone Trial (EMIAT) and Canadian Amiodarone Myocardial Infarction Arrhythmia Trial (CAMIAT). EMIAT randomized 1486 patients with an LVEF of <40% after a MI to amiodarone versus placebo.³⁴ Amiodarone failed to demonstrate any overall survival benefit; however, there was a 35% risk reduction in arrhythmic death. Published the same year was the CAMIAT, which randomized 1202 survivors of MI who had NSVT or frequent PVCs (>10/h) to amiodarone or placebo.³³ Amiodarone was similarly associated with a 38% reduction in resuscitated VF or arrhythmic death, with the greatest benefit observed in patients with HF. There was again no significant difference in all-cause mortality between amiodarone and placebo, likely explained by an increase in post-MI complications and pump failure.

The Grupo de Estudio de la Sobrevida en la Insuficiencia Cardíaca en Argentina (GESICA) trial was one of the first trials to specifically address the efficacy of amiodarone in patients with HF.⁷⁹ This unblinded trial, performed before the use of β -blockers, randomized 516 patients with an LVEF of <35% and NYHA class II to IV HF without symptomatic arrhythmias to amiodarone or placebo. After a mean follow-up of 13 months, there was a significant RRR of 28% in all-cause mortality. There was a 27% RRR in the secondary outcome of SCD that was not statistically significant. The Survival Trial of Antiarrhythmic Therapy in Congestive Heart Failure (CHF-STAT) was a study of 674 patients with a history of ischemic or nonischemic cardiomyopathy, an LVEF of <40%, and >10 PVCs/h randomized to amiodarone or placebo.⁸⁰ After a mean follow-up of 45 months, although there was significant suppression of PVCs in the amiodarone arm, no difference in all-cause mortality or SCD was observed. Subgroup analysis demonstrated a trend toward increased mortality in patients with nonischemic cardiomyopathy ($P=0.07$). Similar to the GESICA trial, only 4% of participants were on β -blocker therapy.

One of the pivotal trials of amiodarone, Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT), randomized 2521 patients with ischemic and nonischemic cardiomyopathy and class II and III HF to ICD therapy, amiodarone therapy, or placebo.³⁸ There was no difference in all-cause mortality between amiodarone and placebo. This established amiodarone's arrhythmic safety profile in HF, a condition associated with few safe AAD options.

A meta-analysis by Piccini et al⁸¹ of all randomized controlled trials examining the use of amiodarone versus placebo, which included 15 trials encompassing 8522 patients, found that although amiodarone was associated with a 26% reduction in SCD, overall mortality was not reduced. Furthermore, amiodarone use was associated with nearly a 2- and 6-fold increased risk of pulmonary and thyroid toxicity, respectively. This corroborates the importance of balancing 1 risk against

another, that is, reducing ventricular arrhythmias at the expense of serious long-term toxicities.

Angiotensin-Converting Enzyme Inhibitor

Although many studies have focused on AADs for medical management in the prevention of SCD, conventional HF therapies decrease sudden death in specific patient populations. Inhibition of the angiotensin-converting enzyme (ACE) has many effects on the cardiovascular system, including counteracting LV remodeling, increase in baroreflex sensitivity leading to increased vagal tone, decrease concentrations of angiotensin II that is involved in adrenergic transmission, and normalization of the circadian blood pressure profile (especially with evening dosing).^{82–86} Furthermore, many clinical trials have demonstrated increased survival with ACE inhibitors (ACE-I) in HF with reduced LVEF.^{87,88} Part of this survival advantage can be attributed to a reduction in SCD, as seen in the Trandolapril Cardiac Evaluation study, which demonstrated a 24% RRR in SCD.⁸⁹ A meta-analysis evaluating 15 trials consisting of 15 104 patients found ACE-I to significantly reduce SCD.⁹⁰

Aldosterone Antagonists

Aldosterone is implicated in myocardial interstitial fibrosis and hypertrophy. Blockade of its receptor prevents cardiac remodeling, improves heart rate variability, and reduces the early morning rise in heart rate.^{91,92} Two pivotal trials established the efficacy of aldosterone blockade in patients with HF. The Randomized Aldactone Evaluation Study (RALES) enrolled patients with NYHA class II to IV HF with an LVEF of <40% to spironolactone or placebo and found a 29% reduction in SCD in the spironolactone arm.⁹³ This was followed by Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS), which randomized patients post MI with LV dysfunction and diabetes mellitus to eplerenone or placebo.⁹⁴ There was a 21% RRR in SCD. The effect of eplerenone persisted despite revascularization and on optimum medical therapy with ACE-I, β -blockers, aspirin, and statins (hydroxymethylglutaryl coenzyme A reductase inhibitors).

Statin Therapy

Statins have been shown to be efficacious in the primary and secondary prevention of CHD and stroke.^{95,96} There are many pleiotropic effects of statins, including anti-inflammatory properties⁹⁷; however, a direct antiarrhythmic effect has not yet been demonstrated. Those on statins with an ICD in MADIT II had a lower risk of cardiac death, VT, and VF.⁴² Investigators in the Cholesterol Lowering and Arrhythmia Recurrences after Internal Defibrillator Implantation (CLARIDI) study prospectively randomized 106 patients with a history of CAD and life-threatening ventricular arrhythmias requiring ICD implantation to high-dose atorvastatin (80 mg/d) or placebo and found a 40% RRR in VT and VF recurrence at 12-month follow-up.⁹⁸ The effects of statin therapy in reducing arrhythmias in patient with nonischemic cardiomyopathy with an ICD were assessed in a post hoc analysis of the Defibrillators In Non-Ischemic Cardiomyopathy Treatment Evaluation (DEFINITE) trial that found statin therapy to be associated with a significant reduction in total mortality and arrhythmic death.^{99,100}

ICD Therapy in Primary Prevention of SCD

ICD implantation is recommended for primary SCD prevention based on LVEF and NYHA functional class, both of which have been used in multiple randomized clinical trials (Table 2). Tables 3 and 4 summarize the groups in whom randomized trials support ICD implantation for primary prevention of SCD. The first of the randomized trials was MADIT, which randomized 196 patients with ischemic cardiomyopathy with an LVEF of $\leq 35\%$, documented episode of NSVT and inducible VT on EPS without suppression with IV procainamide to ICD therapy or conventional medical therapy (75% on amiodarone).⁴¹ There was a dramatic 54% RRR in death in the ICD arm compared with medical therapy.⁴¹ On the basis of MADIT I, the Food and Drug Administration approved the prophylactic use of ICD in patients who met MADIT's entry criteria.

