Secondary prevention of sudden cardiac death

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The prevention and treatment of sudden cardiac death (SCD) remains a significant public health challenge. For patients with a history of sudden death attributable to ventricular arrhythmia, implantable cardioverter-defibrillator (ICD) therapy is a mainstay of treatment, although these patients remain at high risk for recurrent ventricular arrhythmia and defibrillator therapies. In this review, we summarize landmark clinical trials evaluating the efficacy of ICD therapy in secondary prevention patients, review clinical outcomes including mode of death in survivors of SCD, and highlight the role for systematic diagnostic evaluation. We additionally discuss the invasive electrophysiological management of these patients, including ICD selection and programming as well as the role and timing of antiarrhythmic drug therapy and catheter ablation. Finally, we frame future challenges and needs to advance the care for secondary prevention patients.

KEYWORDS Cardiac arrest; Epidemiology; Implantable cardioverter-defibrillator; Prevention; Sudden death; Ventricular arrhythmia

Introduction

Sudden cardiac death is estimated to account for 15%–20% of global mortality and remains a pressing public health challenge.[1] Sudden death is frequently attributed to lethal ventricular arrhythmia and coronary heart disease (CHD) is the most common underlying substrate in the Western world.[2] For survivors of cardiac arrest attributed to ventricular tachycardia (VT) or ventricular fibrillation (VF), or those with sustained VT not due to a reversible cause, contemporary consensus guidelines recommend implantation of an implantable cardioverter-defibrillator (ICD) in patients with greater than 1 year life expectancy.[3] While the use of ICD therapy in this context is seemingly straightforward, there remain substantial knowledge gaps regarding the secondary prevention of sudden death.

This review summarizes the landmark clinical trials evaluating the efficacy of ICD therapy for secondary prevention, reviews clinical outcomes in survivors of sudden cardiac death, highlights the role for systematic diagnostic evaluation, discusses the invasive electrophysiological management in this population, and frames future challenges and needs to advance the care for secondary prevention patients.

Landmark Trials in Secondary Prevention
Anti-arrhythmic Versus Implantable Defibrillator Trial

The Anti-arrhythmic Versus Implantable Defibrillator (AVID) trial (enrollment 1993–1997) evaluated the efficacy of ICD therapy in 1016 patients with resuscitated VF arrest, sustained VT with syncope, or sustained VT with a left ventricular ejection fraction (LVEF) ≤40% and symptoms suggestive of hemodynamic compromise (Table 1).[4] The majority of participants had underlying CHD (81%) and left ventricular (LV) systolic dysfunction (mean LVEF 32% ± 13%). Approximately one-half of trial participants qualified on the basis of a resuscitated VF arrest, the remainder with sustained VT. Participants were randomized to ICD therapy vs antiarrhythmic drugs (AAD), which was predominantly amiodarone (96% of the AAD arm at hospital discharge). Over a mean follow-up of 18 months, after which the trial was prematurely terminated on the basis of ICD efficacy, crude mortality was 15.8% in the ICD arm vs 24% in the AAD arm. At 3 years, the average unadjusted survival attributed to ICD therapy was 2.7 months and the estimated number needed to treat to save 1 life with an ICD was 12. There were notable differences in background medical therapy and morbidities between the randomized groups, including a greater prevalence of β-blocker therapy in the ICD vs AAD arm (eg, 42% vs 16% at hospital discharge) and lower prevalence of heart failure (55% vs 60%). While the survival benefit of ICD therapy persisted following adjustment for these differences, the possibility of residual confounding could not be entirely excluded. In subgroup analysis, there was no statistical difference in survival benefit of ICD therapy when stratified by qualifying indication (VF arrest vs sustained VT), prevalent CHD, or LVEF, although numerically, the survival benefit of ICD therapy was observed to accrue only in patients with an LVEF ≤35%.[5]

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KEY FINDINGS

- Landmark randomized clinical trials have established the efficacy of implantable cardioverter-defibrillator (ICD) therapy in patients with a history of arrhythmic sudden death. The survival benefit of ICD therapy in the secondary prevention of sudden death was primarily observed in patients with significantly reduced left ventricular function (left ventricular ejection fraction ≤35%).

- Patients historically excluded from randomized trials of ICD efficacy in secondary prevention, including those thought to have a reversible etiology of arrhythmia (eg, acute ischemia, electrolyte aberration), remain at increased risk of arrhythmic and all-cause mortality.

- A systematic diagnostic protocol in secondary prevention patients including coronary evaluation, imaging (transthoracic echocardiography, cardiac magnetic resonance imaging), and, when appropriate, exercise testing, provocative drug challenge, genetic and invasive electrophysiology testing, is vital to the delineation of arrhythmic arrest etiology and guidance of subsequent therapy.

- The subcutaneous ICD may be reasonable to consider in select secondary prevention ICD recipients. The use of a long detection interval for fast ventricular arrhythmias (cycle length ≤320 ms) is associated with reduced ICD therapies in secondary prevention patients.

- In patients meeting criteria for secondary prevention ICD, early catheter ablation may reduce the risk of ICD therapies and recurrent ventricular arrhythmia as compared to antiarrhythmic drug therapy. For patients treated with antiarrhythmic drug therapy with recurrent ventricular arrhythmia, catheter ablation lowers the risk of recurrent ventricular arrhythmia as compared to escalated antiarrhythmic drug therapy.

Cardiac Arrest Study Hamburg

The Cardiac Arrest Study Hamburg (CASH) evaluated the efficacy of ICD vs medical therapy (amiodarone or β-blocker) in 288 patients with resuscitated cardiac arrest and sustained ventricular arrhythmia (VT or VF), enrolling between 1986 and 1997.[6] The original design of the study included propafenone as a randomized arm, but this was discontinued in light of interim analysis demonstrating a significant 61% increased mortality when compared to participants randomized to ICD therapy. An important limitation of CASH was the notably long recruitment period (11 years), over which time there were notable changes in therapies—both procedural and pharmacotherapy—for patients with coronary disease and cardiomyopathy. Notable exclusion criteria for the study included arrests occurring within 72 hours of acute myocardial infarction (MI),

cardiac surgery, electrolyte abnormalities, or proarrhythmic medications. VF was the most common qualifying subtype of cardiac arrest (84% of trial participants). The majority of participants had symptomatic heart failure (80%) and CHD was the most common underlying substrate (73%). There were differences in background medical therapy among the groups, most notably the 0% prevalence of β-blocker use in the ICD and amiodarone arms of the study. Over a mean follow-up of 57 months, crude mortality was lower in the ICD arm compared to the AAD arm (36.4% vs 44.4%), although this difference was not statistically significant (1-sided P = .08). In cause-specific mortality analysis, ICD therapy was associated with a significant reduction in sudden death as compared to AAD therapy (13% vs 33%, P = .005). Subgroup analysis did not identify any difference in ICD efficacy within strata of LV function, NYHA class, or prevalent CHD, although—as observed in AVID—there was a numerically greater reduction in mortality associated with ICD therapy in patients with LVEF ≤35%. Likewise, the absolute risk reduction in mortality associated with ICD vs AAD therapy (∼8%) was similar in the 2 studies.

