Strategies for the prevention and treatment of sudden cardiac death

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Abstract: Cardiovascular diseases account for 40% of all deaths in the West. Sudden cardiac death (SCD) is a major health problem affecting over 300,000 patients annually in the United States alone. Presence of coronary artery disease (CAD), usually in the setting of diminished left ventricular ejection fraction, is still the single major risk factor for SCD. Additionally, acute myocardial ischemia, structural cardiac defects, anomalous coronary arteries, cardiomyopathies, genetic mutations, and ventricular arrhythmias are all attributed to SCD, demonstrating the perplexity of this condition. With the recent advancements in cardiovascular medicine, the incidence of SCD is expected to increase steeply as the prevalence of CAD and heart failure is uprisong in general population. Considering SCD, the major challenge confronting contemporary cardiology, multiple strategies for prevention against SCD have been developed. β-blockers have been shown to reduce the risk of SCD, whereas implantable cardioverter–defibrillator devices are found to be effective at terminating the malignant arrhythmias. In recent years, multiple clinical trials were carried out to identify patients who may benefit from preventive intervention, including medical therapy and automatic cardioverter–defibrillator implantations. This review article provides insight into the advanced strategies for the prevention and treatment of SCD based on the data available in medical literature to date.

Keywords: risk stratification, sudden cardiac death, prevention, treatment

Introduction

Sudden cardiac death (SCD), also known as sudden arrest, is a major health problem worldwide. Estimates for the United States range from less than 200,000 to more than 450,000 SCDs annually, with the most widely used estimates in the range of 300,000–350,000 SCDs annually. It is usually defined as an unexpected death from a cardiac cause occurring within a short time in a person with or without preexisting heart disease because of abrupt loss of heart function (cardiac arrest). A dynamic triggering factor usually interacts with an underlying heart disease, either genetically determined or acquired, and the final outcome is the development of lethal tachyarrhythmias or, less frequently, bradycardia.

There is no comprehensible consensus on the definition of SCD, which is witnessed in only two-thirds of cases. Because the duration of symptoms preceding the terminal event usually defines the sudden nature of death, World Health Organization defines SCD as unexpected death within 1 hour of symptom onset if witnessed or within 24 hours of the person having been observed alive and symptom-free if unwitnessed. Exclusion of noncardiac causes, such as pulmonary embolus or drug overdose, is also critical since sudden cardiac arrhythmias may be the final common pathway in these disease states as well.
According to the Framingham Heart Study, 13% of deceased have died of sudden death during a 20-year follow-up. In more than 80% of cases, sudden death is caused by coronary disease. The mechanism of sudden death is ventricular fibrillation (VF) in 65%–85%, ventricular tachycardia (VT) in 7%–10%, and electromechanical dissociation in 20%–30%. Pathoanatomical finding can be positive on myocardium-like fibrosis, edema, individual necrosis, and cell infiltration, or it can be unchanged.

**Risk factors**

About 80% of individuals who suffer SCD have coronary heart disease; the epidemiology of SCD to a great extent parallels that of coronary heart disease. Based on the recently published data, the following variables have been associated with patients at higher risk of SCD: 1) syncope at the time of the first documented episode of arrhythmia, 2) New York Heart Association (NYHA) class III or IV, 3) VT/fibrillation occurring early after myocardial infarction (MI; 3 days to 2 months), and 4) history of previous MI. Other factors such as age, hypertension, left ventricular hypertrophy (LVH), intraventricular conduction block, elevated serum cholesterol, glucose intolerance, decreased vital capacity, smoking, relative weight, and heart rate also are postulated in identifying individuals at risk for SCD. Even family history of MI has been reported to be associated with the risk of primary cardiac arrest. Another entity of patients at highest risk for early SCD is those with hereditary ion channel or myocardial defects, such as a long QT syndrome (LQTS) or short QT syndrome (SQTS), hypertrophic cardiomyopathy (HCM), and arrhythmogenic right ventricular dysplasia (ARVD).

**Etiology**

**Coronary artery disease**

Coronary artery disease (CAD) is the most common and frequent cause of SCD in the western world. The incidence of ventricular tachyarrhythmias during acute ST-segment elevation MI is 10%, with 85% of these cases occurring within the first 48 hours. Mortality due to acute episodes of MI is high outside of the hospital and most deaths occur within 1 hour of symptom onset, usually associated with acute occlusions of left coronary circulation with accompanying ventricular arrhythmias. Abrupt changes in regional myocardial blood flow due to alterations in coronary artery structure and/or function, such as spasm, platelet thrombi, dissection, or plaque rupture, can provoke acute ischemia that can have a direct effect on the electrophysiologic properties of the heart, leading to ventricular arrhythmias. Interestingly, old healed infarctions are present in ≈50% of hearts of SCD victims at autopsy and in those of survivors of cardiac arrest. Size of myocardial scar has recently been correlated with inducibility of ventricular arrhythmias by programmed electrical stimulation.

**Anomalous origin of coronary arteries**

One of the important, but rare, causes of SCD is the anomalous origin of coronary arteries, especially in adolescents and young adults under the age of 35 years. In a study by Eckart et al, in 39 deaths attributed to coronary artery pathology, 21 of those patients were found to have anomalous coronary origin (ACO) at autopsy. The most common pathology seen in ACO is a left main coronary artery takeoff from the right coronary sinus with a course between the aorta and the right ventricular (RV) outflow tract. Still, the overall incidence of coronary artery anomalies remains low, requiring a high index of suspicion to make a diagnosis. The biggest factors to help make the diagnosis of ACO in a young patient may be the presence of prodromal symptoms. Although transthoracic echocardiography can visualize the origins, computed tomography or magnetic resonance imaging (MRI) coronary angiography is more sensitive and specific for ACO.

**Cardiomyopathies**

Cardiomyopathies represent the second major group of patients who experience SCD. LV dysfunction is a major independent predictor of total and sudden cardiac mortality in patients with ischemic and nonischemic cardiomyopathy. Studies have shown that in survivors of cardiac arrest who have a LV ejection fraction (EF) <30%, the risk of SCD exceeds 30% over 1–3 years if the patients do not have inducible VT, whereas it ranges between 15% and 50% in those who have inducible ventricular tachyarrhythmias despite therapy with drugs that suppress the inducible arrhythmias. SCD in this patient population may be due to acute or progressive pump failure or primary arrhythmia, leading to electrical or hemodynamic instability and death.

