

Implantable Cardioverter-Defibrillators for Secondary Prevention of Sudden Cardiac Death: A Review

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First used in humans in 1980, the implantable cardioverter defibrillator (ICD) was designed to recognize and treat malignant ventricular arrhythmias and thus prevent arrhythmic death.¹ Among patients with an aborted episode of sudden cardiac arrest (SCA) due to ventricular arrhythmias without a reversible cause, the ICD is considered an important therapy for secondary prevention of SCA and is supported by class IA guideline recommendations in selected patients.² In the United States, a quarter of ICD procedures included in the National Cardiovascular Data Registry (NCDR) ICD Registry are performed for secondary prevention indications.³ Herein, we review the epidemiology and prognosis of patients suffering SCA, review the evidence for secondary prevention ICDs, and contemporary studies of this patient population.

The Epidemiology of Sudden Cardiac Arrest

Out-of-hospital cardiac arrest is a leading cause of death among adults in the United States (~300 000 events per year). Yet, determining its cause can be difficult, creating challenges to understanding its epidemiology.⁴ In the United States SCA is witnessed only about two-thirds of the time; frequently the initial rhythm is unknown, the “suddenness” of symptoms cannot be ascertained with certainty, and the

primary sources of information (if available) are bystanders or, less frequently, emergency medical services (EMS).⁵ National standards for surveillance to monitor the incidence and outcomes of SCA do not exist.⁶ Existing registries and clinical trials typically rely on assessments by EMS providers, and regional or cultural differences in the EMS system contribute to variability in these data. Despite limitations, available data do provide some insights on the epidemiology of SCA.

Various registries have been developed to improve the care of patients suffering SCA. Participation in these registries allows meaningful comparisons among patient populations, interventions, and outcomes and identifies opportunities to improve care. One such registry is the Cardiac Arrest Registry to Enhance Survival (CARES), a large database of out-of-hospital cardiac arrest patients, predominantly limited to cases with presumed cardiac etiologies. It was established in 2005 for public surveillance and continuous quality improvement and encompasses 31 states and 80 million people.⁷⁻⁹ From 2005 to 2010, a total of 31 689 of 40 274 (79%) out-of-hospital cardiac arrest records submitted were presumed to be of cardiac etiology (myocardial infarction or arrhythmia) in CARES.⁷ The mean age at cardiac arrest was 64 years, and 61.1% were male. Among all patients who suffered cardiac arrest, ventricular arrhythmias accounted for 23.7% of cases, and the majority of patients had either asystole (45.1%) or pulseless electrical activity (19.4%). Another large database is the Resuscitation Outcomes Consortium, an organized research program that consists of multiple regional and satellite clinical centers. This registry collects extensive primary data from EMS first responders and is used to improve resuscitation outcomes. Data from the Resuscitation Outcomes Consortium suggest that 326 200 persons in the US experience EMS-assessed out-of-hospital cardiac arrests per year.⁶ Similar to the CARES database, 23% of patients had an initial rhythm of ventricular tachycardia/ventricular fibrillation (VT/VF).¹⁰

The strongest risk factor for arrhythmic SCA is underlying coronary heart disease, which confers a 6- to 10-fold increase in risk. Other factors include male sex, increasing age, and black race.¹¹⁻¹³ Among patients with coronary heart disease,

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This article was handled independently by N. Mark Estes III, MD, as a guest editor. The editors had no role in the evaluation of the manuscript or in the decision about its acceptance.

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J Am Heart Assoc. 2017;6:e005515. DOI: 10.1161/JAHA.117.005515.

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left ventricular systolic dysfunction is one of the most significant predictors of overall mortality, in part due to a rate of SCA that increases with decreasing left ventricular ejection fraction (LVEF).^{14,15} Other forms of structural heart disease associated with high SCA risk, including hypertrophic cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy, congenital anomalies, sarcoid cardiomyopathy, and left ventricular hypertrophy are rarer, accounting for fewer cases of SCA. Although the majority of cases of SCA in the young are related to structural heart disease, about one in 10 among those younger than 45 years occur in the absence of identifiable structural abnormalities.^{16,17} Conditions without apparent structural heart disease that confer a higher risk of SCA include primary electrical disorders such as Brugada syndrome, congenital or acquired long QT syndrome, catecholaminergic polymorphic VT, and Wolfe-Parkinson-White syndrome.