Canadian Implantable Defibrillator Study

The Canadian Implantable Defibrillator Study (CIDS) evaluated the efficacy of ICD therapy vs amiodarone in 659 participants with resuscitated VT/VF arrest, sustained VT and syncope, sustained VT and symptoms of hemodynamic compromise in the setting of LV dysfunction (LVEF ≤35%), or syncope and the presence of nonsustained VT or inducible VT by programmed stimulation.[7] The trial enrolled between 1990 and 1997. Similar to AVID, approximately one-half of participants qualified on the basis of resuscitated VT/VF arrest (50.1%), the majority had LV dysfunction (mean LVEF 33.3%) and CHD (75%), and the prevalence of β-blocker use was numerically higher in those randomized to ICD therapy (33.5% vs 21.4% at hospital discharge). Over a mean follow-up of 3 years, there was no statistical difference in all-cause and arrhythmic mortality in patients randomized to ICD therapy compared to amiodarone. There were numeric absolute risk reductions in all-cause mortality (ICD vs amiodarone: 23.3% vs 27.0%) and arrhythmic mortality (ICD vs amiodarone: 9.8% vs 11.9%) at 3 years, although these did not reach statistical significance. Similar to AVID and CIDS, the potential efficacy of ICD therapy was not different within strata of qualifying arrhythmia, LV function, prevalent CHD, or heart failure although there was numerically greater benefit in those with LVEF ≤35%.

Meta-analysis

In response to the premature termination of AVID[4] (which may have therefore overestimated treatment efficacy) and the relatively smaller sample sizes of CIDS[7] and CASH[6] (which may have therefore been underpowered to detect a treatment effect), a meta-analysis of these 3 trials was

Table 1 Landmark trials in secondary prevention

	AVID[4]	CIDS[7]	CASH[6]	Meta-analysis[8]
Study enrollment	1993–1997	1990–1997	1987–1998	-
Subjects	1016	659	191	
ICD, n	507	328	99	934
AAD, n[†]	509	331	189	932
Enrollment criteria	VF arrest, VT syncope or HD compromise	VT/VF arrest, VT syncope or HD compromise, high-risk syncope[‡]	VT/VF arrest	-
Age, years	65 ± 11	63 ± 10	58 ± 11	64 ± 10
LVEF, %				
ICD	32 ± 13	34 ± 15	44 ± 17	34 ± 15
Amiodarone	31 ± 13	33 ± 14	46 ± 19	33 ± 14
Any CAD	82%	83%	75%	69%
Heart failure, NYHA ≥3, %	7	11	18	10.5
Nonischemic cardiomyopathy	15%	10%	11%	12%
Qualifying arrhythmia, %				
VF	45	48	86	52%
VT, syncope	21	13	14	43%
VT, other	34	25	0	-
Syncope	0	14	0	4%
Medical therapy in ICD arm, %				
β-blocker	44	53	0	42
RAAS inhibitor	69	-	45	63
Medical therapy in AAD arm, %				
β-blocker	20	23	0	19
RAAS inhibitor	68	-	44	64
Primary endpoint				
Mean follow-up, months	18 ± 12	36	57 ± 34	28 ± 23
1-year mortality				ARR 3.5%/year
ICD	10.7	9.5	8.1	
AAD	17.7	11.2	15.2	
2-year mortality				
ICD	18.4	14.8	17.2	
AAD	25.3	21.0	27.2	
Relative risk reduction ICD				
Total mortality	0.62 (0.47–0.81)	0.82 (0.61–1.10)	0.83 (0.52–1.33)	0.72 (0.60–0.87)
Arrhythmic mortality	0.43 (0.27–0.66)	0.68 (0.43–1.08)	0.32 (0.15–0.69)	0.50 (0.37–0.67)
Estimated ICD benefit				
Number needed to treat to save 1 life	12	-	-	29
Prolongation of life	2.7 mo (at 3 y)	-	-	2.1 mo (at 3 y), 4.4 mo (at 6 y)
Mortality benefit subgroups of interest				
LVEF				
<35%				0.66 (0.53–0.83)
≥35%				1.20 (0.81–1.76)
NYHA class				
<III				0.75 (0.48–1.17)
III				0.74 (0.59–0.91)
Qualifying arrhythmia				
VT				0.73 (0.54–0.99)
VF				0.78 (0.61–1.01)
Discharge β-blocker				
Yes				0.58 (0.38–0.89)
No				0.88 (0.71–1.09)

AAD = antiarrhythmic drug; AVID = Antiarrhythmics vs Implantable Defibrillator Study; CAD = coronary artery disease; CASH = Cardiac Arrest Study Hamburg; CIDS = Canadian Implantable Defibrillator Study; EPS = electrophysiology study with programmed stimulation; HD = hemodynamic; ICD = implantable cardioverter-defibrillator; LVEF = left ventricular ejection fraction; NSVT = nonsustained ventricular tachycardia; NYHA = New York Heart Association functional class; RAAS = renin-angiotensin-aldosterone system; VF = ventricular fibrillation; VT = ventricular tachycardia.
[†]AAD therapy in AVID was 97% amiodarone, 4% sotalol. AAD therapy in CIDS and CASH was amiodarone.
[‡]High-risk syncope includes unmonitored syncope with documented sustained VT (≥10 seconds) or inducible sustained monomorphic VT (≥30 seconds) by programmed ventricular stimulation.

performed to further evaluate the relative efficacy of ICD therapy compared to amiodarone for the secondary prevention of sudden death.[8] As highlighted above, the inclusion criteria for CIDS and AVID were similar,[4,7] whereas participants in CASH[6] were more likely to have had antecedent VF arrest (84% of CASH vs ~50% of CIDS/AVID), higher LV function (mean LVEF CASH 45% vs 32%–34% in CIDS/AVID), and lower rates of β-blocker therapy (0% of ICD and amiodarone arm of CASH) (Table 1). Despite these differences, statistical tests for heterogeneity across the studies were nonsignificant, and taken together, ICD therapy was associated with a 28% relative risk reduction in all-cause mortality and 50% relative risk reduction in arrhythmic mortality when compared to amiodarone.[8] Over a mean follow-up of 6 years, ICD therapy was estimated to prolong life by 4.4 months, with an estimated number needed to treat to save 1 life of 29.

In subgroup analysis, the survival benefit of ICD therapy was only observed in patients with LVEF ≤35% (hazard ratio [HR]: 0.66) but not those with LVEF >35% (HR 1.2; *P*, interaction = .01), whereas there were no differences in ICD efficacy within strata of qualifying rhythm (VF vs VT), history of MI or prevalent CHD, etiology of cardiomyopathy, or New York Heart Association functional class. When stratified by β-blocker use at hospital discharge, the survival benefit of ICD therapy was numerically greater in those with background β-blocker use (HR 0.58) compared to those without (HR 0.88), although this difference was not statistically significant. Therefore, while there was an imbalance in β-blocker therapy in the ICD vs. AAD arms of AVID and CIDS, the findings of the meta-analysis would not support the inference that this imbalance necessarily magnified the efficacy of ICD therapy in these trials.