HCM is a genetically heterogeneous heart muscle disorder characterized by myocardial hypertrophy in the absence of abnormal loading conditions. It has a prevalence of 0.2% = 1 in 500 young adults, and although it is well-known that patients with HCM die suddenly from ventricular arrhythmia, recent data suggest that the overall risk is relatively small with annual SCD rates of 1% or less. Mutations in the genes encoding the β-myosin heavy chain (MYH7), myosin-binding protein C (MYBPC3), and cardiac
There is a high risk of sudden cardiac death (SCD) in individuals with heart disease. The goal for physicians is to diagnose small clinical risk markers for SCD in heart disease patients. Among these clinical parameters were:

1. Prior aborted cardiac arrest (VF) or spontaneous sustained VT, with a reported 7-year mortality rate of 33%;
2. Nonsustained VT (NSVT), proved to be a significant independent risk factor for SCD, especially in the young;
3. Unexplained syncope; three studies reported a significant increase in SCD in patients with unexplained syncope;
4. Extreme left ventricle thickness ≥30 mm; there is no clear consensus among all studies; however, the average reported HR for extreme LVH was 3.10 (95% CI: 1.81–4.40);
5. Abnormal blood pressure response (ABPR) to exercise testing; some of the included studies found significantly more SCD in heart disease patients with an ABPR; in one study, the risk was only increased for patients aged 50 years or younger; the average reported HR for ABPR was 1.30 (95% CI: 0.64–1.96); and
6. Family history of premature SCD; three recent studies demonstrated that family history of SCD (FHSCD) was an independent but weak predictor for SCD.

Several genes encoding desmosomal proteins have been identified in plakophilin-2 (PKP2), desmoglein-2 (DSG2), and desmocollin-2 (DSC2). Because most mutations in ARVC are “private” mutations, more than 50% of affected individuals do not harbor a mutation in one of the known causal genes, but failure to establish this genetic diagnosis does not exclude the disease. However, in a suspicious borderline patient, identification of a causal gene may allow confirmation of the diagnosis in a borderline index case. Bauce et al insist that these patients have any single mutation, it warrants further gene mutation screening on the same gene, with attention given to the three major desmosomal genes: PKP2, DSP, and DSG2. The electrocardiogram (ECG) may show anterior preordial T-wave inversion, particularly in lead V2 and/or a QRS complex duration ≥ 110 milliseconds in the right precordial leads, epsilon waves, which are reproducible small deflections seen just beyond the QRS complex in lead V1 or V2 also has been documented. The left ventricle and ventricular septum can be involved in 50%–67% of cases, often later in the disease, representing a poor prognosis. Exercise can precipitate VT in these patients, and the most common arrhythmia is sustained or nonsustained VT originating from the right ventricle, typically with a left bundle branch block pattern and inferior axis. Patients with ARVD typically present with palpitations (27%), syncope (26%), or SCD (23%) and usually present between the second and the fifth decade of life. The gold standard test for diagnosis is myocardial biopsy, showing fibrofatty infiltration; however, RV angiography or MRI are becoming acceptable imaging modalities. Table 1 lists the criteria for diagnosis of ARVD according to the progress...
report of the modification for the diagnosis of ARVD. These patients may also show abnormalities in voltage mapping of the RV. If ARVD is clinically suspected, then referral to an ARVD tertiary care center or registry site may be appropriate. Treatment of ARVD may include antiarrhythmic drugs, radiofrequency catheter ablation, and ICD placement.

Left ventricular hypertrophy
LV hypertrophy is independently attributed to a high cardiovascular mortality and, in particular, to SCD in patients who had a history of hypertension or ischemic heart disease. Multiple disease states can result in hypertrophy, including valvular heart disease, obstructive and nonobstructive HCM, primary pulmonary hypertension with RV hypertrophy, and various congenital heart disorders. LV hypertrophy modulates arrhythmia susceptibility via electrical heterogeneity from local scarring, which is postulated to result from local subendocardial ischemia and subsequent remodeling. Interestingly, myocardial scarring is found mostly in hypertrophied regions, and the extent of scarring has been correlated with clinical markers of sudden death, including ventricular wall thickness.

Infiltrative myocardial diseases
Primary amyloidosis, a protein deposition disorder, may involve the heart in one-third of cases. Sudden death is common in these patients with involvement of heart. Although the sinus node is the most common site of amyloid deposition, infra-His conduction is also commonly affected and is associated with malignant arrhythmias. Amyloid deposition in the ventricular myocardium leads to electrical heterogeneity and delayed activation, which are risk factors for sudden death.

Congenital cardiac anomalies
Tetralogy of Fallot, transposition of the great arteries, aortic stenosis, and pulmonary vascular obstruction are the major congenital anomalies, which are associated with higher risk of SCD. SCD has also been described as a late complication after surgical repair of complex congenital cardiac lesions, such as Tetralogy of Fallot and transposition of the great arteries, and in patients with primary or secondary pulmonary hypertension. In Tetralogy of Fallot, QRS prolongation relates to RV size and predicts patients at risk for SCD.

SCD in young competitive athletes
The true incidence of SCD in young athletes is not known with certainty. In the United States, it has been reported as 1,200,000 young athletes per year in Minnesota high schools. A prospective study in Italy has reported an incidence of SCD of 2.1 per 100,000 athletes per year from cardiovascular diseases. The most common causes are inherited cardiovascular disorders. In the United States, HCM accounts for 36% of the total deaths, followed by congenital coronary artery anomalies, which accounts for 17% of the total deaths. ARVC and ion channelopathies represent 4% and 3% of the total deaths, respectively. But in Europe, the most common cause is primary HCM, followed by ARVC and ion channelopathies, respectively.

