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INVASIVE ELECTROPHYSIOLOGY AND PACING (EK HEIST, SECTION EDITOR)

For Whom the Bell Tolls

Refining Risk Assessment for Sudden Cardiac Death

Ivaylo Tonchev[1] · David Luria[1] · David Orenstein[1] · Chaim Lotan[1] · Yitschak Biton[1,2]

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Abstract
Sudden cardiac death is one of the most important causes of death worldwide. Advancements in medical treatment, percutaneous interventions, and device therapy (ICD and CRTD) showed consistent reduction in mortality, mainly in survivors of SCD and in patients with ischemic cardiomyopathy and depressed left ventricular function. Patients with non-ischemic cardiomyopathies, mildly reduced LV function, and channelopathies have increased risk for SCD. Identifying the subgroup of these patients before they experience life-threatening or fatal events is essential to further improve outcomes. In this review, we aimed to summarize the current knowledge for risk stratification and primary prevention, to describe the gaps in evidence, and to discuss future directions for screening and treating patients at risk for SCD.

Purpose of Review The purpose of this review is to provide a comprehensive description of the etiologies of sudden cardiac death, risk stratification strategies, and to describe the current medical and interventional therapies. We aimed to discuss the current gaps in our knowledge of primary prevention of SCD and to review novel approaches and interventions.

Recent Findings The incidence of SCD has decreased in the last two decades due to improved pharmacological treatment and ICD implantation in SCD survivors and in patients with reduced left ventricular function and ischemic cardiomyopathy. The efficacy of ICD in patients with non-ischemic cardiomyopathy is challenged by new findings from the DANISH trial. Catheter ablation is new emerging strategy to prevent SCD in patients with scar relater or PVC-triggered ventricular arrhythmias.

Summary Despite the new treatments, SCD is still a major burden. ICD remains the cornerstone for patients with ischemic cardiomyopathy, whereas appropriate risk stratification of the patients with non-ischemic cardiomyopathy and channelopathies is needed to further improve outcomes. The future of ablation as the treatment and prevention of SCD remains to be studied.

Keywords Ablation therapy · Cardiac resynchronization therapy · Implantable cardioverter defibrillator · Sudden cardiac death · Primary and secondary prevention · Ventricular arrhythmia

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✉ Yitschak Biton
yitscb@gmail.com; bitony@hadassah.org.il

Ivaylo Tonchev
ivailortonchev@gmail.com

David Luria
dluria@hadassah.org.il

David Orenstein
davido@hadassah.org.il

Chaim Lotan
lotan@hadassah.org.il

[1] Hadassah Medical Center, Heart Institute, Hebrew University in Jerusalem Medical School, Kyriat Hadassah, PO Box 12000, 91120 Jerusalem, Israel

[2] Heart Research Follow-up Program, Division of Cardiology, Department of Medicine at the University of Rochester Medical Center, Rochester, NY, USA

Introduction

Sudden cardiac death (SCD) is defined as sudden and unexpected death occurring within an hour of the onset of the symptoms, or occurring in patients found dead within 24 h of being asymptomatic, presumably due to cardiac arrhythmia or hemodynamic catastrophe [1]. Within all cardiovascular disease (CVD), 25% are secondary to SCD, mainly tachyarrhythmia [2, 3]. SCD is associated with high social, health utilization and economic burden, and thus precise risk stratification is important. Recently, Shubi et al. showed that in a large Canadian SCD registry, patients who died suddenly utilized healthcare systems more frequently before the fatal event, but were not diagnosed to be at high risk. This study, however, did not identify predictors of SCD [4].

This review aims to discuss the current understandings of SCD in patients with structurally normal and abnormal hearts, current strategies of risk stratification, treatments, gaps in evidence, and future perspectives.

Pathophysiology, Mechanisms, and Epidemiology of SCD

The primary mechanism of SCD is thought to be tachyarrhythmia, predominantly ventricular, followed by premature ventricular complexes (PVCs), bradyarrhythmias, and non-arrhythmic mechanisms (rupture of an aortic aneurysm or pump failure) [5]. The mechanisms of ventricular arrhythmia (VA) are a complex interaction between arrhythmogenic substrate (myocardial scar, patchy fibrosis, channelopathies) and triggered activity induced by early or late afterdepolarizations [6].

In terms of risk stratification, patients can be divided into two major groups, either structural heart disease (SHD) or structurally normal heart. SHD can be further divided into patients with myocardial scar due to ischemic heart disease (IHD) and non-ischemic cardiomyopathies with patchy fibrosis and adverse remodeling. The latter group is represented by outflow tract VAs, channelopathies, bradyarrhythmias, or high-risk accessory atrioventricular aberrant pathways (Wolff Parkinson White (WPW)).

These patients are highly sensitive to altered cardiac metabolism, electrolytes disturbances, autonomic tone changes, and shifts in ion channels that can interfere with the cardiac action potential.

Patients with Structurally Abnormal Hearts

The rate of SCD in patients with IHD is consistently decreasing, whereas the proportion of patients with hypertensive heart disease and myocardial fibrosis has increased [7]. This decrease is attributed to better revascularization and better control of IHD risk factors [8, 9].

Patients admitted with MI are prone to VA prior to the reperfusion and in the next 48 after revascularization. Late VA (after 48 h) or ventricular fibrillation (VF) is associated with increased mortality [10]. In the settings of acute MI and VA event, urgent and complete revascularization is advised, even in comatose survivors with signs of STEMI [11, 12]. In the FAST MI 2005 registry, early VF (within 48 h) during ACS was associated with five-fold increase in-hospital mortality, but not with long-term mortality [13]. A recent study including almost 39,000 patients with acute MI, the lowest risk of VF, cardiac arrest, or death was associated with potassium concentrations of 3.5–4.5 mmol/L [14], and therefore, aggressive control of electrolytes is warranted.

Several studies showed genetic predisposition for SCD in the context of MI, and that family history of SCD is an independent risk factor for sudden death [15–18]. Two genome-wide association studies compared patients with STEMI with and without VF. The AGNES study showed association with single-nucleotide polymorphism located in the 21q21 locus [19]. In the second study, 2q24.2 locus signal correlated with increased risk of SCD; however, they could not replicate the results of the AGNES study [20].

Dilated cardiomyopathy is one of the most common cardiomyopathies accounting for a significant part of SCD, occurring unpredicted in 26% of the cases without IHD etiology and mainly out of the hospital [21].