Longitudinal clinical outcomes in secondary prevention
Pre-ICD Era
Survivors of resuscitated VT/VF arrest have long been known to have increased mortality. Observational cohort studies in the 1970s and 1980s identified a significant rate of recurrent cardiac arrest in this population.[9–11] For example, Furukawa and colleagues[9] observed a curvilinear incidence of recurrent VT/VF arrest in survivors of out-of-hospital cardiac arrest (OHCA) without acute MI, with an 11% incidence in the first 6 months of follow-up, which then reduced to 4% per subsequent 6-month interval. Myerburg and colleagues[12] observed a similar kinetics of recurrent sudden death in survivors of VT/VF OHCA, with a 10% incidence at 1 year and then 5% per year for the subsequent 3 years. In a mode-of-death analysis, these authors observed that two-thirds of mortality was attributable to sudden death (16 of 24 deaths) over 5 years of follow-up.

Randomized controlled trials
In randomized controlled trials of ICD efficacy for secondary prevention (AVID, CIDS, CASH), total mortality at 1 year ranged from 11% to 17% in the AAD arms and 8% to 11% in the ICD arms of these studies. In mode-of-death analysis in AVID, the incidence of arrhythmic sudden death in the antiarrhythmic arm was 8% at 1 year, in general concordance with older observational cohort studies.[13] Overall in AVID, 40% (79 of 202) of the deaths were adjudicated as arrhythmic and the incidence of arrhythmic death was numerically greater in those who qualified on the basis of VF arrest compared to VT (56% vs 44% in the AAD arms for qualifying VF vs VT), although the survival benefit of ICD therapy was observed independent of qualifying arrhythmia.[13] In those randomized to ICD therapy in AVID, ICD therapy was common and rates of ICD therapy were significantly greater than arrhythmic mortality observed in the AAD arm of the study.[14] For example, over a 3-year follow-up, 75% of patients with index VT and 48% of patients with index VF received appropriate ICD therapy. Recurrent VT was more common in those with index VT vs VF (74% vs 30%); and conversely, subsequent VF was more common in those with index VF vs VT (28% vs 18%). The discordance between rates of ICD therapy and rates of adjudicated arrhythmic death in the AAD arm of AVID highlights the important limitation of using appropriate ICD therapy in historic randomized trials as a surrogate for survival benefit in this population.

Contemporary observational cohorts
Contemporary longitudinal cohorts have identified similar mortality in secondary prevention ICD recipients. For example, in an evaluation of 46,685 patients enrolled in the National Cardiovascular Data Registry between 2006 and 2009, 1-year mortality was 10% and 2-year mortality 16.4% in patients undergoing ICD implantation.[15] Intriguingly, 2-year mortality rates were similar in patients qualifying on the basis of resuscitated cardiac arrest and VT when compared to those qualifying on the basis of syncope in the setting of structural heart disease, even though the latter group was an inclusion criterion in only 1 of the landmark randomized trials in this population (CIDS).[7] The concordance of mortality rates in this contemporary cohort compared to historic randomized trials is striking given the higher penetrance of factors that would be predicted to lower mortality, including goal-directed medical therapy (β-blockers, renin-angiotensin-aldosterone system antagonists), lower prevalence of ischemic heart disease, and more flexible ICD programming. An important limitation of these contemporary administrative database cohort studies is delineation and adjudication of mode of death, which is critical in understanding the impact of secular trends in medical and interventional care on mortality risk in secondary prevention patients.

Patients excluded from randomized trials
Notable exclusion criteria from landmark secondary prevention trials were the presence of reversible causes of arrhythmia (ie, acute ischemia, electrolyte or metabolic derangement, use of proarrhythmic pharmacotherapy),[4,6,7]
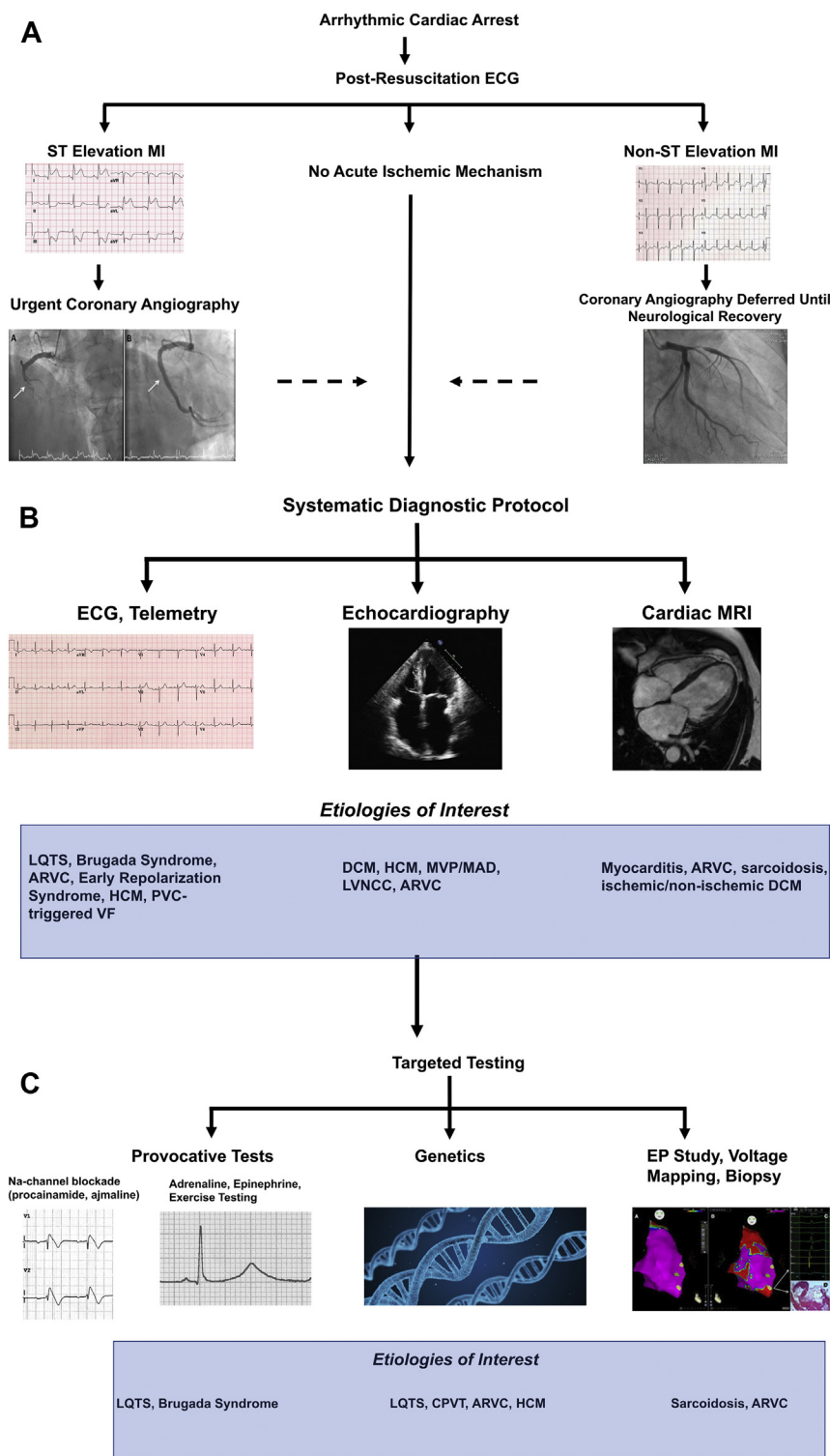
Figure 1   Systematic protocol for evaluation of secondary prevention patient. Shown is a proposed systematic protocol for the evaluation of a patient following an arrhythmic cardiac arrest. **A:** The illustration highlights the role of a postresuscitation electrocardiogram (ECG) and reflects the indication for urgent coronary angiography vs deferred coronary angiography. **B:** The illustration highlights the role for systematic imaging (echocardiography, cardiac magnetic resonance imaging [MRI]), ECG, and continuous telemetry in patients without an acute ischemic mechanism of ventricular arrhythmia. Etiologies of interest potentially suggested by various modalities are highlighted. **C:** The illustration emphasizes the role of targeted testing in secondary prevention patients, particularly those with normal left ventricular function and without an acute ischemic mechanism of arrhythmia. Provocative testing for Brugada syndrome and long QT syndrome, targeted genetic testing, and invasive electrophysiology testing (including programmed stimulation, voltage mapping, and voltage-guided endomyocardial biopsy) can play an important role in elucidating the etiology of arrhythmic arrest and subsequently guide management for patients and families. ARVC = arrhythmogenic right ventricular cardiomyopathy; CPVT = catecholaminergic polymorphic ventricular tachycardia; DCM = dilated cardiomyopathy; EP = electrophysiology; HCM = hypertrophic cardiomyopathy; LQTS = long QT syndrome; LVNCC = left ventricular noncompaction cardiomyopathy; MAD = mitral annular disjunction; MVP = mitral valve prolapse; PVC = premature ventricular contraction.