Table 1 Criteria for the diagnosis of ARVD: diagnosis depends on two major and two minor criteria

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Major</th>
<th>Minor</th>
</tr>
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<tbody>
<tr>
<td>Family history</td>
<td>Familial disease confirmed at necropsy or surgery</td>
<td>Family history of premature sudden death (&lt;35 y) caused by suspected ARVD or family history of ARVD</td>
</tr>
<tr>
<td>ECG (depolarization/conduction abnormalities)</td>
<td>Epsilon waves or prolongation of the QRS complex (≥110 ms) in the right precordial leads (V1–V3)</td>
<td>Late potentials seen on signal averaged ECG</td>
</tr>
<tr>
<td>Repolarization abnormalities</td>
<td>–</td>
<td>Inverted T waves in the right precordial leads in patients &gt;12 in the absence of right bundle branch block</td>
</tr>
<tr>
<td>Tissue characterization of walls</td>
<td>Fibrofatty replacement of myocardium on endomyocardial biopsy</td>
<td>–</td>
</tr>
<tr>
<td>Global or regional dysfunction and structural alterations</td>
<td>Severe dilatation and reduction of RVEF with minimal LV involvement</td>
<td>Mild global RV dilation or ejection fraction reduction with normal LV</td>
</tr>
<tr>
<td></td>
<td>Localized RV aneurysms</td>
<td>Mild segmental dilation of the RV</td>
</tr>
<tr>
<td></td>
<td>Severe segmental dilation of the RV</td>
<td>Regional RV hypokinesia</td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>–</td>
<td>Left bundle branch lack type ventricular tachycardia (sustained and nonsustained); ECG, Holter, exercise testing</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Frequent ventricular extrasystoles (more than 1,000/24 h) (Holter)</td>
</tr>
</tbody>
</table>

Abbreviations: ARVD, arrhythmogenic right ventricular dysplasia; ECG, electrocardiogram; RV, right ventricular; RVEF, right ventricular ejection fraction; LV, left ventricular.
specifically in the Veneto region of Italy, the most common cause of SCD in athletes is ARVC, accounting for 22% of the total deaths, followed by anomalous origin of coronary arteries, accounting for 12% of the total deaths.

**Primary electrophysiologic abnormalities**

Patients with primary electrophysiologic abnormalities correspond to a group in whom mechanical function of the myocardium is normal and an electrophysiologic derangement represents the primary cardiac problem.

**Long QT syndrome**

The LQTS is an electrical disorder of ventricular repolarization, characterized by an increased risk of life-threatening polymorphic ventricular arrhythmias (torsade de pointes) and SCD. Because torsades de pointes can cause seizures due to cerebral anoxia, LQTS is important to consider in patients with apparent drug-resistant seizure disorders.\(^5^2\) Both emotional stress and exercise have been found to be triggering factors of arrhythmias and syncope in these patients possibly via an increase in catecholamine concentrations.\(^5^3,5^4\) LQTS is a heterogeneous disease that may be congenital or acquired. Both types may have a genetic basis. These syndromes serve as a Rosetta stone for the understanding of inherited ion-channel disorders, leading to life-threatening cardiac arrhythmias. Ionic abnormal changes mainly affecting K\(^+\), Na\(^+\), or Ca\(^{2+}\) currents, which either prolong or shorten ventricular repolarization, can create a substrate of electrophysiologic heterogeneity that predisposes to the development of ventricular tachyarrhythmias and sudden death. Treatment of LQTS varies according to different genotypes. For example, patients with LQT1 are very responsive to \(\beta\)-blockers, whereas those with LQT3 are usually unresponsive.

Risk stratification for patients with LQTS: LQTS outcome varies and is prejudiced by the duration of the QTc interval, environmental factors, age, genotype, and response to treatment.\(^5^5,5^6\) Ventricular arrhythmia is more frequent in LQTS1 and LQTS2, but is more severe in LQTS3.\(^5^7\) Women are more susceptible to malignant arrhythmia during the postpartum period.\(^5^8\) The triggers for lethal cardiac events are listed in Table 2.\(^5^9,6^0\)

High-risk patients with LQTS include those with the following:
1. Congenital deafness (Jervell–Lange–Nielsen syndrome).\(^6^1\)
2. Recurrent syncope due to malignant ventricular tachyarrhythmia.
3. Family history of sudden death.
4. QTc > 500 milliseconds.
5. 2:1 atrioventricular block.
6. T-wave electric alternans.
7. LQTS3 genotype.

Priori et al\(^5^5\) reported that the probability of presenting a major event (syncope, cardiac arrest, sudden death) before the age of 40 years is high (>50%) when QTc is >500 milliseconds in LQTS1, LQTS2, and males with LQTS3. Cardiac arrest survivors and patients with recurrent syncope despite \(\beta\)-blocker treatment usually receive implantation of ICD.\(^6^2,6^3\)

**Congenital LQTS**: Congenital LQTS accounts for 3,000–4,000 sudden childhood deaths per year in the United States.\(^6^4\) The disease incidence is estimated at 1 per 7,000–10,000.\(^5^4\) Although torsades is the most common arrhythmia, premature ventricular complexes, monomorphic VT, bradycardia, and even atrioventricular block have also been observed in some patients with this disorder. QT prolongation was long recognized to have a familial inheritance pattern, but only recently have the genetics been elucidated. Mutations in seven genes have been identified, but three types of mutations are most involved in arrhythmias: LQT1 (42%), LQT2 (45%), and LQT3 (8%).\(^6^5\)

**Acquired LQTS**: Acquired LQTS usually results from electrolyte imbalances or drug therapy. Intracellular deficiencies of potassium and magnesium prolong myocardial

<table>
<thead>
<tr>
<th>Types</th>
<th>Current</th>
<th>Functional effect</th>
<th>Frequency among LQTS</th>
<th>Triggers lethal cardiac event</th>
<th>ECG</th>
</tr>
</thead>
<tbody>
<tr>
<td>LQTS1</td>
<td>K</td>
<td>↓</td>
<td>30%–35%</td>
<td>Exercise (68%), emotional stress (14%), sleep, repose (9%), others (19%)</td>
<td></td>
</tr>
<tr>
<td>LQTS2</td>
<td>K</td>
<td>↓</td>
<td>25%–30%</td>
<td>Exercise (29%), emotional stress (49%), sleep, repose (22%)</td>
<td></td>
</tr>
<tr>
<td>LQTS3</td>
<td>Na</td>
<td>↑</td>
<td>5%–10%</td>
<td>Exercise (4%), emotional stress (12%), sleep, repose (64%), others (20%)</td>
<td></td>
</tr>
</tbody>
</table>

**Table 2** LQTS types: channelopathy, frequency, triggers, and ECG morphology

**Abbreviation**: ECG, electrocardiogram; LQTS, long QT interval syndrome.
repolarization. This may be clinically recognized by serum hypokalemia, hypomagnesia, and progressive prolongation of the QT interval. Hypocalcemia and hypothermia also prolong the QT interval, but generally do not cause ventricular arrhythmias unless severely deranged.