Ischemic Cardiomyopathy

The Multicenter Unsustained Tachycardia Trial (MUSTT) study was designed to determine SCD risk based on inducibility of VT during EPS, the findings of which were used to guide management.³⁹ Seven hundred four patients with a previous MI, NSVT ≥ 4 days after recent MI, and an EF of $\leq 40\%$ were randomized to no therapy or EP study-guided AAD therapy or ICD implantation after failing at least 1 AAD. The 5-year incidence of cardiac arrest or SCD was significantly lower in the EPS-guided arm compared with no AAD therapy (25% versus 32%), driven entirely by ICD therapy. EPS-guided treatment with ICDs, but not AADs, significantly reduced the risk of SCD.³⁹ MADIT and MUSTT both confirmed that VT induced by programmed ventricular stimulation in patients with LV dysfunction and NSVT was a strong predictor of SCD, and the risk can be altered with ICD therapy but not with AADs.^{39,41}

In an attempt to have an effect on the broader population without relying on inducible or ambient arrhythmias, MADIT II randomized 1232 patients with a history of MI (>30 days before) and an LVEF of $\leq 30\%$ to prophylactic ICD or conventional therapy.⁴² The study was prematurely halted after 20 months of follow-up because of significant reduction in all-cause mortality with ICD therapy (14.2% versus 19.8%).⁴² The survival benefit was entirely driven by a reduction in SCD.¹⁰¹ In subgroup analysis, the benefit appeared to be the greatest in those with a QRS duration (QRSd) of >150 ms.¹⁰²

Nonischemic Cardiomyopathy

Several small studies of ICD therapy in patients with nonischemic cardiomyopathy failed to show any survival benefit.^{103,104} A larger study, the DEFINITE⁹⁹ trial, sought to assess the benefit of ICD therapy over conventional treatment in a cohort of 458 patients with nonischemic cardiomyopathy, history of HF, LVEF $\leq 35\%$, and NSVT. At an average follow-up of 2 years, there was a trend toward reduction in all-cause mortality in the ICD arm (7.9% versus 14.1%). Although the study did not reach statistical significance for survival, likely due to insufficient power and observational data precluding NSVT as an independent marker of mortality,^{105,106} subgroup analyses demonstrated a benefit with ICD therapy in patients with

prolonged QRSd, an EF of $>20\%$, and NYHA functional class III HF.¹⁰⁷

The largest study to assess the benefit of ICD therapy in patients with nonischemic cardiomyopathy and HF was SCD-HeFT. As noted above, SCD-HeFT enrolled patients (48% nonischemic) with an LVEF of $\leq 35\%$ and NYHA class II and III HF and randomized them to receiving conventional therapy alone, or amiodarone, or ICD therapy on a background of optimal medical therapy.³⁸ At an average of 3.8-year follow-up, there was a 23% relative reduction in all-cause mortality in the ICD arm compared with optimal medical therapy; the benefit was comparable in patients with ischemic and nonischemic cardiomyopathy. In contrast, treatment with amiodarone conferred no survival benefit over conventional therapy. The study was not sufficiently powered to compare the ICD and amiodarone groups. In subgroup analysis, patients with NYHA functional class II had greater benefit than those with class III, in contrast to the results of DEFINITE.^{38,99}

HF, EF, and ICD Efficacy

In all of the primary prevention trials, a prespecified LVEF threshold was used as a categorical entry criterion. Most of the trials had a cut point that ranged between LVEF of 30% and 40% (Table 2). Both the ventricular arrhythmia and SCD guidelines and Centers for Medicare and Medicaid Services use the LVEF range derived from these clinical trials to provide recommendations for appropriate ICD use. Unfortunately, the lack of a uniform methodology in the assessment of LVEF, only modest reproducibility of LVEF measurements, and poor sensitivity and specificity of LVEF in risk stratification for sudden death hampers its ability to be independently used as an ideal risk-stratification tool on which to base decisions of ICD prophylactic therapy.¹⁰⁸

It is important to distinguish cardiomyopathy from HF as the functional consequence of myocardial damage. HF adds a robust dimension over LVEF by modulating the risk and benefit attributable to LVEF. SCD-HeFT was designed specifically to address the efficacy of ICD therapy in patients with NYHA functional class II and III HF on a background of pre-existing cardiomyopathy.³⁸ MADIT II required only an LVEF of $\leq 30\%$ post MI without necessitating HF as an entry criterion. However, hospitalization for HF was a strong predictor of ICD firing and mortality.⁴² Subgroup analysis of MADIT also demonstrated that an LVEF of $\leq 25\%$ and a history of HF were strong predictors of ICD therapy when compared with an LVEF of $\geq 26\%$ without HF.⁴¹

Timing of ICD Implantation

Several trials assessed the optimal timing of ICD implantation after an MI. The Coronary Artery Bypass Graft-Patch (CABG-Patch) trial randomized 900 patients with an LVEF of $<36\%$ and abnormal signal-averaged ECG¹⁰⁹ to ICD or no antiarrhythmic therapy. Although arrhythmic deaths were less in the ICD arm, there was no mortality benefit with ICD therapy at an average of 32-month follow-up, likely due to a parallel improvement in outcome achieved by coronary revascularization.¹⁰⁹ This suggested that SCD risk stratification should be deferred and reassessed after revascularization. As

importantly, the study reaffirms the importance of coronary revascularization as one of the most effective antiarrhythmic therapies.