In younger patients, IHD is less prevalent while other conditions such as myocarditis, mitral valve prolapse (MVP), hypertrophic cardiomyopathy (HCM), coronary anomalies, conduction disorders, and cardiomyopathies are more important causes of SCD [22–27].

A recent observational study consisting of 2094 adult patients with HCM showed that the systematic enhanced ACC/AHA strategy [(risk factors: family history of SCD, LV hypertrophy > 30 mm, unexplained syncope, non-sustained VT (NSVT)] predication capacity improved by adding late gadolinium enhancement (LGE) identified fibrosis and systolic dysfunction with LVEF < 50% by echocardiography or cardiovascular magnetic resonance (CMR) or LV apical aneurysm). The new score is highly sensitive (87–95%), but less specific in terms of identifying the ones without SCD events (78%). In the same study, European Society of Cardiology (ESC) risk score was applied retrospectively to the same group of patients and was shown to be significantly less sensitive [28•].

The correlation between SCD and MVP remains controversial. A recent systematic review and meta-analysis [29•] demonstrated that the prevalence of MVP among all SCD was 1.9% and that MVP was demonstrated by autopsy in 11.7% of unexplained SCD. The investigators of that study identified several potential predictors of SCD including VA (79% of the patients—bigeminy, multifocal ventricular ectopy, and sustained or non-sustained VT/VF), ST-T wave abnormalities (65.3%),

cardiac fibrosis (in 70.7%), and bi-leaflet MVP (80%) [29•].

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is an inherited cardiomyopathy with structural abnormalities predominantly in the right ventricle (RV), but also with common LV involvement, presenting with VA and an increased risk of SCD. Calkins et al. [30] identified several risk factors including electric instability (frequent PVCs and sustained VA), the extent of the RV and LV structural involvement, cardiac syncope (CS), male sex, proband status, multiple mutations, or a mutation in TMEM43. Radiofrequency ablation (RFA), endocardial or epicardial, seems to have the highest success rates in ARVC-related VT treatment and in eliminating frequent VT episodes and ICD shocks rather than a curative therapeutic approach [31]. In bundle branch reentrant tachycardia patients, antiarrhythmic medical therapy is usually ineffective, whereas RFA is reported as a successful procedure in terms of preventing recurrences [32, 33].

Myocarditis is described as a cause of SCD in athletes [34, 35]. Surprisingly, there are only small series and case reports and most are associated with fulminant myocarditis. Further dedicated research is needed.

Medical Treatment to Reduce SCD in Patients with Abnormal Heart

Adverse remodeling is associated with ion-channel alterations and has the potential to exacerbate the potential for VA. ACEi [36], ARBs [37], and MRAs [38] were shown to improve reverse remodeling and reduce the risk of SCD [39, 40] in patients with depressed LV function. In the AVID trial, statins were shown to reduce the incidence of SCD in high-risk patients [41]. Recently, PARADIGM-HF investigators showed that the angiotensis-receptor-neprilysin inhibitor reduced SCD and deaths from worsening of heart failure (HF) [42]. Beta blockers are highly effective in treating VAs as well as in reducing SCD in patients with or without HF [43]. However, a registry of 34,661 patients with acute MI STEMI or non-STEMI demonstrated that in patients with two or more risk factors for shock, the risk of shock or death was significantly elevated in those under treatment with beta blockers. Consequently, in this setting, beta blockers should not be initiated [44]. In the CAST trial [45], it was shown that the class Ic antiarrhythmics were associated with excessive mortality or non-fatal cardiac arrest rate (7.7%) among post-MI patients as compared with the placebo-treated patients (3.0%), and hence, the use of Ic antiarrhytmics after MI is contraindicated [46, 47]. The use of the class III agent amiodarone was widely investigated; in GESICA trial, the use of amiodarone in patients with severe HF reduced mortality and hospital admissions compared to standard treatment, especially in patients with higher baseline heart rate [48]. In this trial, patients were not on beta-blockers, and therefore, the mortality benefit could be explained by the beta-blockade effect. In Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) in which patients were on a beta-blocker, no benefit from amiodarone, when compared to placebo, was noted [49].

Device Therapy in Patients with Abnormal Heart Structure

ICD is a well-established therapy for secondary prevention of SCD [46, 47]. In antiarrhythmics versus implantable defibrillators (AVID) [50], cardiac arrest study Hamburg (CASH) [51], and Canadian Implantable Defibrillator Study (CIDS) [52] trials, patients who had suffered a cardiac arrest or life-threatening VA were recruited—secondary prevention. Antiarrhythmic vs ICD were compared in these trials, with a statistically significant reduction in the rate of total mortality in the ICD arm only in AVID. In CASH and CIDS, only arrhythmic death was significant, but not all-cause mortality. According to a meta-analysis of these trials, ICD therapy demonstrated a 50% reduction in arrhythmic mortality and a 28% reduction in total mortality. A sub-group analysis of the AVID trial results clearly demonstrated that the benefit was primarily to patients with an LVEF between 20 and 34% [53]. ICD is indicated for the primary prevention of arrhythmias that could lead to mortality in patients with HF who does not suffer from other conditions that limit life expectancy to 1 year, according to the ESC and AHA/ACC/HRS guidelines [46, 47]. In the MADIT (Multicenter Automatic Defibrillator Implantation Trial), 196 patients with prior MI, LVEF < 35%, and positive EPS were randomized to receive an ICD (95 patients) or conventional medical therapy at the time (101 patients) and showed improved survival in the ICD arm [54]. In MADIT II trial [55], 1232 patients with a history of MI and LVEF < 30% were recruited. This trial showed that all-cause mortality reduced by nearly 60% over the average follow-up of 20 months. The analysis from Multicenter Unsustained Tachycardia Trial (MUSTT) showed that non-inducible patients with LVEF < 30% had nearly identical total mortality and SCD rates as patients who were inducible but had an LVEF between 30 and 40%, and hence, a negative EP study in a patient with an LVEF < 30% cannot be reassuring [56].