as well as sustained VT without syncope or hemodynamic compromise. In the AVID study,[4] patients deemed ineligible by these factors were enrolled in a registry and followed prospectively.[16] For registry patients deemed to have a transient or reversible mechanism of arrhythmia, 42% underwent in-hospital revascularization and others underwent adjustment of medical therapy including, for example, potassium repletion. Over the interval 3 years, mortality was 29% in this "transient/reversible" group, which was similar to the mortality in the AAD arm of the parent trial.[4] Similarly, when longitudinal outcomes were evaluated in patients with "stable" VT without hemodynamic compromise, 3-year mortality remained high (34%), although it is important to note that this "stable VT" cohort reflected patients with LV dysfunction (mean LVEF 34% ± 13%).[17]

Since the observations of AVID, other studies have similarly highlighted the limitations and challenge of adjudicating reversible mechanisms of ventricular arrhythmias. For example, Michaud and colleagues[18] systematically evaluated serum potassium on the day of sustained ventricular arrhythmia and found no relationship between serum potassium concentrations and subsequent arrhythmic risk. In a more contemporary analysis of 792 patients deemed to have a reversible mechanism for arrhythmic cardiac arrest, Ladejobi and colleagues[19] observed a 4-year mortality rate of 40%, similar to that observed in the "transient/reversible" subgroup of the AVID registry. ICD use in this contemporary subgroup was associated with 40% relative risk reduction in all-cause mortality. Intriguingly, the mortality benefit of ICD therapy only accrued to patients with reversible mechanisms unrelated to acute ischemia or MI.

While the findings of Ladejobi and colleagues[19] would suggest that contemporary revascularization strategies may abrogate or minimize the survival benefit of ICD therapy in patients with sustained arrhythmias in the setting of acute cardiac ischemia, the role of ICD therapy in this setting remains an open question.[20,21] For example, van Dijk and colleagues[21] evaluated the incidence of ICD therapy in patients with prior MI presenting with sustained arrhythmia (67% VF, 33% VT) in the setting of acute coronary syndrome (22% ST elevation MI [STEMI], 68% non-STEMI, 10% unstable angina) and an LVEF ≥35%. Over a mean follow-up of 5 years, appropriate ICD therapy occurred in 46% of patients. As VF is considered to occur more commonly in the setting of acute ischemia, these authors hypothesized that revascularization may mitigate subsequent arrhythmic risk, particularly for patients with an index ischemic VF arrest. They found, however, that appropriate ICD therapy still occurred in 23% of these patients, highlighting the substantial risk of incident ventricular arrhythmias regardless of presenting rhythm in patients with prior MI presenting with acute coronary syndrome and sustained VT/VF. Similarly, over a mean follow-up of 4 years, Gupta and colleagues[20] identified appropriate ICD therapies in 18% of patients with a history of VT/VF in the setting of acute ischemia. Finally, the relative timing of arrhythmia in relation to reperfusion may further modify arrhythmia risk. Podolecki and colleagues[22] observed

substantial 5-year mortality (36.2%) in patients with early post-reperfusion VT/VF as compared to those without arrhythmia (5-year mortality: 22.6%) or those with pre-reperfusion VT/VF (5-year mortality 26.2%). In the post-reperfusion arrhythmia cohort, the presence of cardiogenic shock, prior MI, and delayed symptom to balloon time were each predicting of incident arrhythmia. The optimal arrhythmic risk stratification in patients presenting with sustained arrhythmias and acute coronary syndrome remains an area of needed investigation, as we discuss below.

Diagnostic evaluation in secondary prevention

Survivors of sudden arrhythmic death warrant a systematic evaluation for etiology of arrhythmia (Figure 1). In patients with evidence of STEMI following return of spontaneous circulation, contemporary resuscitation guidelines recommend urgent coronary angiography.[23] For patients without STEMI, guidelines support coronary angiography in those with a suspected cardiac cause of arrest and a strategy of delaying coronary angiography until after neurologic recovery was associated with similar outcomes as immediate coronary angiography.[24] Coronary computed tomography angiography is also an alternative modality to define coronary anatomy and substrate, with a recent study demonstrating robust sensitivity and specificity for the detection of coronary stenoses.[25] Contemporary rates of coronary angiography in the United States in those hospitalized after VT/VF OHCA range from 87% in those with STEMI to 34% in those without.[26] For patients without STEMI, the survival implications of potential underutilization of coronary angiography in survivors of VT/VF OHCA remains unknown. In a large community-based cohort of OHCA, percutaneous coronary intervention was a potent predictor of survival, even after adjustment for propensity to undergo intervention.[27] Coronary angiography may additionally identify other nonatherosclerotic mechanisms of cardiac arrest, including anomalous coronary anatomy and coronary vasospasm.