MADIT, MUSTT, and MADIT II enrolled patients many months after an MI. The Defibrillator in Acute Myocardial Infarction Trial (DINAMIT) study was designed to test the efficacy of ICD therapy in the immediate peri-MI setting.¹¹⁰ Six hundred seventy-four patients with recent MI (6–40 days before; mean, 18 days), an LVEF of $\leq 35\%$, reduced heart rate variability or elevated resting heart rate (≥ 80 bpm), and absence of sustained VT beyond 48 hours after an MI were randomized (open-label) to prophylactic ICD therapy or optimal medical therapy. At an average follow-up of 30 months, there was no significant difference in all-cause mortality between the 2 arms. Although arrhythmic death was less frequent in the ICD arm, it was balanced by an increase in nonarrhythmic death.¹¹⁰ These findings are the basis for the current guideline recommendations to defer ICD implantation for at least 40 days after a qualifying MI.⁴⁷ Aggressive revascularization and reduction of myocardial ischemia are the bedrock of treatment after an MI, and early implantation of prophylactic ICD does not prevent death.

ICD implantation early after MI was also evaluated in Immediate Risk Stratification Improves Survival (IRIS) trial.¹¹¹ Similar to DINAMIT, there was no difference in all-cause mortality with prophylactic ICD therapy when compared with optimal medical therapy in patients with an LVEF of $\leq 40\%$ and NSVT who have post-MI (5–31 days) at a mean follow-up of 37 months.¹¹¹

Cardiac Resynchronization Therapy

The 2 competing modes of death in patients with cardiomyopathy are pump failure and sudden death because of fatal ventricular arrhythmias. The underlying pathophysiology of HF has some predisposition to life-threatening arrhythmia that is not fully captured by simply the presence of structural heart disease. Ventricular dyssynchrony from conduction delay can impair LV function. Cardiac resynchronization therapy (CRT) or biventricular pacing involves simultaneous pacing of both ventricles and is now well established to reduce HF hospitalizations, mortality, reverse LV remodeling, and improve functional class in patients with LV dysfunction and dyssynchrony.^{112,113} The Comparison of Medical Therapy, Pacing, and Defibrillation in Chronic Heart Failure (COMPANION) study was a parallel, randomized, open-label 3-arm study of 1520 patients with advanced NYHA functional class III and IV HF because of ischemic or nonischemic cardiomyopathy with a QRSd of ≥ 120 ms.¹¹⁴ Patients were randomized to receive conventional medical therapy or in addition, CRT pacing (CRT-P) or CRT+ICD therapy (CRT-D). Compared with optimal medical therapy, CRT-P and CRT-D therapy reduced the combined primary end point of mortality and hospitalization by 20%. Although CRT-D reduced all-cause mortality by 36% compared with best medical therapy, there was only a trend toward mortality reduction in the CRT-P arm.

This uncertainty about a mortality benefit with CRT-P was resolved by the findings of the subsequent Cardiac Resynchronization-Heart Failure (CARE-HF) study.

CARE-HF randomized 813 patients with LV dyssynchrony (median QRSd, 160 ms) and NYHA class III or IV HF to CRT-P or best medical therapy and demonstrated a 36% reduction in mortality with CRT-P. Furthermore, there was reverse ventricular remodeling and progressive improvement in quality of life and NYHA functional class in the CRT-P arm. Notably, 35% of deaths in CARE-HF were sudden, similar to the number of sudden deaths in the CRT-P arm of COMPANION. Thus, both studies confirmed that despite the benefits of biventricular pacing, up to one third of deaths were attributed to a fatal arrhythmia and may have been prevented with defibrillator therapy. Although ICD therapy and CRT reduce mortality in HF through distinct mechanisms, there is likely some overlap. Although there is no randomized trial comparing CRT-P and ICD alone, the results of COMPANION and nonrandomized studies suggest an incremental survival benefit conferred by CRT-D compared with CRT pacing alone.^{114,115}

The incremental effect of CRT in patients with cardiomyopathy and dyssynchrony above ICD therapy alone was tested in 3 major trials of mild (class I/II), moderate (class II/III), and severe (class III/IV) HF. Multicenter InSync Randomized Clinical Evaluation-ICD (MIRACLE-ICD) randomized 369 patients with class III and IV HF to ICD therapy alone or CRT-D and demonstrated improvement in functional status, exercise capacity, and quality of life with CRT-D at 6 months; however, no improvement in survival and rates of hospitalization were observed.¹¹⁶ Resynchronization–Defibrillation for Ambulatory Heart Failure Trial (RAFT) randomized 1798 patients with class II and III HF to CRT-D or ICD alone.¹¹⁷ CRT-D was associated with 5% absolute reduction in death and 6% reduction in hospitalization for HF at 40 months. There was slightly more peri-procedural adverse events with CRT-D compared with ICD. The largest study of CRT in patients with mild HF was MADIT-CRT, which randomized 1820 patients with predominantly class I/II (85% class II) functional status to CRT-D or ICD alone. The trial was stopped early because of a 7% absolute reduction in the composite primary end-point of mortality or HF hospitalization, which was driven almost entirely by a 41% reduction in HF hospitalizations at 2.4-year follow-up. There was no difference in mortality between the 2 arms. Subsequent analysis isolated the benefit of CRT to patients with LBBB, and as such, the Food and Drug Administration has restricted its indication to those with LBBB.¹¹⁸ Those with LBBB demonstrated a mortality reduction with CRT-D at 7-year follow-up.¹¹⁹