The indication for ICD in the first 40 days post-MI is questionable. The Defibrillator in Acute Myocardial Infarction Trial (DINAMIT) did not show any benefit with ICD therapy for patients in the first 40 days post-MI and LVEF < 35%. The ICD arm was associated with a statistically significant decrease in death by arrhythmic causes, but a statistically significant increase in death by non-arrhythmic causes, and hence no difference in overall survival rates [57]. The IRIS trial did not show reduction in overall mortality in patients after ICD implantation between 5 and 31 days after MI with LVEF < 40% and heart rate higher than 90 beats per minute. There were less SCD in the ICD group, but the number of non-

SCD was significantly higher [58]. Similarly, in the Beta-blocker Strategy plus, ICD study (EPS guided ICD 5–30 days after acute MI vs conventional medical treatment) did not show mortality difference [59]. In this group of patients, wearable defibrillators (WD) can be a temporary measure. The safety and efficacy of this device were shown in Wearable Defibrillator Investigative Trial II [60]. The randomized VEST trial showed no significant arrhythmic mortality reduction with WD; however, the all-cause mortality was significantly reduced [61].

While ICD is a well-established therapy for ischemic cardiomyopathy, its role in NICMP (non-ischemic cardiomyopathy) is less established. The Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation (DEFINITE) trial was set to assess if ICD therapy can abort SCD in 458 patients with NICM with LVEF < 36% and documented PVCs or non-sustained VT. Patients with ICD had significant reduction in SCD but not all-cause mortality. In a subanalysis, male patients with NYHA III and LVEF between 20 and 35% benefited the most from ICD [62]. Importantly, in the recent DANISH trial [63••], there was no benefit with ICD in terms of all-cause mortality and only SCD was reduced significantly. The current guidelines are still based on the old SCD-HeFT trial in which ICD therapy vs amiodarone was compared among 2521 patients with LVEF < 35% (either ischemic or non-ischemic) and NYHA II-III on conventional therapy and divided into 3 groups—placebo, amiodarone, and shock-only single-lead ICD. The use of ICD was associated with decreased risk of death of 23% compared to placebo [49]. The results did not vary according to either ischemic or non-ischemic causes of CHF, but a greater reduction of mortality in patients with NYHA II was noted. The trials of ICD for primary and secondary prevention are summarized in Table 1.

Biventricular pacing is known to reduce mortality in selected groups of patients with depressed LV function and prolonged QRS. Table 2 summarizes the trials. In the MIRACLE trial, CRT-P therapy has been shown to reduce HF, and mortality in patients with NYHA III-IV, LVEF < 35%, and wide QRS [64]. The beneficial effect of biventricular pacing with ICD in a similar group of patients was proved also in MIRACLE-ICD [65]. Similar effects were shown in the RAFT trial [66] in patients with NYHA II-III, in addition to, a decrease of all-cause mortality and cardiovascular mortality. In the COMPANION trial, the combined primary endpoint of risk of death or first hospitalization in both CRT-P and CRT-D arms was met; however, the mortality reduction was limited to the CRT-D arm [67]. The initial outcomes and the long-term mortality follow-up of CARE-HF trial showed significant reduction of death in patients with CRT [68, 69]. In MADIT-CRT, patients with ICMP and NICMP with NYHA I-II showed a reduction of HF events, without a difference in risk of death [70] in the short term. In the long-term trial, only patients with LBBB had significant mortality reduction [71].

There is a notion that ICD shocks might be associated with increased mortality [72]; this was recently debated by Biton et al. showing that the underlying rate of the VA and not the shock is associated with mortality [73]. MADIT-RIT and PROVIDE trial demonstrated that more conservative ICD programming schema for primary prevention can reduce the rate of inappropriate shocks without increasing mortality [74, 75].

Catheter Ablation for the Prevention of SCD

In patients with ICM and NICM, scar-related reentry is known to be the mechanism of monomorphic VT. Prior studies showed that patients treated with VT ablation after an ICD shock had a significantly lower risk of death and HF as compared with patients managed with antiarrhythmics (Table 3). The adverse event rates after VT ablation were similar to patients with ICDs but without VT [76–78]. In SMASH-VT trial, VT substrate-based ablation was performed on patients with IHD during ICD implantation, and the patients were compared to patients with ICD implantation and no VA [79]. The patients receiving ablation and ICD showed reduced ICD shocks at 2-year follow-up and a trend toward reduced mortality compared to those receiving ICD without ablation. In VTACH trial, prophylactic VT ablation before defibrillator implantation seemed to prolong time to recurrence of VT in patients with stable VT, previous MI, and reduced LVEF [78]. Della Bella et al. enrolled 528 patients with SHD who experienced electrical storm, incessant VTs, or recurrent paroxysmal VTs for RFA VT ablation. After follow-up of 26 months, it was shown that the group of patients with successful VT ablation had significantly lower recurrences of VTs and lower cardiac death and SCD [80]. In the VANISH trial, RFA of VT was associated with greater quality-adjusted life-years (QALYs) and less SCD, episodes of VT within 24 h, and appropriate ICD shocks than escalated drug therapy [81]. Sauer et al. demonstrated similar results in terms of survival rate in patients with ischemic and NICM after successful ablation of VT [82]. To date, three studies, STAR VT, BERLIN-VT, and PARTITA, are evaluating the use of early VT ablation in preventing sudden death.

SCD in Patients with Structurally Normal Hearts

Long QT syndrome (LQTS) is the most studied channelopathy. The risk of SCD in patients with LQTS is increased due to polymorphic VT [83–85]. Barsheshet et al. showed that the risk of SCD and Torsades de Points (TdP) can be predicted by previous events of TdP or another form of VA, CS without documented arrhythmia, QTc > 500 ms, and low potassium levels [86]. Additional risk factors are female sex, age, pre-

Table 1 Summary of trials of ICD therapy for primary and secondary prevention of sudden cardiac death