Prognosis After Sudden Cardiac Arrest

The prognosis of patients with cardiac arrest conveyed in popular television shows is strikingly optimistic (up to 75% survival).¹⁸ Despite advances in the care and treatment of heart disease, increased bystander CPR and awareness, hypothermia protocols, and shortened time to defibrillation, outcomes among patients with SCA remain relatively poor. In the CARES database, fewer than 10% of out-of-hospital cardiac arrest patients survived to discharge.^{7,19,20} In a prospective observational study in North America, the median survival among EMS-treated cardiac arrests was 8.4%.¹⁰ Survival among a large nationwide cohort of patients in Japan experiencing out-of-hospital SCA was 2.8% in 2009.²¹

Prognosis is markedly different when stratified by the mechanism of SCA. Patients with an initial rhythm of asystole or are in pulseless electrical activity have worse outcomes. Among patients in the CARES database, survival after asystole was 2.3%, after pulseless electrical activity 7.4%, and after ventricular arrhythmias, survival was 27.1%.⁷ Other studies have shown survival to hospital discharge after asystole and pulseless electrical activity to be 2% and 11%, respectively, and survival to hospital discharge among those with VT/VF as high as 40%.²²⁻²⁵ Among 12 000 patients in Seattle, survival after a cardiac arrest with VF was nearly 10 times higher than among those without VF.²⁴ Hemodynamically unstable VT portends even greater survival, up to 65% to 70%.²⁶ In a recent randomized controlled trial (RCT) evaluating use of antiarrhythmic medications in patients who suffered a VT/VF arrest, survival to hospital discharge was ~23%.²⁷

While a minority of patients suffering SCA survive to discharge, an even smaller portion have a meaningful functional recovery. Whereas 9.6% of patients survived to

discharge in the CARES database, only 7.4% achieved functional recovery by the time of hospital discharge.²⁰ Only 17% had a favorable neurological status in the randomized control trial mentioned above.²⁷ Patients surviving with a meaningful functional recovery and an estimated life expectancy of at least one year are those considered for secondary prevention ICDs. As an approximation, if 300 000 patients experience SCA per year, 25% will be related to VT/VF (75 000 patients).⁴ If half of these survived to discharge, and of these, 80% had a meaningful functional recovery, less than 10% of the population with SCA would be considered candidates for this therapy.

Randomized Controlled Trials of ICDs and Guidelines

Not long ago, the idea of an implanted automated device to effectively detect and treat life-threatening arrhythmias was considered radical. When Drs Mirowski and Mower first introduced the concept of the defibrillator, the idea was assailed; a leader in ventricular arrhythmias at the time commented that “the implanted defibrillator system represents an imperfect solution in search of a plausible and practical application.”²⁸ In the first pilot study of ICDs, patients were required to have had survived at least 2 episodes of cardiac arrest not associated with an infarction, with at least one episode of documented VF.²⁹ Since then, there have been remarkable technical advances. The ICD is now widely used in high-risk patients based on evidence from RCTs that supports the use of ICDs for both primary and secondary prevention of SCA.³⁰⁻³⁵ In particular, 3 randomized controlled trials evaluated the impact of ICD therapy for secondary prevention indications (Table 1).

The first published and largest of the secondary prevention RCTs was the Antiarrhythmics Versus Implantable Defibrillators (AVID) trial, which enrolled 1016 patients between 1993 and 1997 in North America.³⁰ Patients were required to have one of the following: (1) resuscitation from near-fatal VF, (2) syncope with documented sustained VT, or (3) sustained VT with a LVEF of 40% or less and significant symptoms attributed to the arrhythmia. Patients were randomized to receive an ICD or antiarrhythmic medical therapy. Almost all patients (96%) randomized to the antiarrhythmic group were treated with amiodarone. The study population was comprised predominantly of white (87%) men (80%) with coronary artery disease (81%), a mean age of 65, mean LVEF of 31%. The index arrhythmia in nearly half (45%) was ventricular fibrillation. After a mean follow up of 18 months, fewer deaths occurred in the ICD group than in the antiarrhythmic drug group (crude death rate 15.8±3.2% vs 24±3.7%), corresponding to an average increase in life expectancy due to the