Subcutaneous ICD

Although the transvenous ICD has become the mainstay therapy to prevent SCD in high-risk patients, the quest to avoid the intravascular lead and all the potential hazards over the course of decades of generator and lead revisions has led to the advent of the entirely subcutaneous ICD (S-ICD System, Cameron Health/Boston Scientific), which does not require transvenous or epicardial leads. The S-ICD is a shock-only device that is considered a potential therapy in patients who have an indication for ICD therapy and do not have symptomatic bradycardia or episodes of VT that may be reliably terminated

with antitachycardia pacing, given that any pacing therapy would be delivered subcutaneously and would be unreliable and painful. The S-ICD system comprises a larger pulse generator than the conventional transvenous ICD system and is implanted in the left thoracic mid axillary region with a subcutaneous lead that is tunneled across the chest to the region of the xiphoid process and subsequently tunneled up just left of the sternal border up to the level of the manubrium¹²⁰ (Figure). Therapy is an 80-J biphasic shock delivered transthoracically with ≤ 30 s of postshock subcutaneous pacing. Sensing occurs from 2 of its 3 subcutaneous electrodes situated at the lead tip, a proximal sensing electrode of 14 cm from the tip, and the generator itself, and thus, signals are more susceptible to myopotentials and external noise.

Some of the concerns with the S-ICD system include oversensing of T waves and noise resulting in inappropriate shocks, undersensing of low-amplitude true arrhythmia episodes, and prolonged charge times resulting in delayed therapy. Experience with S-ICD comes from feasibility studies and European registries,^{120,121} which preceded approval by the Food and Drug Administration in 2012 on the basis of the Investigational Drug Exemption (IDE) study findings.¹²² The IDE study was a prospective, nonrandomized, multicenter study of 321 attempted S-ICD implants, which demonstrated a >90% rate of successful conversion from induced VF with first-shock success of 93%. Thirteen percent of patients received inappropriate shocks. Seven patients (2.2%) did not receive the S-ICD device because of incomplete or failed VF conversion during testing.¹²² In a recent analysis of 472 patients from the EFFORTLESS registry of real-world experience with the S-ICD system, 169 spontaneous episodes were treated in 59 patients.¹²³ The efficacy for first shock termination for spontaneous VT/VF was 88% and reached 96% after the fifth shock.

The S-ICD system may be preferred for those at higher risk of endovascular infections (eg, dialysis patients), and the S-ICD system was associated with a higher risk of cutaneous infections, likely attributed to a larger and multiple incisions. The IDE study reported a 5.6% risk of infections with 1.3% requiring explantation.¹²² The registry data suggest a 4% risk of infection of which 2.2% required explantation.¹²³ Although this rate may be higher than what is known of transvenous ICD systems, the risk of a blood stream infection requiring removal of the transvenous lead is associated with far greater morbidity and mortality.

There are many questions that remain unanswered about the optimal candidate for S-ICD. The device is still in its infancy, and undoubtedly, there will be major improvements in the subsequent iterations. The lack of antitachycardia pacing delivery poses a major limitation to those at risk for VT. It is difficult to predict who is least likely to use antitachycardia pacing. There is optimism in implanting the S-ICD in those at high risk of blood-stream infection, limited or difficult venous access, and those who are young, particularly with inherited high-risk conditions (eg, Brugada, LQTS, and HCM) that face life-long risk of complications from the transvenous ICD.

Treatment Heterogeneity

On the basis of current guideline recommendations, many patients may be eligible for ICD therapy for primary prevention of SCD largely determined by LVEF, functional HF class, and duration of cardiomyopathy. Exploration of the wide-treatment heterogeneity to identify subgroups of patients who may derive a greater benefit from ICD use is imperative. Data on risk stratification by subgroups have largely been inconclusive and underpowered. This becomes particularly important because the cause and pathophysiology of the disease and competing risks for death may be so varied. The existing trials are challenged by limitations in enrollment of under-represented minorities, women, elderly, and those with symptomatic HF, which comprise a large-percentage of those receiving ICDs in a real-world setting. A meta-analysis of 14 studies confirmed that ICD effectively reduces mortality and SCD.¹²⁴ The evidence is weak to support any differences in efficacy by age, sex, and QRSd and indeterminate by NYHA HF class, LVEF, diabetes mellitus, LBBB, blood urea nitrogen level, and interval after MI.¹²⁴ It is imperative to individualize decision-making about ICD therapy despite meeting a guideline-directed indication. A critical appraisal of comorbid and competing conditions should be undertaken in all patients being considered for this therapy. Future attempts to identify patients who are at low risk and unlikely to benefit from ICD therapy are mandated for better risk stratification.

ICD Use in the Poorly Represented—the Missing Gap in Clinical Trials

Recommendations about appropriate ICD therapy are outlined in guidelines sponsored by all the major cardiovascular societies. The indications are generally limited to a homogenous patient population who meet specific inclusion and exclusion criteria included in the respective clinical trials. Although useful, clinicians are often asked to make recommendations about ICD therapy in patients who are under-represented in clinical trials, and thus, they are not included in guideline-directed indications. A consensus document was recently provided to help clinicians make decisions in common clinical scenarios of patients who were specifically not included in guideline indications.¹²⁵ This document is surmised from subgroup analyses, registry data, and expert opinion and do not provide indications by class, but rather, by 4 distinct phrases: “is recommended,” “can be useful,” “can be considered,” and “is not recommended.”¹²⁵

Consensus documents facilitate decision-making about ICD therapy in 4 distinct clinical scenarios that were not consistently included in randomized trials. These include the role of ICD therapy in patients (1) within 40 days after an MI, (2) within 90 days after coronary revascularization, (3) within the first 3 months after diagnosis of nonischemic cardiomyopathy, and (4) with an abnormal troponin level not because of MI.¹²⁵ These recommendations are outlined in Tables 5 and 6.