Trial name	Year	Population	Study design	Inclusion criteria	Mean follow-up	Number of patients with ICD	Control group	Primary endpoint	Secondary endpoint and subgroup analysis
Primary prevention-ischemic cardiomyopathy									
MADIT	1996	196	Multicenter, randomized, controlled trial	NYHA I-III; LVEF ≤ 35%; Post MI-yes; EPS-yes	27 months	95	101 (OPT)	All-cause mortality 15.8% vs 38.6% $P = 0.009$	Death from cardiac causes 11.6% vs 26.7 $p < 0.05$
MUSTT	1999	351	Multicenter, open-label, randomized, controlled trial	NYHA I-III; LVEF ≤ 40%; CAD- yes; EPS-no	39 months	161	158 (AAD)	Cardiac arrest or arrhythmic death 25% vs. 32% [RR 0.73; 95% CI 0.53–0.99; P = 0.04]	Overall mortality 42% vs. 48% [RR 0.80; 95% CI 0.64–1.01; $P = 0.06$]; CV 34% vs. 40% [$P = 0.05$]; CA or arrhythmic death (5 years, among EPS-guided patients, ICD vs. AAD without ICD)9% vs. 37% [$P < 0.001$]Overall mortality (5 years, among EPS-guided patients, ICD vs. AAD without ICD)24% vs. 55% [RR 0.40; 95% CI 0.27–0.59; $P < 0.001$]
MADIT II	2002	1232	Multicenter, randomized, controlled	NYHA I-III; LVEF ≤ 30%; Post MI-yes; EPS-no	20 months	742	490 (OPT)	All-cause mortality 14.2% vs. 19.8% (HR 0.69; 95% CI 0.51–0.93; $P = 0.016$)	New or worsened heart failure 19.9% vs. 14.9% ($P = 0.09$)
DINAMIT	2004	674	Multicenter, open-label, randomized, controlled	NYHA I-III; LVEF ≤ 35%; Recent MI-yes; EPS-no	30 months	332	342 (OPT)	All-cause mortality 7.5% vs. 6.9% (HR 1.08; 95% CI 0.76–1.55; $P = 0.66$)	Arrhythmic death 1.5% vs. 3.5% (HR 0.42; 95% CI 0.22–0.83; $P = 0.009$); Non-arrhythmic death 4.1% vs. 2.4% (HR 1.72; 95% CI 0.99–2.99; $P = 0.05$);
Primary prevention-non-ischemic or combined cardiomyopathy									
DEFINITE	2004	458	Multicenter, reviewer-blinded, parallel-group, randomized, controlled	NYHA II-III; LVEF ≤ 35%; NICM-yes; EPS-no; ambient arrhythmias	2.4 years	229	229 (OPT)	All-cause mortality 9.4% vs. 17.5% (HR 0.65; 95% CI 0.40–1.06; $P = 0.08$)	Arrhythmogenic SD 1% vs. 6% (HR 0.20; 95% CI 0.06–0.71; $P = 0.006$); HF death 3% vs. 4.8% (No *P*value given); Men with an ICD had a reduced mortality RR 0.49 95% CI 0.27–0.90; $P = 0.018$; NYHA class III patients with an ICD had a reduced mortality RR 0.37; 95% CI 0.15–0.90; $P = 0.02$
SCD-HeFT	2005	2521	Multicenter, double-blinded, parallel-group, randomized, placebo-controlled	NYHA II-III; LVEF ≤ 35%; both ICM and NICM; EPS-no;	45.5 months	829	845 amiodarone and 847 placebo	ICD vs. placebo22% vs. 29% (HR 0.77; 97.5% CI 0.62–0.96; $P = 0.007$)Amiodarone vs. placebo28% vs. 29% (HR 1.06; 97.5% CI 0.86–1.30; $P = 0.53$)	

Table 1 (continued)

Trial name	Year	Population	Study design	Inclusion criteria	Mean follow-up	Number of patients with ICD	Control group	Primary endpoint	Secondary endpoint and subgroup analysis
DANISH	2016	1116	Multicenter, open-label, randomized, controlled	NYHA II-III; LVEF ≤ 35%; NICM-yes; EPS-no	68 months	556	560 (OPT)	All-cause mortality 120 (21.6%) vs. 131 (23.4%) (HR 0.87; 95% CI 0.68–1.12; $P = 0.28$)	CV death 77 (13.8%) vs. 95 (17.0%) (HR 0.77; 95% CI 0.57–1.05; $P = 0.10$); SCD 24 (4.3%) vs. 46 (8.2%) (HR 0.50; 95% CI 0.31–0.82; $P = 0.005$); < 59 years: 17/167 vs. 34/181 (HR 0.51; 95% CI 0.29–0.92; $P = 0.02$) ≥ 59 to < 68 years: 36/173 vs. 50/202 (HR 0.75; 95% CI 0.48–1.16; $P = 0.19$) ≥ 68 years: 67/216 vs. 47/177 (HR 1.19; 95% CI 0.81–1.72; $P = 0.38$); NT-proBNP < 1177 pg/mL: 32/266 vs. 74/268 (HR 0.59; 95% CI 0.38–0.91; $P = 0.02$) ≥ 1177 pg/mL: 57/292 vs. 88/290 (HR 0.99; 95% CI 0.73–1.36; $P = 0.96$)
Secondary prevention for both ischemic and non-ischemic cardiomyopathy									
AVID	1997	1016	Multicenter, randomized, controlled	resuscitated VF; sustained VT with syncope or LVEF < 40%	18.2 months	507	509 (OPT)	All-cause mortality 15.8% vs 23.97%, $p < 0.02$	Time to first hospitalization 60% vs 56% $p = 0.04$
CASH	2000	288	Prospective, multicenter, randomized	resuscitated CA due to VA more than 72 h after MI;	57 months	99	189 (amiodarone-92 or metoprolol-97)	All-cause mortality 36.4% vs 44.4% $p = 0.081$	Survival free of sudden death 13% vs 33% 1-sided $p = 0.005$ (HR 0.423 [97.5% CI upper bound 0.721])
CIDS	2000	659	Randomized multicenter	Resuscitated CA due to VA more than 72 h after MI; VA causing syncope, pre-syncope or angina; unmonitored syncope with subsequent documentation of either spontaneous VT > 10 s or sustained (> 30 s)	2.9 years	328	331 (OPT)	All-cause mortality 8.3% vs 10.2% $p = 0.142$ (19.7% relative risk reduction [RRR]; 95% confidence interval [CI], 27.7% to 40.0%)	Arrhythmic death 3.0% vs 4.5% $p = 0.094$ (32.8% RRR; 95% CI, 27.2% to 57.8%)