Short QT: Recently, patients with a QTc interval of less than 360 milliseconds (typically < 300 milliseconds) and a high risk of sudden death due to VF have been discovered. This phenotype is now described as congenital SQTS.66 These patients often have permanent or paroxysmal atrial

### Table 3 Role of ICDs in the prevention against SCD: multiple prospective randomized multicenter clinical trials

<table>
<thead>
<tr>
<th>Name of trials</th>
<th>Sample size</th>
<th>Type of study</th>
<th>Population</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>AVID</td>
<td>1,016</td>
<td>Secondary prevention</td>
<td>Survived VT/VF/cardiac arrest; VT with syncope; VT with LVEF ≤ 40%</td>
<td>31% reduction in total mortality with ICD therapy (HR, 0.66; 95% CI: 0.51–0.85; P &lt; 0.02)</td>
</tr>
<tr>
<td>MADIT</td>
<td>196</td>
<td>Primary prevention</td>
<td>Prior MI; LVEF ≤ 35%; asymptomatic NSVT; NYHA class I–II; inducible VT refractory to IV propranolol on EP study</td>
<td>54% reduction in total mortality with ICD therapy (HR, 0.46; 95% CI: 0.26–0.92; P = 0.009)</td>
</tr>
<tr>
<td>MADIT II</td>
<td>1,232</td>
<td>Primary prevention</td>
<td>Prior MI; LVEF ≤ 30%</td>
<td>31% reduction in total mortality with ICD therapy (HR, 0.69; 95% CI: 0.51–0.93; P = 0.02)</td>
</tr>
<tr>
<td>SCD-HeFT</td>
<td>2,521</td>
<td>Primary prevention</td>
<td>NYHA class II/III CHF (ischemic and nonischemic); LVEF ≤ 35%</td>
<td>Overall: 23% reduction in mortality with ICD therapy (P = 0.007)</td>
</tr>
<tr>
<td>DEFINITE</td>
<td>458</td>
<td>Primary prevention</td>
<td>Nonischemic dilated cardiomyopathy; LVEF ≤ 36%; NSVT or PVCs</td>
<td>Reduction in total mortality with ICD therapy (P = 0.08); 35% reduction in death from arrhythmia with ICD therapy (P = 0.006) HR, 0.65; 95% CI: 0.40–1.06</td>
</tr>
<tr>
<td>CABG PATCH</td>
<td>900</td>
<td>Primary prevention</td>
<td>Patients scheduled for CABG; LVEF ≤ 35%; positive signal averaged ECG result</td>
<td>No reduction in total mortality with ICD therapy (P = 0.64)</td>
</tr>
<tr>
<td>DINAMIT</td>
<td>674</td>
<td>Primary prevention</td>
<td>Recent MI (within 4–40 days), LVEF ≤ 35%; impaired cardiac autonomic modulation (heart rate variability)</td>
<td>No reduction in death from any cause with ICD therapy (P = 0.66); 50% reduction in risk of arrhythmic death with ICD therapy (P = 0.009); HR, 1.08; 95% CI: 0.76–1.55</td>
</tr>
<tr>
<td>COMPANION</td>
<td>1,520</td>
<td>CRT study</td>
<td>NYHA class III/IV; LVEF ≤ 35%; QRS interval ≥ 120 ms; hospitalization for CHF within 12 mo</td>
<td>24% reduction in total mortality with CRT alone (P = 0.06); 36% reduction in mortality with CRT/ICD (P = 0.003); HR, 0.64; 95% CI: 0.48–0.86</td>
</tr>
<tr>
<td>CARE-CHF</td>
<td>813</td>
<td>CRT study</td>
<td>NYHA class III/IV; LVEF ≤ 35%; LVEDD ≤ 30 mm; QRS interval ≥ 120–149 ms; additional criteria for dyssynchrony</td>
<td>Reduction in all-cause mortality with CRT vs conventional therapy (P &lt; 0.002); CRT reduced the interventricular mechanical delay, end-systolic volume index, and area of the mitral regurgitant jet, increased LVEF; and improved symptoms and quality-of-life scores (P &lt; 0.01) HR, 0.64; 95% CI: 0.48–0.85</td>
</tr>
<tr>
<td>MADI-CRT</td>
<td>1,820</td>
<td>CRT study</td>
<td>Ischemic or nonischemic cardiomyopathy, LVEF ≤ 30%, QRS interval ≥ 130 ms; NYHA class I/II</td>
<td>34% relative reduction in the risk of all-cause mortality or first heart failure event (P = 0.001); HR 0.66; 95% CI: 0.52–0.84</td>
</tr>
<tr>
<td>CASH</td>
<td>288</td>
<td>Secondary prevention</td>
<td>Survived VT/VF/cardiac arrest</td>
<td>23% reduction in total mortality with ICD therapy (HR, 0.82; 95% CI: 0.60–1.11; P = 0.08)</td>
</tr>
<tr>
<td>CIDS</td>
<td>659</td>
<td>Secondary prevention</td>
<td>Survived VT/VF/cardiac arrest; VT with syncope; VT with LVEF ≤ 35% and cycle length ≤ 400 ms</td>
<td>33% reduction in death from any cause with ICD therapy (P = 0.14); reduction in risk of death from arrhythmia with ICD therapy (P = 0.09) HR, 0.85; 95% CI: 0.67–1.10</td>
</tr>
</tbody>
</table>

Abbreviations: ICD, implantable cardioverter defibrillators; AVID, antiarrhythmic vs implantable defibrillator; VT, ventricular tachycardia; VF, ventricular fibrillation; LVEF, left ventricular ejection fraction; CIDS, Canadian Implantable Defibrillator Study; CASH, Cardiac Arrest Study Hamburg; CHF, congestive heart failure; CABG, coronary artery bypass graft; COMPANION, Comparison of Medical Therapy, Pacing, and Defibrillation in Chronic Heart Failure; DINAMIT, Defibrillator in Acute Myocardial Infarction Trial; HR, hazard ratio; CI, confidence interval; MADIT, Multicenter Automatic Defibrillator Implantation Trial; MI, myocardial infarction; NSVT, nonsustained ventricular tachycardia; SCD, sudden cardiac death; SCD-HeFT, SCD in Heart Failure Trial; DEFINITE, Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation; CRT, cardiac resynchronization therapy; CARE-CHF, Cardiac Resynchronization in Heart Failure Study; CASH, Cardiac Arrest Study Hamburg; CIDS, Canadian Implantable Defibrillator Study.
fibrillation (24%) and occasionally have depression of the PR interval. Mutations in five genes have been identified to cause SQTS. Quinidine can be efficacious in SQTS by prolonging the QT interval, normalizing the QT response to RR-interval change, and preventing cardiac events in some patients. ICDs are still needed for primary and secondary prevention (Table 3).