Table 1. Characteristics of Patients Receiving an ICD Among Secondary Prevention Randomized Controlled Trials

	AVID (n=507) ³⁰	CASH (n=99) ³¹	CIDS (n=328) ³²
Inclusion	<ol style="list-style-type: none"> 1 Patients resuscitated from near-fatal VF 2 Sustained VT with syncope 3 Sustained VT with an LVEF <40% and symptoms suggesting severe hemodynamic compromise due to the arrhythmia 	<ol style="list-style-type: none"> 1 Patients resuscitated from cardiac arrest secondary to documented sustained ventricular arrhythmias 	<ol style="list-style-type: none"> 1 Documented VF 2 Out-of-hospital cardiac arrest requiring defibrillation or cardioversion 3 Documented, sustained VT causing syncope 4 Documented, sustained VT at a rate >150 beats/min causing presyncope or angina in a patient with LVEF <35% 5 Unmonitored syncope with subsequent documentation of either spontaneous VT >10 seconds or sustained monomorphic VT induced by programmed ventricular stimulation
Mean age (SD)	65±11	58±11	63±9.2
Male, %	78	79	85
Coronary artery disease, %	81	73	...
LVEF (%), (SD)	32±13	46±19	34.3±14.5
NYHA			
I or II, %	48	82	37.8
III, %	7	18	...
Presenting arrhythmia			
Ventricular fibrillation, %	44	84	47
Ventricular tachycardia, %			
Sustained VT	55	16	...
VT with syncope	13
Other VT	25
Medications			
β-Blocker	38.1% (ICD); 11% (AAD) at 12 months	0 in ICD or amiodarone arm	37% (ICD); 21.2% (AAD) at 12 months
Angiotensin-converting enzyme inhibitor	68.4% (ICD); 65.5% (AAD) at 12 months	40% to 45% at discharge	Not recorded
Digitalis	45.8% (ICD); 37.9% (AAD) at 12 months	15% to 26% at discharge	34.5% (ICD); 21.9% (AAD) at 12 months
Diuretic agent	56% (ICD); 59.3% (AAD) at 12 months	25% to 33% at discharge	Not recorded
Mineralocorticoid receptor antagonist	Not recorded	Not recorded	Not recorded

AAD indicates antiarrhythmic drug; AVID, Antiarrhythmics Versus Implantable Defibrillators; CASH, Cardiac Arrest Study Hamburg; CIDS, Canadian Implantable Defibrillator Study; ICD, implantable cardioverter defibrillator; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; VF, ventricular fibrillation; VT, ventricular tachycardia.

ICD of 2.7 months at 3 years. Patients treated with an ICD had significantly greater survival than those receiving antiarrhythmic drugs throughout the entire observation period of up to 24 months.

Two smaller RCTs were conducted outside of North America. The first, the Cardiac Arrest Survival in Hamburg (CASH) trial, randomized 288 patients between 1987 and 1996.³¹ CASH enrolled patients who had been resuscitated from cardiac arrest due to documented sustained ventricular

arrhythmias. Important exclusions were likely secondary causes, including cardiac arrest within 72 hours of acute myocardial infarction, the presence of severe electrolyte abnormalities, or use of proarrhythmic medications. Patients were randomized to an ICD or antiarrhythmic treatment (amiodarone, metoprolol, or propafenone) in a 1:3 ratio. In 1992, after the proarrhythmic effect of class Ic antiarrhythmics in the setting of structural heart disease was identified, 5 patients randomized receiving propafenone were excluded.

Most patients enrolled in CASH were men (80%) with coronary artery disease (75%), a mean age of 57 years, and mean LVEF of 45%. At a mean follow-up of 57 months (compared with 18-month follow-up in AVID), the crude death rates were 36.4% in the ICD group and 44.4% in the antiarrhythmic drug group. Although survival free of SCA was significantly higher in patients randomized to ICD (hazard ratio [HR] 0.42, 97.5%CI upper bound 0.72), overall survival was not (HR 0.77, upper bound of the 97.5%CI 1.11).