Table 2 Summary of trials of CRT therapy for prevention of sudden cardiac death

Trial name	Year	Population		Major Inclusion criteria	Mean follow-up	Number of patients with CRT	Control group	Primary endpoint	Secondary endpoint and subgroup analysis
MIRACLE	2000	453	Randomized, multicenter, double-blind, parallel-controlled	NYHA III-IV; LVEF ≤ 35%; both ICM and NICM; EPS-no; QRS ≥ 130 ms	> 6 months	228	225 (OPT)	6MWT $P = 0.005$; QOLs $P = 0.001$; NYHA $P < 0.001$	Combined time to death or hospitalization for worsening of HF (95% confidence interval, 4 to 63%; $P = 0.03$); all-cause mortality $p = 0.40$; death or worsening of HF $p = 0.03$
MIRACLE-ICD	2003	369	Randomized, multicenter, double-blind, parallel-controlled	NYHA III-IV; LVEF ≤ 35%; both ICM and NICM; EPS-no; LBBB with QRS ≥ 130 ms	6 months	187	182 (ICD)	6MWT $P = 0.36$; QOLs $P = 0.02$; NYHA $P < 0.007$;	Survival at 6 months $p = 0.96$; VT/VF22% vs 26% $p = 0.47$; risk of death or all-cause hospitalization 48.3% (95% CI, 40.6–55.6%) for the control group vs 47.4% (95% CI, 40.0–54.4%) for the CRT group ($P = .88$)
COMPANION	2004	1520	Prospective, randomized, double-blind multicenter, controlled	NYHA III-IV; LVEF ≤ 35%; both ICM and NICM; EPS-no; sinus rhythm; QRS ≥ 120 ms and PR interval > 150 ms	16.2 months	1080	440 (OPT)	All-cause mortality or hospitalization for any cause in CRTP group $P = 0.014$; adjusted $P = 0.015$ by the log-rank test) and in CRTD group $P = 0.010$; adjusted $P = 0.011$)	Reduction in the risk of death from any cause in CRTP$P = 0.059$; adjusted $P = 0.06$) and in CRTD $P = 0.003$; adjusted $P = 0.004$); death from or hospitalization for cardiovascular causes CRTP$P = 0.002$ and in CRTD $P < 0.001$
CARE-HF	2005	813	Multicenter, randomized, double-blind, controlled	NYHA III-IV; LVEF ≤ 35%; both ICM and NICM; EPS-no; QRS ≥ 120 ms dyssynchrony confirmed by echo if QRS 120-149 ms	29.4 months	409	404 (OPT)	Death from any cause or an unplanned hospitalization for a major cardiovascular event (39% vs. 55%; hazard ratio, 0.63; 95% confidence interval, 0.51 to 0.77; $P < 0.001$)	All-cause mortality 20% vs. 30%; hazard ratio, 0.64; 95% confidence interval, 0.48 to 0.85; $P < 0.002$; death from any cause or hospitalization for worsening HF $P < 0.001$); QLOs $P < 0.001$;
MADIT-CRT	2009	1820	Multicenter, randomized, open label, controlled	NYHA I-II; LVEF ≤ 30%; both ICM and NICM; EPS-no; QRS ≥ 130 ms; sinus rhythm	2.4 years	1089	731 (ICD)	All-cause mortality or non-fatal HF event 25.3% vs. 17.2% (HR 0.66; 95% CI 0.52–0.84; $P = 0.001$; ICM, NYHA class I or II: 29.2% vs. 20.4% (HR 0.67; 95% CI 0.52–0.88; $P = 0.003$)NICM, NYHA class II: 20.6% vs. 13.2% (HR 0.62; 95% CI 0.44–0.89; $P = 0.01$)	HF event 22.8% vs. 13.9% (HR 0.59; 95% CI 0.47–0.74; $P < 0.001$) ICM, NYHAI or II: 26.2% vs. 16.1% (HR 0.58; 95% CI 0.44–0.78; $P < 0.001$) NICM, NYHA II: 18.8% vs. 11.2% (HR 0.59; 95% CI 0.41–0.87; $P = 0.01$); all-cause mortality 7.3% vs. 6.8% (HR 1.00; 95% CI 0.69–1.44; $P = 0.99$) ICM,

Table 2 (continued)

Trial name	Year	Population		Major Inclusion criteria	Mean follow-up	Number of patients with CRT	Control group	Primary endpoint	Secondary endpoint and subgroup analysis
									NYHA I or II: 8.7% vs. 8.9% (HR 1.06; 95% CI 0.68–1.64; $P = 0.80$) NICM, NYHA II: 5.5% vs. 4.3% (HR 0.87; 95% CI 0.44–1.70; $P = 0.68$)
RAFT	2010	1798	Multicenter, double-blind, randomized, controlled	NYHA II-III; LVEF ≤ 30%;both ICM and NICM; EPS-no; Intrinsic QRS ≥ 120 ms or a paced QRS duration ≥ 200 ms; ventricular rate (≤ 60 per minute at rest and ≤ 90 per minute during a 6-min walk test	40 months	888	899 (ICD)	Mortality or hospitalization for heart failure 33.2% vs. 40.3% (HR 0.75; 95% CI 0.64–0.87; $P < 0.001$; NNT = 14) NYHA class II: 27.3% vs. 34.7% (HR 0.73; 95% CI 0.61–0.88; $P = 0.001$; NNT = 14)NYHA class III: 55.9% vs. 63.8% (HR 0.76; 95% CI 0.58–0.99; $P = 0.04$; NNT = 13)	All-cause mortality 20.8% vs. 26.1% (HR 0.75; 95% CI 0.62–0.91; $P = 0.003$) NYHA II: 15.5% vs. 21.1% (HR 0.71; 95% CI 0.56–0.91; $P = 0.006$) NYHA III: 40.9% vs. 47.1% (HR 0.79; 95% CI 0.58–1.08; $P = 0.14$); CV mortality 14.5% vs. 17.9% (HR 0.76; 95% CI 0.60–0.96; $P = 0.02$) NYHA II: 10.5% vs. 13.7% (HR 0.73; 95% CI 0.54–0.99; $P = 0.04$) NYHA III: 30.1% vs. 35.6% (HR 0.77; 95% CI 0.54–1.10; $P = 0.15$); Hospitalization for HF 19.5% vs. 26.1% (HR 0.68; 95% CI 0.56–0.83; $P < 0.001$)NYHA II: 16.2% vs. 21.8% (HR 0.70; 95% CI 0.55–0.89; $P = 0.003$) NYHA III: 31.7% vs. 44.3% (HR 0.63; 95% CI 0.45–0.88; $P = 0.006$)
CARE-HF (long-term outcomes)	2012	309	Multicenter, randomized, double-blind, controlled	NYHA III-IV; LVEF ≤ 35%; both ICM and NICM; EPS-no; QRS ≥ 120 ms dyssynchronyby echo, if QRS 120-149 ms	6.5 years			HR for mortality in patients assigned to CRT compared with those assigned to the control group was 0.77 (95% confidence interval 0.63–0.93; $P = 0.007$)	