In addition to coronary angiography, there is emerging evidence that cardiac magnetic resonance (CMR) imaging may have diagnostic and prognostic value in secondary prevention patients.[28–31] Zorzi and colleagues[28] evaluated the diagnostic and prognostic value of systematic coronary angiography and CMR in survivors of OHCA. For patients with obstructive coronary disease, a clinically relevant culprit lesion was identified in 55%. In this subgroup, CMR was able to identify acute changes consistent with ischemia (ie, myocardial edema on T2 sequences) that were concordant with the territory subtended by the culprit vessel. CMR was additionally able to identify patterns of late gadolinium enhancement (LGE) suggestive of ischemic scar in the remaining patients with nonculprit coronary stenoses. For those with nonobstructive coronary artery disease, CMR identified a potential structural mechanism for arrhythmia in 42%, including dilated cardiomyopathy, acute myocarditis, mitral valve prolapse with associated LGE, hypertrophic cardiomyopathy, and arrhythmogenic right ventricular cardiomyopathy. Over a mean follow-up of 36 months, the presence of acute myocardial

edema at CMR was associated with a benign arrhythmia course. Others have similarly found incremental diagnostic utility for CMR in this population, including reassignment to a new or alternate diagnosis in 25%–76% of patients when compared to standard transthoracic echocardiography.[29–31] Prognostically, both the presence and extent of LGE by CMR have been associated with incident arrhythmia and mortality in survivors of OHCA.[31] For example, Neilan and colleagues[31] found a 7-fold increased risk of ICD therapy or death in those with LGE, even after adjusting for LVEF and other clinical sudden death risk factors. An LGE burden of >8.1% of the myocardium was a particularly high-risk subgroup with a 78% incidence of ICD therapy or death. These data raise the intriguing role of CMR imaging in secondary prevention patients, as a means to delineate etiology of ventricular arrhythmia and to additionally adjudicate the potential "reversibility" of underlying mechanism and prognosticate the risk of incident arrhythmia.

For patients with apparently unexplained cardiac arrest including no evidence of coronary artery disease, normal echocardiogram, and normal electrocardiogram, a systematic diagnostic protocol including CMR, signal-averaged electrocardiogram, exercise testing, provocative drug challenge (procainamide for Brugada syndrome, adrenaline or epinephrine for long QT syndrome), and selective genetic and electrophysiological testing can be valuable (Figure 1).[32] Invasive electrophysiology testing can include programmed stimulation, voltage-based phenotyping, and voltage-guided endomyocardial biopsy.[33] Employing such a systematic protocol in the Cardiac Arrest Survivors with Preserved Ejection Fraction Registry (CASPER), Krahn and colleagues[32] identified an etiology of cardiac arrest in 56% of patients, which additionally led to clinically relevant diagnoses in 24% of screened family members. Of those with a delineated etiology, the majority (69%) were reflective of an underlying electrical syndrome (eg, long QT syndrome, catecholaminergic polymorphic VT, Brugada syndrome) and the remainder an underlying structural disease (eg, arrhythmogenic right ventricular cardiomyopathy, myocarditis). In this cohort of unexplained cardiac arrest with a preserved ejection fraction, a history of syncope and a family history of sudden death were independently predictive of the presence of a pathogenic genetic variant.[34] While the role of invasive electrophysiology phenotyping in the CASPER protocol was left to the discretion of investigators, in the future, the potential utility of detailed electrical phenotyping—particularly in the era of high-density mapping[35]—may offer important insights into novel electrical phenotypes and further guide risk stratification.

Electrophysiology management of secondary prevention patients
Implantable cardioverter-defibrillator type and programing
For survivors of VT/VF cardiac arrest or those with sustained VT not due to a reversible cause, and those with structural heart disease, syncope, and inducible VT on electrophysiology study, contemporary consensus guidelines recommend implantation of an ICD in patients with greater than 1 year life expectancy.[3] Options for defibrillator therapy include transvenous (TV-ICD) and subcutaneous (S-ICD) ICDs. S-ICDs have been associated with lower rates of device and lead complications as compared to transvenous defibrillators,[36] although they do not have the capacity for antitachycardia pacing (ATP), cardiac resynchronization therapy, or antibradycardia pacing. In a contemporary analysis of S-ICD implantation in secondary prevention patients, Boersma and colleagues[37] identified a 16% incidence of appropriate therapies for VT/VF and a 12.3% incidence of inappropriate therapies over 3-year follow-up. First-shock conversion rate in the cohort was 90% and similar to conversion rates in TV-ICDs.[38] In this context, an S-ICD is a reasonable alternative to TV-ICD in secondary prevention patients without an indication for cardiac resynchronization, antibradycardia pacing, or a documented history of ATP-terminable monomorphic VT. An S-ICD may also be favored in patients whose presenting arrhythmia is VF to the extent that future arrhythmias are less likely to be ATP-terminable, although post hoc analysis of AVID did identify a 30% incidence of VT in those with an index VF arrest.[14]

For those undergoing TV-ICD implantation, consideration of ICD programming is paramount. Post hoc analysis of the Avoid Delivering Therapies for Nonsustained Arrhythmias in ICD Patients III (ADVANCE III) trial demonstrated that for secondary prevention patients a long detection setting (30 of 40 intervals for ventricular arrhythmia with cycle length ≤320 ms) was associated with a 25% reduction in overall ICD therapies and a 34% reduction in number of shocks compared to nominal settings (18 of 24 intervals).[39] Similar reductions in rates of treated VF episodes were observed in secondary prevention ICD recipients in the PainFree SST study randomized to longer detection intervals (30 of 40) for ventricular arrhythmias with cycle length ≤320 ms.[40] In the PainFree SST analysis, there was no accompanying increase in the incidence of syncope in the longer detection interval arm; and taken together, these studies generally support the use of extended detection intervals for fast ventricular arrhythmias in patients undergoing a secondary prevention ICD. Ultimately, a tailored approach for ICD programming is warranted, integrating physiological/hemodynamic reserve and observed hemodynamic compromise with slower sustained VT.