The last published RCT, the Canadian Implantable Defibrillator Study (CIDS), enrolled 659 patients between 1990 and 1997.³² Patients were included if they had any of the following: (1) documented VF, (2) out-of-hospital cardiac arrest requiring defibrillation or cardioversion, (3) syncope resulting from documented sustained VT, (4) documented sustained VT at a rate of ≥ 150 beats/min causing presyncope or angina with an LVEF $\leq 35\%$, or (5) syncope of undocumented etiology with subsequent documented spontaneous VT ≥ 10 seconds or sustained (≥ 30 seconds) monomorphic VT induced by programmed ventricular stimulation. Patients were randomized to an ICD or amiodarone. Although risks of adverse outcomes were lower in those treated with ICDs, the differences were not significant (relative risk difference for arrhythmic death 32.8%; 95%CI -7.2% to 57.8%; and for all-cause mortality 19.7%; 95%CI -7.7% to 40% and for in the ICD arm and the amiodarone arm, respectively).

Two meta-analyses compiled the data from these three trials. The first found significant reductions in deaths from all causes (HR 0.72; 95%CI 0.60-0.87) and arrhythmia (HR 0.50; 95%CI 0.36-0.67) with the ICD vs amiodarone.^{36,37} There was no significant difference in nonarrhythmic death (HR 0.93; 95%CI 0.73-1.17). In analysis of subgroups, patients with LVEF $>35\%$ and those implanted with an ICD during the "epicardial era" (prior to July 1, 1991) compared with those randomized after this time had significantly less benefit from the ICD. The second meta-analysis calculated a 7% (95%CI 0.05-0.10) absolute reduction in arrhythmic death with the ICD, corresponding to a number needed to treat of 15 to prevent 1 death at a mean follow-up of 2 years.³⁷

Based on these RCTs, guidelines recommend ICD therapy for patients who survive SCA due to ventricular arrhythmias if they are expected to survive at least a year with good functional status (Table 2). The most recent US guidelines for secondary prevention ICDs, published in 2008,² include a Class IA recommendation for an ICD in patients surviving cardiac arrest due to documented VF or hemodynamically unstable sustained VT after evaluation to exclude any completely reversible causes. A Class IB recommendation is given for those with structural heart disease and spontaneous sustained VT and for patients with syncope of undetermined origin with hemodynamically significant sustained VT or VF induced during programmed ventricular stimulation (Class IB).

Table 2. Guidelines for Secondary Prevention ICD Implantation²

Class I*
Survivors of cardiac arrest due to VF or hemodynamically unstable sustained VT without a reversible cause
Patients with structural heart disease and spontaneous sustained VT
Patients with syncope of undetermined cause with sustained VT or VF induced during electrophysiology study
Class IIa*
Patients with unexplained syncope, significant LV systolic dysfunction, and nonischemic cardiomyopathy
Patients with sustained VT and normal or near-normal ventricular function
Class IIb*
Patients with syncope and advanced structural heart disease in whom thorough invasive and noninvasive investigations have failed to define a cause
Class III
Not indicated for patients not expected to survive at least 1 year
Not indicated for patients with incessant VT or VF
Not indicated for patients with syncope of undetermined cause in a patient without inducible ventricular arrhythmias and no structural heart disease
Not indicated when VF or VT is amenable to surgical or catheter ablation
Not indicated for patients with ventricular arrhythmias related to completely reversible disorder in the absence of structural heart disease

ICD indicates implantable cardioverter defibrillator; LV, left ventricle; VF, ventricular fibrillation; VT, ventricular tachycardia.

*all recommendations for secondary prevention ICD implantation are predicated on "a reasonable expectation of survival with good functional status for more than one year."²

The gaps and limitations of these RCTs performed 2 decades ago are discussed further below.

Prognosis of Patients After ICD Implantation for Secondary Prevention

Although the RCTs demonstrated a survival benefit ICD therapy among patients surviving SCA, the overall morbidity and mortality in this population remain high. At 3 years, the survival rate for ICD-treated patients in the AVID trial was 84%, compared with 76% for patients treated with antiarrhythmic medications; the vast majority of deaths (78%) were related to cardiac causes.³⁸ By comparison, in a contemporary population of patients undergoing ICD placement for secondary prevention indications, survival was 89.6% and 83.6% at 1 and 2 years, respectively.³⁹ This difference in outcomes is likely in part related to improvements in use of goal-directed medical therapy for heart failure and coronary artery disease.