AAD anti-arrhythmic drug, *CA* cardiac arrest, *CAD* coronary artery disease, *CRTD* cardiac resynchronization therapy, *EPS* electrophysiological study, *ICD* implantable cardiac defibrillator, *ICM* ischemic cardiomyopathy, *LVEF* left ventricular ejection fraction, *LBBB* left bundle branch block, *MI* myocardial infarction, *NNT* number needed to treat, *NICM* non-ischemic cardiomyopathy, *OPT* optimal medical treatment, *SCD* sudden cardiac death, *VA* ventricular arrhythmia, *VF* ventricular fibrillation, *VT* ventricular tachycardia, *QOLs* quality of life scale, *6MWT* 6-min walk test

Table 3 Trials of catheter ablation for the prevention of sudden cardiac death

Trial name	Year	Population	Study design	Inclusion criteria	Mean follow-up
SMASH-VT	2007	128	Prospective, unblinded, randomized, controlled, multicenter	MI; ICD;VT hemodynamically unstable or syncope; inducible VT on EPS;	2 years
VTACH	2010	110	Multicentre, randomized, controlled	stable VT, previous myocardial infarction, and reduced left-ventricular ejection fraction LVEF; < 50%	22.5 months
Sauer et al.	2010	208	Single center, retrospective cohort study, uncontrolled	ICM (144) and NICM [64]; ICD; VT or positive EPS for VT;	51 months
Della Bella et al	2013	528	Single center, uncontrolled	VTNICM and ICM; NYHA I-IV; LVEF below and above 30% (subgroups)	26 months
VANISH	2016	259	Multicenter, open-label, randomized, controlled trial	MI; Episode of VT on AAD within 6 months; appropriate ICD shocks; recurrent VT or VT below detection rate	27.9 months
Ongoing trials	Patients to be enrolled	Inclusion criteria	Study design	Aim	Primary endpoint
BERLIN-VT	163	Prior MI; LVEF 30–50%; ICD indication and documented VT	Multicenter, prospective, randomized, controlled	To evaluate the impact of prophylactic VT ablation on all-cause mortality and unplanned hospitalizations HF or symptomatic VT/VFwhen compared to VT ablation after the third appropriate ICD shock	all-cause mortality and hospital admission secondary to cardiac causes
STAR VT	1453	ICM and NICM; documented or inducible monomorphic VT; ICD/CRTD	Multicenter, randomized, open-label, controlled	To evaluate the impact of scar-based VT ablation vs routine drug therapy on freedom from ICD shocks and cardiovascular-related hospitalizations	ICD shock reduction (VT recurrences) both appropriate and inappropriate
PARTITA	590	implanted with ICDfor primary or secondary prevention of sudden cardiac death	multicentre, randomized, controlled trial	To assess whether the burden of NSVT or episodes treated with anti-tachycardia pacing, correlates with appropriate ICD shock therapies and to evaluate if the timing of RFA of VT affects the prognosis of ICD recipients.	Appropriate ICD shock; worsening heart failure; hospitalizations or deaths from any cause

Trial name	Ablation (*N*)	Control group (*N*)	Primary endpoint	Secondary endpoint
SMASH-VT	64	64	Survival free from any appropriate ICD therapy 12% vs 33% $p = 0.007$, HR 0.35 (0.15–0.78))	death - 9% vs 17% $p = 0.29$, HR 0.59 (0.22–1.59)
VTACH	52	55 (ICD)	time to first recurrence of VT or VF-18.6 months vs 5.9 months	survival free from VT or VF 47% vs 29% $p = 0.045$
Sauer et al.	327 procedures mean 1.5 per patient		survival advantage was noted in patients with hemodynamically stable VT ($p = 0.02$) and without inducible VA programmed stimulation following the procedure ($p < 0.01$)	
Della Bella et al	PVS after procedure with noninducibility of any VT-371 (77%) group A	PVS after procedure with inducibility of nondocumented VT in 12.4% group B, andinducibility of index VT in 10.6% group C	VT recurrence-(A) 28.6% vs (B) 39.6% vs (C) 66.7%, log-rank $P < 0.00$)	Occurrence of cardiac and sudden cardiac death (A) 8.4% vs (B) 18.5% vs (C) 22%, log-rank $P = 0.002$
VANISH	132	127 (escalated therapy)	Composite of death, VT stormor appropriate ICD shock after a 30-day treatment period-59.1% vs 68.5% $p = 0.04$	Mortality-27.3% vs 27.6% $p = 0.86$
Ongoing trials	Secondary endpoint			
BERLIN-VT	time to first ICD shock			
STAR VT	serious adverse events within the 30-day follow-up, associated with catheter ablation			
PARTITA	N of patients with cardiac deaths; electrical storm (ES) recurrences; VT recurrences			

AAD anti-arrhythmic drug, *CRTD* cardiac resynchronization therapy, *EPS* electrophysiological study, *ICD* implantable cardiac defibrillator, *ICM* ischemic cardiomyopathy, *LVEF* left ventricular ejection fraction, *MI* myocardial infarction, *NICM* non-ischemic cardiomyopathy, *PVS* programmed ventricular stimulation, *RFA* radiofrequency ablation, *SCD* sudden cardiac death, *VA* ventricular arrhythmia, *VF* ventricular fibrillation, *VT* ventricular tachycardia

existing cardiovascular diseases, resting heart rate, and mutation location. Genetic information can inform the risk of SCD. Moss et al. have shown that in LQTS1, the location, type, and biophysical function of the KCNQ1 mutation are an important independent risk factor for CS or SCD [87]. In patients with LQTS2, the type and location of the KCNH2 mutations are in correlation with an elevated risk of life-threatening cardiac events [88]. Gender is playing a major role in LQTS1 and LQTS2, female patients have a longer baseline QTc, associated with more TdP episodes [89].Buber et al. demonstrated that the perimenopausal period is associated with an elevated risk of CS in LQTS2 [90]. Currently, there is no data about the correlation of type and location of the mutation in LQTS3. According to Wilde, Moss et al., females had a higher probability of a first cardiac event than did males, especially in the 30 to 40 years of age [91].