Wearable Cardioverter Defibrillator

Current guidelines recommend ICD implantation in patients who are beyond 40 days after the index MI and 3 months if coronary revascularization occurred.⁴⁷ Similarly, a minimum

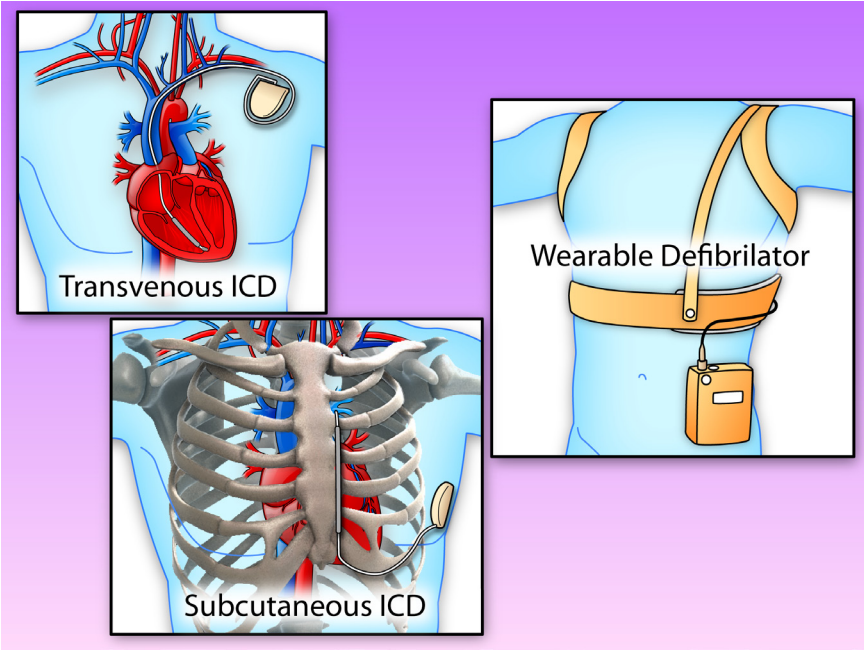


Figure. Types of implantable and wearable defibrillators. ICD indicates implantable cardioverter-defibrillator (Illustration credit: Ben Smith).

of 3 months is required to reassess LV function in patients with nonischemic cardiomyopathy before ICD implantation. These recommendations are despite the increased risk of SCD in post-MI patients and are the result of findings from 2 studies, IRIS and DINAMIT, which demonstrated no mortality benefit with early ICD therapy post-MI.^{110,111} A wearable cardioverter-defibrillator (WCD; LifeVest; Zoll, Pittsburgh, PA) was approved by the Food and Drug Administration in 2002 to bridge the gap in which patients may be at high risk for SCD but are unable or unwilling to undergo ICD implantation (Figure). Appropriate candidates for a WCD are those who are deemed high risk for SCD in the early period after MI or revascularization with low LVEF, awaiting reimplantation of ICD after an extraction for infected device or awaiting cardiac transplantation.

A registry analysis from the manufacturer’s database demonstrated that among 8543 patients with acute MI and LVEF $\leq 35\%$ who were ineligible for ICD therapy and received WCDs, 133 patients (1.6%) had received ICD shocks, of whom 91% survived the event.¹²⁶ The success rate of appropriately converting ventricular tachyarrhythmia events was 81.6% with a 3-month survival of 73% compared with 96% in patients who were not treated. In another retrospective analysis, Zishiri et al¹²⁷ compared 90-day mortality in 809 of the 4958 patients with an LVEF of $\leq 35\%$ after recent revascularization who were sent home with a WCD. The 90-day mortality was higher in the 4149 patients discharged without the WCD (7% versus 3% post-CABG, $P=0.03$; 10% versus 2% post-PCI, $P<0.0001$).

Although some patients may have improvement in LVEF and will no longer be at heightened risk, there will be a small

Table 6. ICD Use Recommendations in the Missing Gap Population From Clinical Trials (B)

		ICD Implantation Recommendations
Abnormal troponin not secondary to MI and otherwise candidate for primary or secondary prevention ICD	...	Recommended
First 3 mo after initial diagnosis of NICM	...	Not recommended
Within 3 to 9 mo after initial diagnosis of NICM if recovery of LVEF is unlikely	...	Can be useful
ICD implantation within 90 days after revascularization in patients who have previously (prior to revascularization) met criteria for secondary prevention because of resuscitated cardiac arrest from VT/VF	Abnormal LVEF	Recommended
	Previous cardiac arrest unlikely to be from myocardial ischemia and have normal LVEF	Recommended
	Previous arrest unlikely to be from myocardial ischemia and who subsequently were found to have CAD that is now revascularized and have normal LVEF	Can be useful
	Previous arrest from myocardial ischemia who are now completely revascularized and have normal LVEF	Not recommended

ICD, implantable cardioverter-defibrillator; LVEF, left ventricular ejection fraction; NICM, nonischemic cardiomyopathy; VF, ventricular fibrillation; and VT, ventricular tachycardia

but definite cohort of patients who will remain at high risk for SCD during the mandated gap period for ICD eligibility. In a real-world setting, a management strategy that incorporated the WCD was safely used to bridge a decision for appropriate ICD therapy in patients with acquired, inherited, and congenital heart disease. An updated analysis of the Prospective Registry of Patients Using the Wearable Defibrillator (WEARIT-II Registry) demonstrated that among 2000 at-risk patients (ischemic cardiomyopathy [40.3%], nonischemic cardiomyopathy [46.4%], or congenital or inherited heart disease [13.4%]) prescribed a WCD, 41 patients experienced a total of 120 sustained ventricular tachyarrhythmia events.¹²⁸ ICDs were subsequently implanted in 785 of the patients (39%) and were most often not implanted because of improved LVEF. How to best risk stratify these patients remains an elusive and important question. A randomized clinical trial, Vest Prevention of Early Sudden Death Trial (VEST), is near completion and will assess the efficacy of WCDs in this vulnerable window.¹²⁹