Interventions to reduce arrhythmic risk in secondary prevention
The incidence of ICD therapies in secondary prevention patients has declined over the past 30 years,[14,41] likely owing to a combination of improved revascularization techniques, idealized pharmacotherapy for heart failure, and liberalized ICD programming. Nevertheless, rates of appropriate ICD

Table 2 Randomized trials of early catheter ablation in secondary prevention implantable cardioverter-defibrillator recipients

	SMASH-VT[48]	VTACH[47]	SMS[49]	BERLIN-VT[42]
Study enrollment	2000–2004	2002–2006	2009–2016	2015–2018
Subjects, n				
ICD	64	52	57	83
ICD + ablation	64	55	54	76
Enrollment criteria	History of MI, planned/recent ICD, prior unstable VT or syncope and inducible VT	History of MI, stable VT‡ with planned secondary prevention ICD	History of MI, unstable VT, cardiac arrest or syncope with unstable VT	History of MI, LVEF 30%–50%, indication for secondary prevention ICD
Ablation details	Substrate ablation in sinus rhythm.†	Entrainment/activation mapping when able. Substrate modification otherwise.§	Entrainment/activation when able. Substrate modification otherwise.	Substrate ablation targeting late potentials (maximum 1 hour).¶
Age, years				
ICD	66 ± 10	64 ± 8	66 ± 8	66 ± 9
ICD + ablation	67 ± 9	68 ± 8	68 ± 8	66 ± 10
LVEF, %				
ICD	33 ± 9	34 ± 8	30 ± 7	41 ± 6
ICD + ablation	31 ± 10	34 ± 10	32 ± 7	41 ± 6
Any CAD, %	100	100	100	100
NYHA functional class				
I or II	80	-	-	78
III or IV	20	-	-	22
Previous revascularization, %	67 (any)			
Surgical		50	42	25
Percutaneous		50	46	54
Qualifying arrhythmia, %				
VF	18	0	0	-
VT	49	100	66	100
Syncope with inducible VT	21	0	34	-
Recent VF/VT treated with ICD	12	0	0	-
Medical therapy in ICD arm, %				
β-blocker	98	75	91	71
RAAS inhibitor	92	-	100	71
Aspirin	61	-	-	-
Class I or III drugs	0	35	32	33
Medical therapy in ICD + ablation arm, %				
β-blocker	94	75	91	76
RAAS inhibitor	92	-	90	62
Aspirin	81	-	-	-
Class I or III drugs	0	35	29	41
Primary endpoint	Survival free of any appropriate ICD therapy	Recurrence of any sustained VT/VF	Time to recurrent VT/VF	Death or hospitalization for HF or VT
Mean follow-up, months	23 ± 6	23 ± 9	28 ± 13	13 ± 9
Absolute event incidence, %				
Primary endpoint				
ICD	33	47	46	28
ICD + ablation	12	29	46	33

Sustained VT/VF			
ICD	-	71	-	48
ICD + ablation	-	53	-	40
Appropriate ICD therapy			
ICD	33	47	42	47
ICD + ablation	12	27	37	34
Relative risk reduction ablation/ICD vs ICD			
VT-free survival	0.35 (0.15–0.78)	0.61 (0.37–0.99)	0.43 (0.22–0.85)	0.62 (0.38–1.00)
All-cause mortality	0.59 (0.22–1.59)	1.32 (0.35–4.94)	0.82 (0.34–1.97)	2.97 (0.60–14.7)

BERLIN-VT = Preventive Ablation of Ventricular Tachycardia in Patients with Myocardial Infarction; CAD = coronary artery disease; HF = heart failure; ICD = implantable cardioverter-defibrillator; LVEF = left ventricular ejection fraction; MI = myocardial infarction; NYHA = New York Heart Association; RAAS = renin-angiotensin-aldosterone system; SMASH-VT = Substrate Mapping and Ablation in Sinus Rhythm to Halt Ventricular Tachycardia; VF = ventricular fibrillation; VT = ventricular tachycardia; VTACH = Ventricular Tachycardia Ablation in Coronary Heart Disease.
†Ablation protocol included VT induction and delineation of arrhythmic substrate including border zone, electroanatomic area of infarction, late/fractionated potentials within scar. Ablation was guided by pace mapping and carried from the presumed exit of VT into substrate with additional ablation along border zone. Entrainment mapping was attempted if VT was transiently stable.
‡Stable VT was defined as sustained VT not leading to cardiac arrest or syncope and during which the systolic blood pressure was higher than 90 mm Hg.
§For patients with inducible VT, ablation endpoint was noninducibility. For those with noninducible VT, endpoint was elimination of channels within arrhythmic substrate and/or ablation with linear lesions based on pace mapping along infarct scar target sites.
¶Ablation protocol included programmed stimulation for VT with targeting of all inducible morphologies. Sinus rhythm mapping was performed with late potentials delineated. Ablation was guided by elimination of late potentials. Ablation endpoint was defined as the elimination of all late potentials and the noninducibility of any VT.

therapy remain high even in contemporary cohorts employing long-detection programming (3-year rates of 8%–47%).[37,39,42] These substantial rates of ICD therapies have significant clinical implications as they have been associated with both an increased mortality and significant reductions in quality of life.[43,44] Thus, there has been long-standing interest and need for strategies to reduce incident ventricular arrhythmia that complement the therapeutic role of ICD implantation.

Pharmacotherapy

Pharmacologic strategies for arrhythmia suppression include use of β-blockers and antiarrhythmic drugs. In the Optimal Pharmacological Therapy in Cardioverter Defibrillator Patients (OPTIC) study, which included 412 patients undergoing secondary prevention ICD (mean LVEF 34%, history of MI in 80%), investigators observed a 40% incidence of appropriate ICD therapy at 1-year in those randomized to β-blocker therapy as compared to 24% in those randomized to sotalol and 10% in those randomized to amiodarone.[41] Of note, rates of study drug discontinuation over 1 year owing to side effects was 5% for β-blockers, 18% for amiodarone, and 24% for sotalol. Recent meta-analysis of randomized trials evaluating the efficacy of antiarrhythmic drug therapy for patients with ICDs and a history of ventricular arrhythmia identified an approximate 70% relative risk reduction in VT recurrence and ICD therapies with amiodarone as compared to standard cardiomyopathy pharmacotherapy including β-blockade.[45] Comparatively, there was no significant risk reduction in either VT recurrence or ICD therapies in meta-analyzed trials of sotalol compared to standard cardiomyopathy pharmacotherapy. Taken together, these data would generally support the use of amiodarone therapy to reduce recurrent VT/VF in the secondary prevention population, at the expense of drug-related side effects in a significant minority.

Catheter ablation

In light of these limitations, there has been significant interest in the role of catheter ablation to mitigate ventricular arrhythmia risk in patients with secondary prevention ICDs.[42,45–51] In addition to evaluating the relative efficacy of catheter ablation in the secondary prevention population, there has also been significant interest in delineating the optimal timing of intervention, given the previously established link between ICD therapies with worse survival and reduced quality of life.[43,44]