Heart failure and LV systolic dysfunction are common among patients who receive ICDs for secondary prevention. In this patient population the most common causes of death include SCA and progressive heart failure.⁴⁰ Yet, patients with more severe heart failure are more likely to die of progressive heart failure. Among patients in the Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF), more severe heart failure was associated with higher mortality rate and higher absolute rate of SCA, yet with a decreasing proportion of SCA in total deaths.⁴¹ Although the ICD can treat both serious bradyarrhythmias and tachyarrhythmias, it should have no effect on other causes of death (in the absence of cardiac resynchronization therapy) including progressive pump failure. Indeed, ICD therapy conferred no survival benefit for nonarrhythmic cardiac death among patients in the secondary prevention RCTs.³⁰⁻³²

Additionally, SCA due to arrhythmia may still occur despite the use of an ICD. Although death frequently occurs due to progressive heart failure, arrhythmic death can occur for several reasons, including failure to detect or terminate VT/VF, lead failures (including lead fractures and insulation defects), incessantly recurrent VT/VF, VT below the lower rate limit for detection (inappropriate programming), or electromechanical dissociation after an appropriate ICD shock.⁴² Prior to two decades ago, most sudden deaths among patients with an ICD were related to electromechanical dissociation occurring after appropriately detected and treated ventricular arrhythmias.⁴² Among patients in the AVID trial, arrhythmic death was seen in 24 patients with an ICD.³⁸ In the patients whose ICD was interrogated after death (7/24), 4 had no shocks delivered with bradycardia likely the terminal arrhythmia, and 3 had appropriate detection and shock but failed to convert the tachyarrhythmia. In a recent analysis of patients with implantable devices whose device was interrogated at the time of autopsy, among 7 patients with an ICD who had sudden death, 4 deaths were related to VT/VF undersensing, 2 were related to unsuccessful defibrillations, and 1 was related to VT in the monitor zone.⁴³ In the modern era of high-output devices, the risk of failed appropriate shock is low, occurring in about 3% of patients, and defibrillation testing is no longer performed routinely.⁴⁴

Contemporary Studies

Few contemporary studies of patients receiving ICDs for secondary prevention have been performed since the RCTs. This is an important knowledge gap for several reasons. First, improvements in goal-directed medical therapy for LV systolic dysfunction, including angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, β -blockers, and aldosterone antagonists, may reduce the risks for SCA and thus

attenuate the benefits of therapy observed in the original trials (Table 2). In the AVID trial only 44% to 45% of patients in the ICD arm were on β -blockers at 12- and 24-month follow-up despite a mean LVEF of 32%.³⁰ Improved adherence to medical therapy may reduce the need for ICD therapies and improve heart failure-related mortality, thus diminishing the benefit seen in the ICD arm. Additionally, no trials even described the use of mineralocorticoid receptor antagonists (MRA), which significantly reduced sudden death among RCTs and has been shown to decrease the burden of premature ventricular complexes and nonsustained VT.⁴⁵⁻⁴⁸ Because the use of MRAs was negligible (3%) among patients with heart failure and LV systolic dysfunction prior to the publication of the Randomized Aldactone Evaluation Study in 1999, it can be assumed that few if any patients who today would be eligible for such therapy were taking MRA agents during the RCTs.⁴⁹

One observational study provides some insight into the benefit of ICDs in more contemporary practice. Using the Veterans Administration database, Chan and colleagues identified 1442 patients with a new secondary prevention indication ICD (new-onset VT/VF/cardiac arrest).⁵⁰ At 3 years of follow-up, patients who received an ICD had significantly lower risks of death from all-causes (OR 0.52; 95%CI 0.45-0.6) and cardiovascular causes (OR 0.56; 95%CI 0.49-0.65).⁵⁰ The association between ICD therapy and death risk (28% lower) was similar to that seen in the AVID trial (31%). Furthermore, the risk difference was similar among patients on optimal medical therapy and those not receiving optimal therapy, suggesting benefits to the ICD beyond contemporary medical treatment.