Prevention of Sudden Death in Rare Disorders

There are a host of uncommon clinical entities that confer an increased risk of SCD that do not generate large enough cohorts to support and adequately powered randomized clinical trial. Thus, indications for treatment are derived from registry and small cohort studies and facilitated by expert opinion that is translated into practice guidelines. It is incumbent on the treating physician to address these gaps of knowledge when discussing therapies with patients. These clinical conditions include inherited channelopathies, such as LQTS, Brugada syndrome, and CPVT, among others. Other less common forms of structural heart disease include ARVD/c, HCM, and infiltrative diseases, such as cardiac sarcoidosis. Although indications for ICD therapy may be ambiguous and criteria suggesting increased risk differ among the various conditions, a family history of sudden death or history of unexplained syncope in almost all of these diseases portends an increased risk of SCD and may warrant aggressive use of ICD (Table 7).

Furthermore, during the past 20 years, molecular genetic studies have found a growing link between mutations in ion channels and cellular membrane structures with inherited arrhythmias and cardiomyopathies. As more genes are identified, the role of genetic testing will increase to diagnosis, prognosticate, and potentially alter treatment in those suspected of having an inherited disorder and their family members. The Heart Rhythm Society has recognized the importance of genetic testing and recommends collection of tissue (whole blood, blood spot card, or frozen tissue) in sudden unexpected deaths (age, <35 years) for genetic analysis.¹³⁰

Long QT syndrome

LQTS is a heterogeneous disorder of ventricular repolarization that increases the risk of torsades de pointe PMVT and subsequent SCD. Congenital LQTS accounts for 3 to 4000 SCD per year in the United States with mutations in 3 genes (LQT1-*KCNQ1*, LQT2-*KCNH2*, and LQT3-*SCN5A*) accounting for most of the increased risk in arrhythmias.¹³¹ The burden of ventricular arrhythmia is higher in LQT1 and LQT2; however, those with LQT3 have an increase in severity of malignant ventricular arrhythmias and are at higher risk of SCD.¹³² The

Table 7. ICD Consideration Under High-Risk Conditions Associated With Sudden Cardiac Death

Diagnosis	High-Risk Features That Warrants ICD
Hypertrophic cardiomyopathy	Spontaneous sustained VT Nonsustained VT Family history of SCD Syncope LV thickness, >30 mm Abnormal blood pressure response to exercise
ARVD/C	Induction of VT during EPS Nonsustained VT on noninvasive monitoring Male sex Severe RV enlargement Extensive RV involvement Age, <5 y at presentation LV involvement Unexplained syncope
Congenital LQTS	Syncope while on β -blocker Persistent QTc, >550 ms >1 genotype (compound heterozygotes)
SQTS	No identifiable evidence-based high-risk features
Brugada syndrome	Spontaneous Brugada type 1 pattern on ECG History of unexplained syncope
CPVT	Sustained VT while on β -blockers Syncope while on β -blockers

ARVD/C indicates arrhythmogenic right ventricular dysplasia/cardiomyopathy; CPVT, catecholaminergic polymorphic ventricular tachycardia; EPS, electrophysiology study; ICD, implantable cardioverter-defibrillator; LQTS, long QT syndrome; LV, left ventricular; RV, right ventricular; SCD, sudden cardiac death; SQTS, short QT syndrome; and VT, ventricular tachycardia.

most common type is LQT1, caused by mutations in *KCNQ1* and accounting for 30% to 35% of all cases. The typical phenotype with patients with LQT1 is a cardiac event during exercise and rarely occurs with rest.²⁰ Given the catecholamine trigger that precipitates ventricular arrhythmias in this patient population, they are responsive to β -blocker therapy. Priori et al¹³³ found that 90% of patients on β -blocker therapy remained free from syncope or cardiac arrest over an average of 5.4 years. Patients with LQT2 (25%–30% of LQTS) often develop cardiac events with emotional stress or auditory stimulation and only <15% occur with exercise. β -Blockers are not as effective in reducing cardiac events in patients with LQT2 compared with patients with LQT1. LQT3 (7%–10% of LQTS) is the least responsive to β -blocker therapy and has a higher incidence of SCD, with events more likely to occur at rest or during sleep.¹³³ β -Blockers remain first line therapy in patients with LQT1 and 2 and are used in some patients with LQT3.²² In patients whom a cardiologist has a high clinical suspicion for LQTS based on history and ECG phenotype and in asymptomatic patients with idiopathic prolonged QTc (>500 ms in adults), comprehensive genetic testing for LQTS is recommended. Furthermore, first degree relatives of the index case should also receive mutation-specific genetic testing even if they are asymptomatic with a normal ECG (class I).¹³⁰

Acquired LQTS is most commonly seen in structural heart disease, secondary to electrolyte imbalances and drug therapy. Drug treatment, particularly when idiosyncratic and electrolyte imbalance, may simply unmask a genetically based reduction in repolarization reserve. Low intracellular levels of both potassium and magnesium lead to reduced repolarizing K currents and concomitant prolongation of the QT interval. Electrolyte repletion and discontinuing offending pharmacological agents are the mainstays of therapy.