Early catheter ablation in secondary prevention ICD recipients

There have been 4 randomized controlled trials evaluating the merit of *early* catheter ablation in patients with ischemic heart disease who qualify for a secondary prevention ICD (Table 2).[42,47–49] In the Substrate Mapping and Ablation in Sinus Rhythm to Halt Ventricular Tachycardia (SMASH-VT) trial (enrollment 2000–2006),[48] 128 patients with a

history of MI and either spontaneous VT/VF or syncope with inducible VT were randomized to substrate-based catheter ablation or no ablation, in the background of ICD therapy. The majority of patients (88%) underwent ICD implantation after catheter ablation, with the remainder having an existing ICD with first-time arrhythmia as their qualifying event. Over a mean follow-up of 22 months, those randomized to catheter ablation had a 65% relative reduction in appropriate ICD therapies (12% vs 33%) compared to those with ICD without ablation. Of note, antiarrhythmic drugs were not used in either treatment arm and mean LVEF was 32%. There was no evidence of adverse effects attributable to catheter ablation, with no difference in heart failure status or LV function between the groups over 12 months following randomization. In the Ventricular Tachycardia Ablation in Coronary Heart Disease (VTACH) study (enrollment 2002–2006),[47] 107 patients with ischemic heart disease, LVEF ≤50%, and stable VT (ie, not leading to syncope or cardiac arrest) were randomized to ICD therapy alone vs ICD therapy and catheter ablation (including activation and entrainment mapping in VT). At 2 years, those randomized to catheter ablation had a 44% relative risk reduction in appropriate ICD therapy (26.9% vs 47.3%) and greater time to first VT/VF (15.9 months vs 11.3 months). The mean number of appropriate ICD therapies per patient per year was reduced with ablation, from 3.4 ± 9.2 to 0.6 ± 2.1. There were no differences in prospectively collected quality-of-life data, though these were only available in a subset of the trial population. There were no differences in incident heart failure between the 2 randomized arms. In comparison to SMASH-VT, approximately one-third of patients were treated with amiodarone.

In the Substrate Modification Study (SMS; enrollment 2009–2016),[49] 111 patients with ischemic heart disease, LVEF ≤40% and a history of unstable VT (including cardiac arrest) or syncope with induction of hemodynamically significant VT were randomized to catheter ablation and ICD implantation (n = 54) or ICD implantation alone (n = 57). Approximately one-third of each treatment group was treated with a class III antiarrhythmic at baseline. Over a mean follow-up of 2.3 years, there was no difference in the primary endpoint of time to recurrent VT/VF, which was present in 46% of each arm. By comparison, when analyzed using models sensitive to multiple endpoint recurrences, catheter ablation was associated with a 57% relative risk reduction in spontaneous VT/VF episodes and 67% relative risk reduction in ICD therapies (ATP or shock) for ventricular arrhythmia, both concordant with risk reductions in SMASH-VT[48] and VTACH.[47] There were no differences in quality-of-life scores between the 2 treatment groups. Possible explanations for the null findings of SMS compared to previous studies include differences in ablation strategy (ie, potentially more substrate ablation in SMASH-VT as compared to SMS), as well as differences in arrhythmic risk and/or ICD programming (ie, higher rates of appropriate ICD therapy in SMS compared to SMASH-VT). Most recently, the Preventive Ablation of Ventricular Tachycardia in Patients with Myocardial Infarction (BERLIN VT) study

(enrollment 2015–2018)[42] evaluated an early vs delayed ablation strategy in 159 patients with ischemic heart disease, LVEF between 30% and 50% (mean LVEF 41%), and documented VT necessitating ICD implantation. The trial was terminated prematurely for futility, with numerically greater deaths and heart failure admissions in those randomized to an early ablation strategy (ie, at the time of ICD implantation) vs deferred (ie, after the third ICD therapy). Of note, none of the deaths in the early ablation strategy were arrhythmic and heart failure events were attributed to the use of irrigated catheters employed during ablation. In secondary outcome analysis, over a mean follow-up of 33 months, early ablation was associated with a 45% relative risk reduction in appropriate ICD therapies (34.2% vs 47.0%) and 38% relative risk reduction in sustained VT/VF (39.7% vs 48.2%)—both closely harmonized with the findings of the VTACH study.[47] Quality-of-life scores were significantly improved in the early ablation arm compared to deferred ablation. Notable limitations of BERLIN VT included the nonharmonized deployment of AAD between treatment arms as well as the protocol-specified limit on catheter ablation (60 minutes), which fell substantially below average ablation times in other contemporary VT ablation studies.[52]

Catheter ablation vs escalated antiarrhythmic drug therapy in secondary prevention

In addition to studies evaluating the efficacy of *early* catheter ablation for secondary prevention ICD recipients, there has also been substantial interest in evaluating treatment strategies in patients with ICD therapies despite antiarrhythmic drugs. In the Ventricular Tachycardia Ablation versus Escalated Antiarrhythmic Drug Therapy in Ischemic Heart Disease (VANISH) study (enrollment 2009-2014),[51] 249 patients with ischemic heart disease, ICD, and VT within the last 6 months while taking amiodarone or another class I/III antiarrhythmic were randomized to catheter ablation vs escalated antiarrhythmic drug therapy. The ablation protocol employed activation and entrainment mapping of hemodynamically stable VTs, with targeting of central or exit sites preferred. For hemodynamically unstable VTs, pace mapping of the exit and use of latency to infer potential central channel sites was recommended. Over a mean follow-up of 28 months, the primary composite outcome (death, VT storm, or appropriate ICD shock) was less frequent in the ablation group (59.1%) as compared to the escalated drug therapy group (68.5%) (relative risk reduction 28%). This benefit was driven primarily by the arrhythmic components of the composite endpoint (VT storm, appropriate ICD therapy). There was a significant interaction between baseline amiodarone use and catheter ablation efficacy, with a significant reduction in the primary endpoint observed in patients treated with amiodarone at baseline (HR of catheter ablation vs escalated drug therapy: 0.55) but not for patients treated with other antiarrhythmic drugs who were subsequently "escalated" to amiodarone as part of the randomization protocol (HR of catheter ablation vs escalated drug therapy: 1.14).

Taken together, in patients with ischemic heart disease undergoing ICD implantation for secondary prevention, rates of incident VT and appropriate ICD therapy remain high, despite contemporary ICD programming. Early catheter ablation consistently reduces the risk of incident VT/VF and ICD therapy by approximately 40%, although adjudicating the efficacy of ablation in previous randomized trials is limited by heterogeneity of ablation strategy and background use of antiarrhythmic drug use. The recent findings of SMS[49] and BERLIN-VT[42] give some pause to a generalized strategy of early VT ablation in secondary prevention patients undergoing ICD therapy, although the concordance of risk reduction in ICD therapies and recurrent VT/VF across randomized studies of early ablation is notable.[42,47–49] For patients already treated with antiarrhythmic drug therapy, the findings of VANISH support the incremental value of catheter ablation to reduce recurrent VT and ICD shocks, particularly for patients with VT despite amiodarone pharmacotherapy.