An analysis of the NCDR ICD Registry evaluated mortality rates stratified by indication.³⁹ Among 46 685 patients with ICDs implanted for a secondary prevention indication, 78% of patients had SCA or sustained VT, and 22% had syncope. Overall mortality was 10.4% at 1 year and 16.4% at 2 years, and although survival at 1 year was worse among patients with prior SCA/VT than in those with syncope, survival rates were similar at 2 years.

Special Patient Populations

Because of the selection criteria of the RCTs, the benefits in some patient groups are not known. For example, patients with advanced NYHA Class symptoms are associated with higher risk of death related to progressive heart failure, which potentially reduces the impact of ICD therapy. As noted previously, in a meta-analysis of the secondary prevention RCTs, patients with LVEF $\geq 35\%$ had significantly less benefit compared with those whose LVEF was severely reduced.³⁶ Two such groups of patients who require special consideration are the elderly and those with chronic kidney disease.

The elderly have been poorly represented in trials evaluating the use of ICDs; in fact, the mean age of patients enrolled in the secondary prevention RCTs was 63 years.³⁶ Because the competing risk of noncardiac death is higher with the elderly, the ICD may provide less benefit among these patients. The ratio of sudden death to all-cause death falls from 0.51 before the age of 50 to 0.26 after age of 80 among patients with prior myocardial infarction or heart failure.⁵¹ Observational studies provide some insights into outcomes among older patients. In pooled analyses of the secondary prevention trials, older patients (>75 years old), comprising 13.5% of the population enrolled, were more likely than younger patients to die of nonarrhythmic death (8.7% vs 4.0% per year) and arrhythmic death (6.7% vs 3.8% per year).⁵² Younger patients (<75 years) randomized to an ICD had significantly reduced all-cause and arrhythmic death, whereas those at least 75 years old experienced no mortality benefit from therapy (all-cause death HR 1.06; 95%CI 0.69-1.64; arrhythmic death HR 0.90; 95%CI 0.42-1.95). Among patients in the Ontario ICD Database between 2007 and 2010, 1460 underwent secondary prevention ICD implantation.⁵³ Although increasing age was associated with increase in mortality, there was no difference in appropriate shocks with increasing age, suggesting that ICD therapy should not necessarily be withheld simply because of patient age. A second analysis from the NCDR ICD Registry evaluated outcomes of older patients undergoing secondary prevention ICD implantation.⁵⁴ A cohort of 12 420 Medicare patients aged ≥ 65 were identified with matching longitudinal claims data. Overall, the risk of death at 2 years was 21.8%. Additionally, the risk of death, hospitalization, and skilled nursing facility admissions were all significantly elevated across increasing age groups. Although the competing risk of nonarrhythmic death is higher among the elderly, careful evaluation of these conditions should be considered prior to ICD implantation.

Among patients on dialysis, cardiac disease is the major cause of death (39%), with arrhythmia being the single largest contributing cause.⁵⁵ However, randomized studies evaluating the efficacy of ICDs have either excluded or poorly represented patients on dialysis. Given the competing risk of death in addition to higher risks of device-related complications (bleeding, infection, and vascular problems including thrombosis and subclavian stenosis) in this population, ICD therapy may not provide benefits of the same magnitude as suggested by the trials.⁵⁶ A retrospective cohort study evaluated 6042 patients on dialysis who suffered a cardiac arrest or VF episode and survived at least 30 days from the event; only 7.6% underwent ICD implantation.⁵⁷ When compared to those patients who did not undergo ICD implantation, survival was significantly higher; however, unadjusted mortality in this end-stage renal disease cohort was higher than that observed

among patients enrolled in the RCTs. Current guidelines still recommend an ICD for those that have a reasonable expectation of survival for more than 1 year, but the benefits of implementing this recommendation remain unclear.