Brugada syndrome: In 1992, a syndrome consisting of syncopal episodes and/or sudden death due to idiopathic VF in a structurally normal heart with ECG evidence of RV conduction delay was described as Brugada syndrome. In 1998, the genetic nature of the disease and its association to a mutation in the cardiac sodium channel gene were discovered. The syndrome has been linked to mutations in the SCN5A gene, which encodes the α-subunit of the cardiac sodium channel, resulting in loss of function. However, the SCN5A gene is affected less than 30% of the time in pedigrees with the Brugada pattern, highlighting the genetic heterogeneity of the Brugada phenotype. Although it is inherited as an autosomal dominant pattern, there is a striking male to female ratio of 8:1 of clinical manifestations. The estimated worldwide prevalence is 0.10%, but can be as high as 3% in endemic areas of southeast Asia.

Patients with the Brugada syndrome classically have an incomplete right bundle branch block pattern with precordial ST elevation ≥2 mm in leads V1–V3 type 1 (Figure 1). Subsequently, other ECG phenotypes were recognized. In type 2 Brugada pattern, the ST/T waves have ≥1 mm elevation but have a saddleback configuration and are generally accompanied with upright or biphasic T waves. In type 3, the T wave is upright and there is minimal (<1 mm) to no ST elevation.

Recent data suggest that loss of the action potential dome in RV epicardium but not endocardium underlies the ST-segment elevation seen in the Brugada syndrome. Also, electrical heterogeneity within RV epicardium leads to the development of closely coupled extrasystoles via a Phase II reentrant mechanisms, which then precipitate VT and VF.

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**Figure 1** Brugada syndrome: three types of ST-segment elevation, shown mainly in the precordial leads, type I ECG pattern with pronounced elevation of the J point, a coved-type ST segment, and an inverted T wave in V1–2. Type II ECG pattern with saddleback ST-segment elevation by >1 mm. According to a consensus report.
There are no guidelines on pharmacologic therapy for Brugada syndrome. In such patients, quinidine has been shown to preventVF induction by electrophysiologic testing and to decrease arrhythmic event rates,73 but owing to high susceptibility to SCD, ICD implantation has been shown to prevent SCD in high-risk patients with Brugada syndrome.74 In patients with an aborted SCD, VT, or syncpe, an ICD is indicated.63 In patients without these symptoms but with a family history of SCD, ICD implant should be guided by results of provocation75 and electrophysiologic testing.76 The indications for ICD become less clear in asymptomatic patients with the Brugada pattern on ECG, and unfortunately, there is no consensus among physicians. One method for risk stratifying asymptomatic patients is with an electrophysiology study. Patients in whom a sustained ventricular arrhythmia (VF, polymorphic VT, or monomorphic VT lasting > 30 seconds) is inducible are felt to be at high risk and may warrant ICD implantation. However, the specificity of this test in this patient population has been questioned. Thus, the management of asymptomatic patients still remains to be definitively defined.

Catecholaminergic polymorphic VT: Catecholaminergic polymorphic VT (CPVT), also called familial polymorphic VT, is a rare disease characterized by VT with a continuously varying QRS morphology and axis. Unlike torsade de pointes, the baseline QT interval is normal in CPVT. Arrhythmias typically begin in childhood. The classic presentation is syncope, VT (generally nonsustained), or VF; reproducible with exercise, isoproterenol infusion, and emotional stress, all leading to adrenergic surges.77 Thirty percent of reported cases are familial with normal structural heart78 and have been linked to mutations in the cardiac ryanodine receptor (RyR2) gene and less commonly in the calsequestrin-2 (CASQ2) gene. More recently, CPVT has been reported in families with mutations encoding the ankyrin-B protein.79

Patients with Andersen–Tawil syndrome may have bidirectional VT upon adrenergic stimulation.80 It has been suggested that some CPVT cases can be explained by KCNJ2 mutations. This is important to consider for RyR2- and CASQ2-negative patients since KCNJ2 mutations are usually associated with a more benign prognosis and sudden death is considered an exceptional event in these cases.81

Because of the catecholaminergic mechanism of triggering, β-blockers have historically been used as the mainstay of therapy. At normal doses, β-blockers successfully reduce but do not eliminate ventricular ectopy.82 Implantable defibrillators have been shown to successfully terminate ventricular arrhythmias in patients with CPVT. Therefore, recommended treatment includes prescribing the maximally tolerated dose of β-blockade to reduce frequency of arrhythmias in conjunction with ICD implantation to prevent SCD.

Pathophysiology of arrhythmia
The most common electric sequence of events in SCD is the degeneration of VT (abnormal acceleration of ventricular rate) into VF, during which disorganized contractions of the ventricles fail to eject blood effectively, often followed by asystole or pulseless electrical activity.8 Polymorphic VT or torsade de pointes may be the initial arrhythmia in patients with genetic or acquired forms of structural heart disease.83 Bradyarrhythmias or electromechanical dissociation may be the primary electrical event in advanced heart failure or in elderly patients.84,85 Among patients with ICDs, arrhythmic death accounts for 20%–35% of deaths, and electromechanical dissociation after shock is a frequent cause of death.86 Asystole may be the first rhythm observed in the field, but this may be a marker of the duration of arrest since coarse VF ultimately degenerates into asystole.