Future efforts should seek to harmonize catheter ablation strategy (including acute ablation endpoints), systematically define use of antiarrhythmic drugs, prospectively guide heart failure management following catheter ablation, and clearly delineate primary endpoints specific to arrhythmic outcomes. These studies ideally should be powered to evaluate potential high-risk subgroups of interest, including stratification by LV function, NYHA class, burden of LGE, and arrhythmic phenotype. Several ongoing studies are poised to enhance our understanding of ablation efficacy and timing in this population. The VANISH 2 (Ventricular Tachycardia Antiarrhythmics or Ablation in Structural Heart Disease 2; NCT02830360) study will evaluate the efficacy of catheter ablation vs antiarrhythmic drug therapy (amiodarone, sotalol) as a first-line intervention in patients with ischemic heart disease and recent VT not treated with antiarrhythmic drugs at baseline. Two additional randomized studies (PARTITA study [Does Timing of VT Ablation Affect Prognosis in Patients with an Implantable Cardioverter-Defibrillator; NCT01547208], IMPRESS study [Initial Management of Patients Receiving a Single Shock; NCT03531502]) are evaluating the role of catheter ablation after an initial ICD shock, although in both studies the use and type of antiarrhythmic drug therapy is not prespecified in the nonablation arm. In addition, the PREVENTIVE VT (Impact of PREVENTIVE Substrate Catheter Ablation on Implantable Cardioverter-defibrillator Interventions in Patients with Ischemic Cardiomyopathy and Infarct-related Coronary Chronic Total Occlusion; NCT03421834) study is evaluating the efficacy of early catheter ablation in patients with a secondary prevention ICD indication and documented coronary artery total occlusion. Finally, we would highlight that the predominance of randomized studies[42,47–49] have focused on patients with ischemic heart disease. How these and ongoing studies generalize to patients with nonischemic arrhythmic substrates, for whom optimal catheter ablation strategies remain a point of active investigation, is uncertain.[53,54]

Novel strategies for arrhythmia risk reduction

Emerging data have linked active inflammation as etiologic in arrhythmic exacerbations in various contexts, including dilated nonischemic cardiomyopathy,[55] premature ventricular contractions,[56] and malignant mitral valve prolapse syndrome.[57] In some instances, anti-inflammatory therapy alone has mitigated arrhythmia risk.[56] The clinical benefit of phenotyping and potentially treating acute myocardial inflammation in secondary prevention patients could be an avenue for future investigation. In addition, pathogenic sympathetic nervous system activity has been linked to increased arrhythmic events in patients with heart failure,[58] including those with ICDs.[59] Modulation of the autonomic nervous system and neuraxial blockade are important therapies for electrical storm[60] and are an established component of antiarrhythmic therapy for specific genetic syndromes, including long QT syndrome.[61] Emerging data suggest that autonomic modulation may be an effective tool in the broader population of secondary prevention patients,[62] though more data are needed.

Systems of care for secondary prevention patients and opportunities for the future

As we look ahead, how do the historical landmark trials in secondary prevention inform our current contemporary practice and what gaps remain? First, the epidemiology of sudden death has changed since the completion of landmark trials (AVID, CIDS, CASH),[4,6,7] with contemporary ICD recipients being older, less likely to have ischemic cardiomyopathy, and more likely to have symptomatic heart failure.[15] In a contemporary analysis of secondary prevention patients, 40% of patients had an LVEF >35% at the time of ICD implant, a population that derived no mortality benefit in a meta-analysis of the original landmark studies.[8] Importantly, when considering the survival benefit of ICD therapy, each of these shifting epidemiologic factors (older age, advanced heart failure, nonischemic cardiomyopathy, and nonsevere LV dysfunction) have each been linked to an increased risk of competing, nonarrhythmic mortality.[63] As we and others have demonstrated, the survival benefit of ICD therapy is closely linked to both the absolute and proportional risk of sudden arrhythmic death.[63,64] In that context, the greater the risk of competing nonarrhythmic mortality, the lower the survival benefit of ICD therapy. There remains, then, an important need to refine both arrhythmic and competing mortality assessment in secondary prevention patients. Indeed, as a recent analysis of ICD recipients in the Veterans Administration System demonstrated,[65] 1-year mortality was 33.3% in those greater than 80 years of age, emphasizing the important considerations of integrating and refining our assessment of competing risk in this population.

Second, important unanswered questions remain regarding the absolute and proportional risks of arrhythmic death in secondary prevention patients in the contemporary era of goal-directed medical therapy and coronary revascularization. For example, several guideline-directed medical

therapy interventions in patients with heart failure, including renin-angiotensin-aldosterone system antagonists,[66,67] mineralocorticoid antagonists,[68] and neprilysin-inhibitors,[69,70] have all been linked to reductions in sudden death. Proposed mechanisms include direct modulation of electrophysiological properties, antifibrotic effects mitigating arrhythmic substrate, modulation of neurohormonal influences, improved LV function (ie, reverse remodeling), and mitigation of nonarrhythmic mechanisms of sudden death.[71–73] Improvements in LV function are associated with a reduced incidence of ICD therapy in primary prevention ICD recipients,[74,75] whereas the risk reduction in secondary prevention is less certain.[76] Future clinical trials could, for example, evaluate staged clinical strategies that involve upfront deployment of goal-directed medical therapy (eg, 3–6 months) with wearable cardioverter defibrillator therapy initially for arrhythmic protection. Subsequent decision-making regarding a permanent ICD implant could be informed by interval reassessment of heart failure status and LV function.

Third, although there have been considerable advancements in the mode and care of coronary revascularization since the era of secondary prevention randomized trials, contemporary mode-of-death analyses continue to identify sudden death as a common mechanism of cardiovascular death in patients undergoing percutaneous[77] and surgical revascularization.[78] Future efforts are needed to further refine arrhythmic risk evaluation in secondary prevention patients with ischemic heart disease. Specific populations of interest include those with residual coronary disease and/or ischemia after "culprit lesion" revascularization.[79] Further, recent observational data have identified an increased rate of appropriate ICD therapy in secondary prevention ICD recipients with chronic total coronary occlusions.[80,81] Whether revascularization or catheter ablation in this context could mitigate arrhythmic risk remains unknown. In addition, for patients with ventricular arrhythmias in the context of acute ischemia, recent data reflect a clinically significant rate of appropriate ICD therapy in this population.[20,21] The relative timing of VT/VF in relation to reperfusion may also be an important risk marker,[22] in addition to other clinical factors including a prior history of MI, index presentation with cardiogenic shock, time to reperfusion, and residual ischemia. Whether additional diagnostic tools, such as use of LGE presence and extent by CMR,[31] might better delineate risk in this population warrants future investigation.

Finally, there remains substantial heterogeneity in the evaluation, management, and care of secondary prevention patients.[26] Looking ahead, we would advocate for national and international research infrastructure that systematically captures hospitalized secondary prevention patients. This infrastructure would be leveraged to deploy systematic diagnostic protocols, prospectively capture longitudinal outcomes (cardiac, neurological, quality-of-life, healthcare use), and facilitate the efficient evaluation of management strategies including catheter ablation. Insights from prospective registries would serve, importantly, in the design of po-

tential contemporary randomized controlled trials evaluating the efficacy of ICD therapy in secondary prevention patients, including key subgroups of interest, such as those with incomplete revascularization and those considered to have "reversible" etiologies of ventricular arrhythmia. This infrastructure development will require partnerships across a range of stakeholders, including federal and local government, medical device companies, clinical trialists, healthcare system leadership, and a range of medical specialties that include emergency medical services, neurology, and cardiology (electrophysiology, imaging, heart failure). Though considerable, this effort is vital given the significant stakes for patients and families as they navigate life after death.

Funding Sources

Disclosures

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