Beta blocker, specifically nadolol [92], is considered to be the mainstay of treatment in LQTS mainly LQT1 and LQT2 with very low risk of SCD [91, 93]. Despite that some LQTS patients will still have life-threatening events while treated with BB and these patients require ICD for secondary prevention. Primary prevention is more challenging, in a registry of patients who received an ICD for primary prevention QTC > 550 ms, prior syncope on BB, and genetic data were found to be predictive of appropriate shocks [94].

Brugada syndrome (BrS) is an inherited channelopathy associated with an elevated risk of SCD. To date, there is no validated universal risk stratification strategy [95]. Procainamide challenge is used for diagnosis, but it is not clear how to interpret the results. In asymptomatic patients, provoked type 1 ECG pattern was not associated with increased risk of death [96]. However, in symptomatic patients, positive test was associated with increased mortality [97]. Several studies have been proposing different risk factors. In the FINGER registry, only CS and spontaneous type 1 ECG pattern were statistically significant predictors [96]. Other risk factors were proposed but not validated in larger studies, including QRS fragmentation, ventricular repolarization period < 200 ms, QRS duration > 120 ms, positive programmed electrical stimulation test, sinus node dysfunction, and male gender [98, 99]. In the SABRUS registry, a quarter of the patients presented with life-threatening arrhythmic event did not meet the current criteria for ICD implantation [100]. Genetic factors might have a greater role in the risk stratification in the near future, as well as the assessment of the arrhythmogenic substrate in the RV [101]. Belhassen et al. showed that treatment with quinidine decreased the inducibility of VF in patients who had inducible VF at baseline EP study [102]. To date, quinidine is reserved for patients who refuse ICD implantation [46, 47]. ICD therapy or RFA should be considered in symptomatic patients or patients with VF storm. In asymptomatic patients with BrS, quinidine therapy or no therapy is both acceptable. There is a subgroup of patients with BrS who manifest with polymorphic VT/VF, triggered by RVOT ectopy PVCs; in this selected subgroup, ablation is a reasonable option [103].

Catecholaminergic polymorphic VT (CPVT) is caused by a mutation in the Ryanodine receptor and causes polymorphic VT with normal QT interval. Flecainide in combination with beta-blockers has demonstrated partial or complete suppression of VA in 76% in a recent review of 15 clinical studies [104]. Short QT syndrome (SQTS) is a rare malignant channelopathy causing VA and SCD. The diagnosis is based on ECG findings (QTc < 330 ms or < 360 ms in combination with CS, arrest, family history of SCD at young age (< 40), or family history of SQTS) and genetic findings. Currently, hydroquinidine is the first-line therapy for SQTS [105]. Early repolarization syndromes have recently been reported to be more malignant than previously thought, especially with elevation in inferior or lateral leads [106, 107]. Idiopathic VF (IVF) is a rare cause of SCD that can overlap with VA syndromes, and hence, full electrophysiological assessment should be performed before calling this diagnosis.

In patients with high-risk accessory pathways (AP), RFA is recommended. It should be noted that post-ablation the mortality is patients with WPW syndrome is similar to the general population [108]. Prophylactic AP ablation is not recommended to all asymptomatic patients with low-risk pathways [109–113].

The Role of PVCs and Non-sustained VT as a Cause of SCD

Frequent PVCs are defined if occurring ≥ 1 time during a standard electrocardiographic recording or ≥ 30 times over a 1-h recording. In a meta-analysis of 11 studies with a total of 106,195 participants, frequent PVCs were associated with increased risk for sudden cardiac death and total cardiac death [114]. It should be noted that the participants in those studies were screened for underlying SHD. In addition, the presence of multifocal PVCs and NSVT association with a higher incidence of mortality is well described in various series [115–117]. In a single study, PVCs that occur during recovery are a powerful predictor of death compared with PVCs occurring during exercise [118]. High PVC burden (> 10,000–20,000 a day) can be associated with a deterioration of the LVEF [119]. Early recognition of LV deterioration and early intervention are critical.

Evaluation, Risk Stratification, and Current Guidelines

Systemic evaluation and risk stratification in patients at risk for SCD or SCD survivors are important [46, 47]. Accurate personal and family history taking, baseline 12-lead electrocardiogram (ECG), 24-h (or more) ECG monitor (Holters, loop/event recorders), exercise stress test, provocative tests,

cardiac imaging (TTE, CMR), and genetic testing are recommended. CAD should be excluded in patients without acute coronary syndrome by non-invasive test when possible in patients above the age of 40 and risk factors for CVD. For patients with a documented VA, cardiac biomarkers, invasive cardiac imaging by cardiac catheterization or CT angiography is recommended to rule out CAD.

Among several non-invasive markers of risk of SCD, only the LV dysfunction (in both ICMP and NICM), in combination with New York Heart Association (NYHA) class, is consistently predictive of SCD and therefore used to identify candidates ICD for primary prevention of SCD [49, 55]. Several biomarkers have been tested. Pro-B-type natriuretic peptide (both NT and B-type) are showing correlation with the risk of VA [120]. Galectin-3 and ST2 showed association with markedly increased risk of cardiac death, all-cause mortality, and heart transplantation [121–123]. ECG markers including heart rate variability, late potentials, microvolt T-wave alternans, and QT interval dispersion were shown to predict SCD in several studies. Relative wall thickness is an echocardiogram marker that was shown to correlate with VA in patients with HF and HCM [124]. To date, none of these markers is used in clinical practice.

CMR can identify arrhythmogenic substrate and guide ablation therapy or inform ICD indication. In an HCM cohort of 177 patients with no or only mild symptoms, myocardial fibrosis detected by CMR was associated with greater likelihood and increased the frequency of VA (including NSVT) on ambulatory Holter ECG [125]. In addition, patients with a VA event and HCM had a wider extension of LGE [126]. Moreover, CMR-detected mid-wall myocardial fibrosis was demonstrated as an independent