Management
Risk stratification
Current parameters for risk stratification of patients with CAD for SCD include medical history (presence of NSVT or syncpe), EF, ECG (QRS duration, QT interval, QT dispersion), signal-averaged ECG, heart rate variability, and baroreflex sensitivity. However, the sensitivity and specificity of these parameters have yet not been studied in detail in large patient populations. The single major parameter associated with higher incidence and studied in many clinical trials is LVEF. At present, only LV dysfunction with reduced EF reliably defines “high risk” for SCD in patients with ischemic and nonischemic cardiomyopathy. The heart failure functional class and history of prior MI or CAD are also important prognostic risk factors along with sudden specific definite indications.44

Prevention
Prevention of sudden death means detection of high-risk patients and application of medical treatment in order to postpone it. The high risk of development of SCD is majorly attributed to fatal ventricular arrhythmias. Electrophysiologic anomalies in cells lead to development of ventricular ectopic activity or ventricular arrhythmias, which comes to the end with fibrillation and eventually death if not terminated in time. As survival rates for out-of-hospital cardiac arrests are extremely low, ranging from 2% to 25% in the United States,87
secondary prevention strategies only address a small portion of patient population at risk of SCD. The accumulated data have allowed guidelines to be formulated, which allow us to predict with more certainty the patients at risk for SCD and address the challenge to identify patients at risk before the first event as primary prevention. However, applying those guidelines in practice requires systems to structure the environment in which care is delivered so that “doing the right thing” becomes automatic. This requires tools that simplify and provide focus by embedding the recommendations for evidence-based care into the care itself.

Pharmacologic therapy

β-blockers

Of the different drugs that have been evaluated, only β-blockers have reduced sudden death in the MI survivor. The Beta-Blocker Heart Attack Trial (BHAT) study showed that β-blockade with propranolol reduced all-cause mortality by 25%, especially in patients with diminished LV function and/or ventricular arrhythmias. A randomized trial of nearly 46,000 patients showed that, in the acute MI setting, early oral administration of high-dose β-blocker drugs has been shown to prevent VF. In the Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure trial, 3,991 patients with NYHA class II–IV heart failure and EF ≤ 40% were randomized to long-acting metoprolol with a dose escalation protocol. At 1-year follow-up, overall mortality was lower in the treated group compared to placebo (7.2% vs 11% per patient-years of follow-up). There was also a 41% relative risk reduction in sudden death with long-acting metoprolol. These data provide unequivocal benefit of β-blockade in acute MI, post-MI, and congestive heart failure for prevention of mortality and SCD.

Antiarrhythmic drugs

The sine qua non for efficacy of common antiarrhythmic drugs in prevention against SCD based on well-designed, placebo-controlled clinical trials has shown no added benefit. Class I drugs (mexiletine, encainide, flecainide), calcium antagonists, and class III drugs (d-sotalol, dofetilide) all failed to reduce or even increase the incidence of SCD after a MI. Amiodarone also has been shown to have no definitive effect on mortality in patients after MI in preventing SCD, as manifested in the SCD in Heart Failure Trial (SCD-HeFT).

Statins

The role of the statins has been well studied in patients with CAD and has been shown to be extremely beneficial in reducing mortality, but whether they play any significant role in preventing SCD remains controversial. A Multicenter Automatic Defibrillator Implantation Trial (MADIT II) substudy demonstrated that, among patients treated with ICDs, those with background statin therapy had a lower rate of ventricular tachyarrhythmias. This finding was intriguing since it was unclear if this observation was due to reductions in coronary events, decreased inflammation, unique antiarrhythmic properties, or unidentified confounders. Recently, the Cholesterol Lowering and Arrhythmia Recurrences After Internal Defibrillator Implantation (CLARIDI) study demonstrated that intensive lipid-lowering therapy using 80 mg of atorvastatin led to a 40% relative risk reduction (from 38% to 21%) in VT/VF recurrence in patients with ICD during a 12-month follow-up. Yet, there are no definite guidelines supporting addition of statins as adjuvant therapy for prevention of SCD beyond conventional indications.

The role of ICD devices in primary and secondary prevention against SCD

Multiple prospective, randomized, multicenter clinical trials have documented improved survival with ICD therapy in high-risk patients with LV dysfunction due to either prior MI or nonischemic cardiomyopathy. On a background of optimal medical therapy (with or without antiarrhythmic drug therapy), ICD therapy has been associated with a 23%–55% mortality reduction, due almost exclusively to a reduction in SCD. Superiority of an ICD over antiarrhythmic drug therapy for secondary prevention against SCD (predominantly amiodarone) was primarily noticed in the Antiarrhythmic Versus Implantable Defibrillator (AVID) trial. The AVID trial enrolled 1,016 patients resuscitated from an episode of VT (if associated with hemodynamic collapse, cardiac symptoms, or occurring in the setting of an EF ≤ 40%) or VF. Patients were randomized to receive either medical therapy alone or medical therapy in conjunction with an antiarrhythmic drug, which was most commonly amiodarone. The trial was stopped prematurely when a survival benefit was noted in patients receiving ICDs compared with those treated with sotalol or amiodarone. The unadjusted survival rates for the ICD vs drug groups were 89% vs 82% at 1 year, 82% vs 75% at 2 years, and 75% vs 65% at 3 years. The major effect of the ICD was to prevent arrhythmic death (4.7% vs 10.8% in patients treated with an antiarrhythmic drug). Results consistent with the AVID trial were also reported from the CIDS studies.
MADIT
To test the efficacy of ICDs in prevention of SCD, the MADIT randomized 196 patients with ischemic cardiomyopathy,100 EF ≤ 35%, a documented episode of NSVT, and inducible VT on electrophysiology study to ICD (n = 95) vs conventional medical therapy (n = 101). After a mean follow-up of 27 months, the relative risk reduction for all-cause mortality in the patients receiving ICDs was 54% (P = 0.009), thus showing the benefit of prophylactic ICD placement in a high-risk population.

MADIT II
However, to make an impact on the overall population at risk for sudden death, high-risk patients need to be identified before an episode of VT or fibrillation (primary prevention). The MADIT II highlighted the possibility of preventing sudden death in patients with CAD. According to this trial, patients with a previous MI and low LVEF (≤30%) on optimal medical therapy were randomized to receive either an ICD or no ICD.96 Patients implanted with an ICD had a mortality rate of 14.2% vs 19.8% in the conventional therapy group (P = 0.016), a 31% relative risk reduction in mortality during a follow-up period of 20 months. The survival benefit was entirely due to a reduction in the incidence of SCD and became apparent at 9 months after device implantation. This trial was novel in that there was no requirement for invasive electrophysiologic testing of prior ventricular arrhythmias. This trial expanded on the findings of MADIT I, which showed the superiority of ICD therapy in patients with CAD and EF 35% or less.