Short QT Syndrome

Short QT syndrome is a rare cardiac channelopathy caused by gain-of-function mutations in potassium channel genes and loss of function mutations in L-type cardiac calcium channel subunits that increases the risk of SCD. The diagnostic criteria are debated, and a QTc threshold is not established; it varies between 330 ms and 370 ms among different authors.¹³⁴ Despite the initial description of the disease over a decade ago, the number of reported cases remains small. The peak incidence of SCD is in the first year of life, and 41% of patients have a cardiac arrest by age 40.¹³⁴ In small observational studies, quinidine has been shown to decrease the risk of SCD by prolonging the QT interval.¹³⁵ Genetic testing may be considered (class IIb) in patients whom a cardiologist has a high index of suspicion in the diagnosis of short QT syndrome. Although it is recommended that relatives of the index case undergo mutation-specific genetic testing (class I), studies suggest that identical mutations can be associated with varying phenotypes.^{130,136}

Brugada Syndrome

In the updated inherited primary arrhythmia syndrome guidelines, the diagnosis of Brugada syndrome was based exclusively on the ECG, specifically on the presence of a basal or provoked type 1 ECG. The precise mechanism of both the ECG change and signature arrhythmia, PMVT are debated.¹³⁷ In any case, Brugada syndrome is genetically and phenotypically heterogeneous. In some cases (16%), loss of function mutations in the *SCN5A* gene that encodes the α -subunit in the cardiac sodium channel is responsible for the Brugada phenotype.¹³⁸ Patients can present with syncopal episodes, VF arrest, or SCD. They have a structurally normal heart and have evidence of RV conduction delay.²⁰

Although ICD therapy is the treatment of choice in high-risk patients, quinidine may suppress ventricular arrhythmias and may be useful as adjunctive therapy or in the setting of VT storm. Belhassen et al¹³⁹ enrolled 25 high-risk Brugada syndrome patients with inducible VF on EPS and demonstrated suppression with quinidine therapy. Long-term follow-up in quinidine-treated patients demonstrated no arrhythmic events; however, 36% discontinued drug therapy because of intolerance. In patients who have failed antiarrhythmic therapy, catheter ablation may be a potential option to decrease their VT/VF burden. Nademanee et al¹⁴⁰ enrolled 9 patients with Brugada syndrome with refractory VF and recurrent ICD firings who underwent catheter ablation. In all patients, low voltage and late fractionated potentials were mapped to the epicardium of the anterior aspect of the RV outflow tract. In their series, 7 of 9 patients were noninducible for VT/VF at

the end of the case with normalization of the Brugada ECG pattern in 8 of 9 patients. After an average follow-up of 20 months, there were no recurrent episodes of VT/VF in 8 of 9 patients while off antiarrhythmic therapy.¹⁴⁰

In patients suspected of having Brugada syndrome, genetic testing may be useful (class IIa) in confirming a diagnosis, and it is recommended in the first degree relatives of the index case after the identification of the specific mutation (class I). The genetic diagnosis may have important prognostic information, as those with an *SCN5A* missense mutation may have a better prognosis than those with a truncated protein.¹⁴¹ Currently, genetic testing for Brugada syndrome in patients with type 2 and 3 ECGs is not routinely recommended.¹³⁰

Catecholaminergic Polymorphic VT

CPVT is a heritable condition characterized by VT with varying QRS morphology and axis (eg, bidirectional VT) that typically begins in childhood. Arrhythmias are typically reproducible with increases in adrenergic tone including exercise and emotional stress. Common mutations associated with CPVT include the ryanodine receptor and calsequestrin-2 gene, and medical therapy has centered on β -blockers.²⁰ Calcium-channel blockers, particularly verapamil, has also been shown to decrease ventricular arrhythmias.¹⁴² In those who continue to have symptoms of syncope and exercise-induced VT, addition of flecainide that inhibits Ca^{2+} release by the ryanodine receptor can be added to help suppress arrhythmias.¹⁴³ Genetic testing is recommended in patients in whom a cardiologist has a high clinical suspicion based on history and provocative testing for CPVT. Mutation-specific testing of first degree family members is recommended after identification of the gene in the index case (class I). Clinical assessment is important, including exercise stress testing in first and second degree relatives as a positive test will require lifestyle modification.¹³⁰

Among patients with congenital LQTS, Brugada syndrome, and CPVT, ICD therapy is generally accepted as secondary prevention in those who have had a cardiac arrest, have sustained ventricular tachyarrhythmias, or have had syncope that is presumed to be arrhythmic (while on β -blocker therapy for LQTS and CPVT).^{3,47,144,145} ICD therapy is also reasonable for primary prevention in Brugada syndrome based on a type 1 electrocardiographic manifestation (≥ 2 mV coved ST-segment elevation with T-wave inversion in 2 contiguous precordial leads) with suspected ventricular tachyarrhythmia or syncope.²²

Arrhythmogenic RV Dysplasia/Cardiomyopathy

ARVD/c is an inherited structural heart disease, which has gained a lot of traction in recent years because of recognition that it may be more common than previously ascribed. Although risk profile markers of SCD in this population have not been defined in large prospective studies, selected patients with ARVD/c are at increased risk of SCD. ICD implantation is recommended for secondary prevention in those with documented sustained ventricular tachyarrhythmias, unexplained syncope, or previous cardiac arrest. Risk markers that facilitate a primary prevention indication include any one of the following: evidence of extensive disease (including the presence

of LV involvement), family history of SCD, inducible VT by EPS, and ambient NSVT on noninvasive monitoring.^{3,47} In patients satisfying clinical criteria for ARVD/c, comprehensive genetic testing may be useful (class IIa) in the index case, but it is most beneficial in populations with a proven founder effect. It is recommended that family members undergo mutation-specific genetic testing only if the genotype is identified in the index case (class I), especially given the variable penetrance and expression that may complicate clinical evaluation.¹³⁰ Given the possible need for lifelong screening with ECGs and transthoracic echocardiograms in first and even second degree relatives, mutation-specific genetic screening is often performed.¹⁴⁶