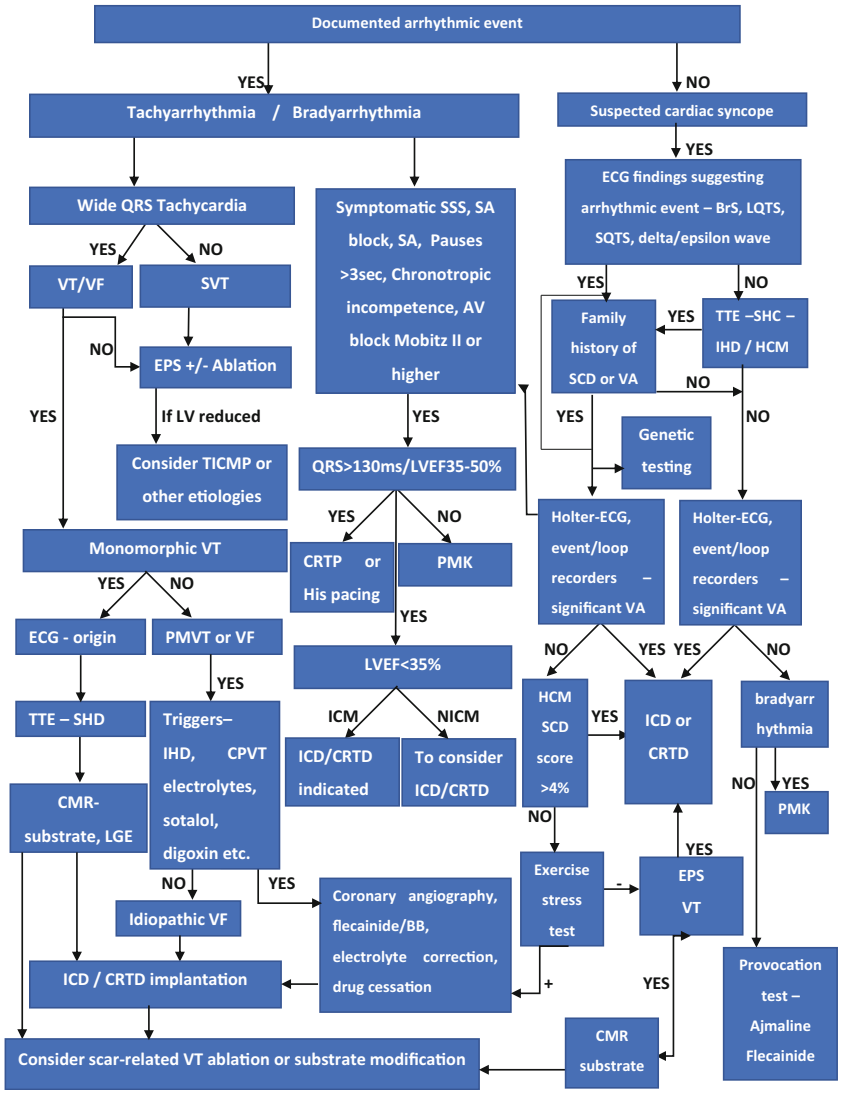

Fig. 1 Assessment of patients presenting with cardiac syncope or aborted cardiac arrest. BB–beta blocker, BrS–Brugada syndrome, CMR–cardiac magnetic resonance, CPVT–catecholaminergic polymorphic ventricular tachycardia, CRTD–cardiac resynchronization therapy, EPS–electrophysiological study, HCM–hypertrophic cardiomyopathy, ICD–implantable cardiac defibrillator, IHD–ischemic heart disease, LGE–late gadolinium enhancement, LVEF–left ventricular ejection fraction, LQTS–long QT syndrome, PMK–pacemaker, PMVT–polymorphic ventricular tachycardia, SA–sinus arrest, SCD–sudden cardiac death, SHD–structural heart disease, SQTS–short QT syndrome, SSS–sick sinus syndrome, VF–ventricular fibrillation, VT–ventricular tachycardia, SVT–supraventricular tachycardia, TICMP–tachycardia-induced cardiomyopathy, TTE–transthoracic echocardiography, VA–ventricular arrhythmia

predictor of mortality in patients with moderate or severe aortic stenosis providing an 8-fold increase in all-cause mortality compared to similar patients without LGE [127]. Additionally, gadolinium kinetics reflecting cardiac amyloid burden can be used as predictor of the mortality risk [128]. The introduction of T2 CMR to identify myocardial siderosis and appropriate intensification of iron chelation treatment was named as a game changer in the treatment protocols [129]. Interestingly, post-mortem MR imaging of the heart, which identified correctly the diagnosis in 12 patients who subsequently had positive findings at conventional autopsy for ARVC, and hence was found useful in determining the cause of sudden death [130]. Moreover, ARVC patients with syncope have greater LGE than those of patients without syncope [131].

Electrophysiology study (EPS) is recommended in patients with symptoms suggestive of VA, with known CAD and myocardial scar and SHD. It may help to differentiate ARVC from RV outflow tachycardia and sarcoidosis and to serve as a risk-stratification tool [30, 132]. EPS is not recommended for risk stratification for VA in the setting of long QT syndrome (LQTS), CPVT, short QT syndrome, or early repolarization syndromes. The utility of EPS is a matter of a debate in BrS [133].

Wide population screening tools are still not available. ECG is not recommended due to cost-benefit considerations and the potential for false positive/negative results. Genetic screening is very expensive and may confer ethical problems. Currently, screening is recommended for selected groups such as athletes. Unfortunately, in a registry from Israel, the incidence rates of SCD in competitive athletes following the implementation of screening programs did not improve [134]. American Heart Association/American College of Cardiology/Heart Rhythm Society (AHA/ACC/HRS) and ESC [46, 47] guidelines are recommending for screening first-degree family members of sudden death victims to identify individuals at risk and adequately prevent sudden death in conditions like CPVT, or ARVC, HCM, and some channelopathies like LQTS [135–139]. Yet, according to a report from 2008, only 40% of family members are screened [140].Figure 1 summarizes the workup for SCD.

Gaps in Evidence and Future Perspectives

Currently, there is no data regarding patients with HF with mildly reduced LVEF; this question will be assessed in the PRESERVE-EF and REFINE-ICD trials. EPS-guided ICD placement in the first 40 days post-MI will be assessed in the PROTECT-ICD trial. New studies are needed to refine the indications for ICD in NICMP.

Conclusion

SCD is a major cause of death despite that advancement is our knowledge and treatment. Future studies will need to be done to accurately identify patients at risk. The implantation of big data, artificial intelligence, and genetic data will open a new era in the understanding and treatment of SCD.

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Compliance with Ethical Standards

Conflict of Interest Ivaylo Tonchev, David Luria, and Yitschak Biton declare that they have no conflict of interest.

David Orenstein reports personal fees from Biotronik, Johnson and Johnson, and Medtronic.

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- • Of importance
- •• Of major importance

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