SCD-HeFT
The significant role of ICD therapy in primary prevention against SCD in both ischemic and nonischemic cardiomyopathy patients was further clarified by the SCD-HeFT.101 This trial enrolled 2,521 patients with NYHA class II or III CHF and an EF of ≤35%. Patients were randomized to receive optimal medical therapy alone (847 patients), optimal medical therapy along with amiodarone (845 patients), or optimal medical therapy along with a conservatively programmed, shock-only, single-lead ICD (829 patients). Placebo and amiodarone were administered in a double-blind fashion. The primary end point of the study was all-cause mortality with mean follow-up of 3.8 years. A 23% reduction in mortality (P = 0.007) was observed with the ICD; the benefit of ICD was similar in both ischemic (HR, 0.79; P = 0.05) and nonischemic cardiomyopathy (HR, 0.73; P = 0.06). In contrast, mortality was similar in patients on either medical therapy alone or medical therapy combined with amiodarone. The benefit of ICD therapy was comparable for ischemic and nonischemic cardiomyopathy.

DEFINITE trial
The Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation (DEFINITE) trial was the MADIT II counterpart. This trial included 458 patients with nonischemic dilated cardiomyopathy, EF ≤ 35%, nonsustained VT or premature ventricular contractions, and NYHA class I, II, or III who were randomly divided to standard medical therapy or ICD.103 At a 2-year follow-up, there was a trend in mortality reduction with ICD (7.9% vs 14.1%; HR, 0.65; P = 0.08). The largest benefit was seen in NYHA class III patients (HR, 0.37). In part, on the basis of the results of this trial, the Centers for Medicare and Medical Services expanded coverage for ICD implementation to patients with nonischemic cardiomyopathy for more than 9 months in duration who have NYHA class III or IV heart failure and EF ≤ 35%.

Timing of ICD implantation
CABG Patch Trial
In the CABG Patch Trial, 900 patients with LVEF of <36% and abnormal signal-averaged ECG who were undergoing elective coronary bypass surgery were randomized to ICD or no antiarrhythmic therapy.104 This trial showed no difference in survival between the two groups at an average of 32-month follow-up. Of note, 88 patients enrolled were not randomized because they were deemed too unstable at time of surgery for ICD placement. Additionally, EFs of these patients were not assessed postoperatively. Nevertheless, results suggest that revascularization should be performed when feasible and that SCD risk stratification should be performed after revascularization.

DINAMIT
In the Defibrillator in Acute Myocardial Infarction Trial (DINAMIT), a randomized, open-label trial comparing ICD therapy to optimal medical therapy, 674 high-risk patients (defined by EF < 35%) were enrolled 6–40 days after MI.105,106 The primary endpoint was death from any cause; death from arrhythmia was a secondary end point. During a mean follow-up of 30 months, there was no difference in overall mortality between the two treatment groups. A reduction in arrhythmia was balanced by an increase in overall mortality (cardiac but nonarrhythmogenic) in ICD group. The reason for this surprising finding is unclear but may be related to impaired cardiac autonomic function early after
MI. The benefits of ICD therapy for prevention of SCD may not become evident until years after MI and may not have been captured in the mean 30-month follow-up of DINAMIT. Current guidelines therefore recommend deferring ICD implantation for at least 40 days following MI.

Aggressive treatment of myocardial ischemia, including revascularization, is the main treatment in these patients, and early implantation of ICD does not reduce overall mortality after early MI (DINAMIT). Implantation of ICD should be deferred in these cases as is currently recommended, with reassessment of LV function after “40 days” to determine whether ICD is still required for primary prevention of SCD (if the LVEF $<35\%$), although in some individuals circumstances it may be considered (eg, in patients with recurrent, sustained arrhythmias).

Cardiac resynchronization therapy
Cardiac resynchronization therapy (CRT), or biventricular pacing, can improve cardiac pump function in advanced heart failure by simultaneous activation of the left and right ventricles in those with underlying or pacing-induced bundle branch block. CRT$^{107}$ is approved in the United States for EF $\leq 35\%$, evidence of dyssynchrony, and class III and IV heart failure despite optimal medical therapy. A brief review of the clinical data supporting their current use is as below.

COMPANION trial: CRT with either a pacemaker or a pacemaker–defibrillator has been shown to be very beneficial in the Comparison of Medical Therapy, Pacing, and Defibrillation in Chronic Heart Failure (COMPANION) trial,$^{108}$ which randomized patients with class III or IV heart failure, normal sinus rhythm, LVEF $<35\%$, LV end diastolic volume $>60$ mm, and QRS interval $>120$ milliseconds. In this trial, CRT with a pacemaker decreased the risk of the primary endpoint (HR, 0.81; $P = 0.014$), as did CRT with a pacemaker–defibrillator (HR, 0.80; $P = 0.01$). The risk of the combined end point of death or hospitalization for heart failure was reduced by 34% in the pacemaker group ($P < 0.002$) and by 40% in the pacemaker–defibrillator group ($P < 0.001$). A pacemaker reduced the risk of the secondary end point of death from any cause by 24% ($P = 0.059$), and a pacemaker–defibrillator reduced the risk by 36% ($P = 0.003$).

CARE-CHF trial: The Cardiac Resynchronization in Heart Failure (CARE-HF) trial was a nonblinded European, which enrolled patients with class III or IV heart failure, LVEF $<35\%$, LV end diastolic volume $>30$ mm, QRS interval $>150$ milliseconds, or QRS $>120$ milliseconds with echocardiographic parameters of dyssynchrony.$^{109}$ This trial confirmed the results of earlier trials that the benefits of CRT are in addition to those achieved with standard pharmacologic therapy in patients with moderate-to-severe heart failure due to LV systolic dysfunction with evidence of cardiac dyssynchrony. CARE-HF is the first trial to show benefit with CRT with respect to survival and the first to show benefit and continued improvement for a period of over 2 years.