Hypertrophic Cardiomyopathy

A second structurally based inherited condition that predisposes to SCD is HCM. Although it is relatively more common than other inherited conditions of SCD, risk stratification for SCD is derived from retrospective analyses of observational studies.¹⁴⁷ Similar to ARVD/c, the presence of a single marker of high risk for SCA is sufficient to recommend prophylactic implantation of an ICD. The major risk factors include previous cardiac arrest, sustained VT, family history of SCD, unexplained syncope, and an LV thickness of ≥ 30 mm.¹⁴⁸ Patients who have had a previous cardiac arrest or sustained VT have a 10% per year risk of ICD firing. Although patients with conventional risk markers have an approximate 4% annual risk of ICD firing.^{147,149} Surgical myectomy or alcohol septal ablation does not eliminate the risk of SCD, and thus, individual risk assessment should be performed in these patients for consideration of ICD implantation. Once the diagnosis is made, genetic testing in the index case and genetic mutation-specific testing in all first degree family members are recommended (class I) and have shown to be cost effective.^{130,148,150} First degree family members should also undergo clinical evaluation with an ECG and echocardiogram and repeated every 3 to 5 years if negative.^{130,148}

Catheter Ablation for VT

ICDs are routinely implanted in patients with cardiomyopathy who are at risk for SCD because of VT. However, ICDs are not capable of preventing VT episodes but rather are effective at terminating VT. Recurrent shocks increase mortality and impair quality of life, and they may cause severe psychological impairment and post-traumatic stress disorder.^{151,152} VT is associated with increased risk of death and HF hospitalizations in ICD recipients.¹⁵³ Radiofrequency catheter ablation for VT, first described >30 years ago, has undergone significant technological advancement over the past decade, and it is increasingly used as a treatment strategy to control incessant VT and treat and prevent sustained episodes of VT.¹⁵⁴

Catheter ablation for VT has been performed and studied predominantly in patients with structural heart disease after ICD placement. Multiple prospective studies have demonstrated reduced VT/VF recurrences after catheter ablation and thereby reducing ICD shocks by as much as 75%.^{155–157}

To date, only 2 randomized prospective multicenter studies have been published in patients with ischemic cardiomyopathy and VT undergoing prophylactic catheter ablation

before ICD intervention to prevent recurrences of VT.^{158,159} The Substrate Mapping and Ablation in Sinus Rhythm to Halt Ventricular Tachycardia (SMASH-VT) trial assessed the role of catheter ablation in patients with previous MI and reduced LVEF undergoing ICD implantation for sustained VT/VF or those with ICDs who presented with first appropriate shock for ventricular arrhythmia.¹⁵⁸ One hundred twenty-eight patients were randomized to catheter ablation or medical therapy without AAD therapy. During an average follow-up period of 22.5 months, catheter ablation led to a 73% reduction in ICD shocks when compared with the medical therapy arm ($P=0.007$); however, no significant differences were seen in mortality between the 2 groups.¹⁵⁸

The Multicenter Catheter Ablation of Stable Ventricular Tachycardia Before Defibrillator Implantation in Patients With Coronary Artery Disease (VTACH) study was a prospective, open label, randomized controlled trial, comparing VT ablation versus medical therapy in patients with stable VT, previous MI, and reduced LVEF who were undergoing ICD implantation for secondary prevention.¹⁵⁹ In contrast to the previous study, use of AADs was allowed. After a mean follow-up of 22 months, the ablation group ($n=52$) had significantly longer time to arrhythmia recurrence compared with the ICD only arm ($n=57$; median, 18.6 months versus 5.9 months), and lower 2-year arrhythmia recurrence rates (53% versus 71%; hazard ratio, 0.61; $P=0.045$).

Catheter ablation is one of the few treatment options in patients with incessant VT or electrical storm. It should be strongly considered in patients with ischemic cardiomyopathy with an LVEF of $<35\%$ and NYHA functional class III HF who present with ≥ 1 ICD shocks.¹⁶⁰ There is nearly an 8-fold increase in mortality in patients with low LVEF presenting with ≥ 2 ICD shocks.¹⁵² In clinical practice, catheter ablation for scar-induced VT is often a second line therapy and used as an adjunct to AAD therapy. There are no data on the relative efficacy of these 2 strategies as there is no current randomized study of AADs versus catheter ablation. Catheter ablation for VT in patients with structural heart disease does not replace the ICD, and there is no current evidence that reduction in ICD interventions leads to improvement in mortality. Long-term outcomes are largely unknown, and success rates from small studies are modest.^{155–157}

Cardiac Denervation

Reduction of sympathetic output to the heart from the neuraxis may have an important role in protecting against ventricular arrhythmogenesis. Cardiac sympathetic denervation mediated by cervicothoracic sympathectomy has shown some promise in the treatment of electrical storm or incessant VT. In one of the largest cohorts of cardiac sympathetic denervation, 90% of patients undergoing sympathectomy for refractory VT or VT storm ($n=41$) demonstrated an average reduction of ICD shocks from 19.6 to 2.3. Continued freedom from ICD shocks ≤ 1 year after Cardiac sympathetic denervation was present in 48% of patients.¹⁶¹ Similarly, percutaneous stellate ganglion block has also been performed in suppressing ventricular tachyarrhythmias in electrical storm.¹⁶²

Conclusions

The past 3 decades have witnessed revolutionary advancements in the understanding, treatment, and prevention of SCD. Randomized trials have curtailed the use of AADs alone for the prevention of SCD. The implantable defibrillator has emerged as a vital treatment option for both, patients who have survived and are at risk for SCD. Despite the euphoria observed with the elusive task of preventing SCD by ICD therapy, SCD continues as an enigmatic problem and a public health menace because the majority of sudden death occurs in patients without severe cardiomyopathy and not known to be at high risk. At the other end of the spectrum, are the large populations who are implanted and will never use the warranty conferred by the ICD. Advancements in preventing SCD must be multidisciplinary through better understanding behind the mechanisms, genetics, epidemiology, and risk stratification combined with expanded national research efforts to establish a well-integrated chain of survival in our communities.^{4,20}

Disclosures

Dr Berger discloses that he serves on the Medical Advisory Board of Boston Scientific Corp and consults for the Zoll Corp. The other authors report no conflicts.

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