MADIT-CRT: In a large randomized study of NYHA class I and II patients, the primary endpoint showed that CRT with an ICD (CRT-D) was associated with 34% relative reduction in the risk of all-cause mortality or the first heart failure event; in addition, there were 41% relative reduction of heart failure events compared to patients with ICD. One-year follow-up confirmed an improvement of 11% in LVEF compared to 3% improvement for patients with ICD.$^{110}$

Summary of a generalized simple systematic approach toward prevention of SCD (ESCAPE pathway)
Multiple pathways have been developed in recent past to address these complex issues faced in the management of SCD; however, most of them lack simplicity and practicality of implementation, which in turn affect their overall outcome and patient care. Here we describe the ESCAPE pathway,$^{111}$ which is a simple novel pathway for primary and secondary prevention of sudden cardiac arrest, aiming to increase physician awareness and incorporate a tool for appropriate referral for ICD evaluation (Figure 2).

Step A: initial evaluation of patients
The initial and foremost thing to observe when assessing for the prevention against SCD is the EF. According to the ACC/American Heart Association (AHA)/ESC 2006 guidelines for the management of patients with ventricular arrhythmias and the prevention of SCD, new criteria include patients with either ischemic or nonischemic cardiomyopathy with EF $\leq 35\%$ and NYHA class II or III heart failure, removing the controversial criteria from 2003 that restricted ICDs to patients with ischemic cardiomyopathy, EF $\leq 30\%$, and QRS $>120$ milliseconds.

On the basis of the initial evaluation of the patients with EF $\leq 35\%$, they can be divided into three subgroups: (A) includes patients with a clear indication for secondary cardiac arrest prevention, (B) includes patients who have a contraindication to ICD or have no proven benefit from ICDs for SCD prevention as per clinical data available to date, and (C) includes patients who neither have any indication for ICD placement at this time as a part of secondary prevention of SCD nor any contraindication.
Group A involves the following patients:
- Survivors of sudden cardiac arrest due to VT/VF.
- With a previous documented episode of hemodynamically destabilizing sustained VT.
- Unexplained syncope in the setting of underlying structural heart disease.
- Patients with high-risk LQTS or SQTS.
- Patients with high-risk Brugada syndrome.
- Patients with high-risk HCM.
- ARVD.

This group of patient population on presentation should be referred directly for ICD implantation for secondary prevention against SCD.

Group B involves patients with a contraindication for ICD implantation and include the following:
- NYHA class IV patients (unless QRS ≤ 120 milliseconds who are eligible for CRT).
- Cardiogenic shock or hypotension.
- Irreversible brain damage from preexisting cerebral disease.
- Other disease (eg, cancer, uremia, liver failure), associated with a likelihood of survival less than 1 year.

Group C patients need further work-up to decide whether or when they should get ICDs and should enter into step B.

Step B: evaluation of heart failure class
To determine the best course of therapy, these patients require assessment of the stage of heart failure according to the NYHA classification.112,113
- **Class I:** No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea (shortness of breath).
- **Class II:** Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnea.
- **Class III:** Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation, or dyspnea.
- **Class IV:** Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased.

Step C: evaluation of CAD or prior MI in NYHA class I patient
Evaluation for any evidence of prior MI or CAD requiring intervention is further necessary.
- Patients with NYHA class I heart failure whose EF is lower or equal to 30% and who are at least 40 days...
post-MI should be referred for an ICD implantation according to MADIT II trial.

- Patients with low EF and ≤40 days post-MI should be managed medically for their heart failure at present.\textsuperscript{114} If repeated imaging at 40 days confirms EF ≤30% (or ≤35% in patients with class II or III NYHA class CHF), these patients should be referred for an ICD implantation.

- Patients with low EF who underwent elective revascularization either by percutaneous intervention or by coronary bypass surgery in ≤3 months should be managed medically with optimal therapy for heart failure, and if repeated imaging at 3 months confirms EF ≤30% (or ≤35% in patients with class II or III NYHA class CHF), these patients should be referred for an ICD implantation.

**Step D: primary prevention of SCD in NYHA class II and III patients with low EF**

According to the ACC/AHA published Update Guidelines for the Diagnosis and Management of Chronic Heart Failure in the Adult.\textsuperscript{113} This treatment includes the following:

- Angiotensin-converting enzyme (ACE) inhibitors are recommended for routine administration to symptomatic and asymptomatic patients with LV EF ≤40% (strength of evidence = A).

- \(\beta\)-blockers shown to be effective in clinical trials of patients with HF are recommended for patients with an LVEF ≤40% (strength of evidence = A).

- Angiotensin receptor blockers (ARBs) are recommended for routine administration to symptomatic and asymptomatic patients with an LVEF ≤40% who are intolerant to ACE inhibitors for reasons other than hyperkalemia or renal insufficiency (strength of evidence = A).

- Administration of an aldosterone antagonist should be considered in patients following an acute MI, with clinical HF signs and symptoms and an LVEF ≤40%. Patients should be on standard therapy, including an ACE inhibitor (or ARB) and a \(\beta\)-blocker (strength of evidence = A). If repeated imaging at 3 months confirms EF ≤35% and still in NYHA class II and III, these patients will be referred for an ICD implantation.

**Step E: primary prevention of SCD is NYHA class III and IV heart failure patients with prolonged QRS (≥120 milliseconds)**

Patients with QRS ≥120 milliseconds and in NYHA class (III or IV) according to COMPANION and CARE-HF trial will be referred for CRT-D, where patients with NYHA class IV but QRS > 120 milliseconds should be treated with optimal medical therapy.\textsuperscript{89}

**Conclusion**

Over the last three decades, revolutionary advances in the understanding and treatment of SCD have been accomplished. Structural and electrical mechanisms of terminal arrhythmias have been elucidated. Over two-dozen genetic mutations and polymorphisms have been identified, which in turn have increased our understanding of ion channel structure and function. At the same time, randomized trials that demonstrated harm from antiarrhythmic drugs have curtailed the use of such drugs alone in the prevention of SCD. The ICD was developed and has proved to be a highly effective therapy in the prevention of SCD to date. Although most cases of SCD occur in patients without these high-risk features, the biggest challenge still remains: to accurately identify patients at risk for SCD for primary prevention.

**Disclosure**

The authors report no conflicts of interest in this work.

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