Defibrillation Threshold Testing in Secondary Prevention ICDs

At the time of device implant, defibrillation threshold testing has historically been used to establish that the ICD will recognize and treat VF with the opportunity to immediately modify the device configuration if defibrillation is not successful. Patients enrolled in the RCTs that investigated the efficacy of the ICD all underwent defibrillation threshold testing. However, it has been shown that such testing does not improve ICD shock efficacy or reduce mortality.^{58,59} Furthermore, first ICD shocks rarely fail to terminate clinical ventricular arrhythmias (<10%), and defibrillation threshold testing adds complexity, time, and cost to the procedure and creates inconvenience for the patient.⁶⁰ Observational studies regarding the safety of defibrillation threshold testing among patients undergoing ICD implantation have yielded conflicting results. Predictors of inadequate defibrillation safety margin testing were examined among patients undergoing ICD implantation in the NCDR ICD Registry.⁶¹ Of the 132 477 ICD recipients with defibrillation testing performed, 12 397 patients (9.4%) had inadequate defibrillation safety margins. From multivariate stepwise logistic regression modeling, a secondary prevention indication was predictive of inadequate defibrillation safety margin (OR 1.17; 95%CI 1.10-1.26).

The Shockless Implant Evaluation (SIMPLE) trial compared the efficacy and safety of ICD implantation without and with defibrillation testing.⁴⁴ Although the majority of patients (73%) had a primary prevention indication, the trial enrolled patients treated with an ICD for secondary prevention. At a mean follow up of 3 years, the primary outcome of arrhythmic death or failed appropriate shock occurred in fewer patients in the no-testing group than in those who underwent testing (7% vs 8%, respectively; HR 0.86; 95%CI 0.65-1.14). Although the primary outcome was similar for all subgroups, there was no specific analysis of the 27% of patients with a secondary prevention indication. The best approach to defibrillation testing among patients undergoing secondary prevention ICD remains unclear, and guidelines do not provide specific recommendations.⁶²

Rate of ICD Therapies

Given the high-risk substrate of patients receiving an ICD for secondary prevention, it is not surprising that ICD therapies are common in this population; in the AVID trial, 51% were

treated with either an ICD shock or antitachycardia pacing within the first year.⁶³ By the second year, 62% of patients had received an ICD shock, and 77% had received antitachycardia pacing. VT was the first arrhythmia treated in 63% of cases, and VF in 13% of cases. In contrast, among patients in the primary prevention SCD-HeFT trial, which enrolled patients with LV systolic dysfunction without a history of sustained ventricular arrhythmias or SCA, a third of patients had received a therapy at median follow up of 3.75 years.⁶⁴ Rates of appropriate therapies among patients with a secondary prevention ICD in the Ontario ICD Database ranged from 11.4 (18–49 years) to 11.9 (>80 years) events per 100 person years.⁵³

Because of the high risk of therapies among patients receiving an ICD for secondary prevention, and because of concerns about the association between ICD shocks and adverse outcomes, contemporary programming strategies to reduce shocks are particularly important in this population.⁶⁵ However, patients with secondary prevention ICDs are poorly represented in trials evaluating programming strategies,^{66–68} perhaps due to concerns that interventions to lower the risk of shocks might increase the rate of arrhythmic death among patients who have already experienced episodes of life-threatening ventricular arrhythmias. One quarter (477/1902) of the population of the ADVANCE III trial had a secondary prevention indication.⁶⁹ At follow up, patients randomized to longer detection intervals had significantly fewer delivered therapies (346 vs 557, incident rate ratio 0.63; 95%CI 0.51–0.78) without a significant change in total mortality (5.5 vs 6.3; HR 0.87; 95%CI 0.57–1.32) or syncope (1.2 and 1.15 events/patient). A post hoc analysis of the 477 patients with a secondary prevention indication demonstrated a similar decrease in overall therapies in those randomized to longer detection intervals without a difference in syncope or death.⁷⁰ Although ICD programming should be tailored to previous knowledge of VT/VF (hemodynamic stability, cycle length), these data suggest that programming with longer detection intervals might reduce rates of ICD therapies without increasing risk of adverse outcomes in a secondary prevention population.

Future Investigation

The original RCTs evaluating the use of secondary prevention ICDs comprised only 934 patients and were performed over 2 decades ago. In 2011 the NCDR recorded 33 860 secondary prevention–indicated ICD implants alone, which underestimates national rates, as not all institutions submit data on secondary prevention ICDs to NCDR.³ Additional trials including patients with a secondary prevention ICD indication would be welcome, especially in those populations where the

guidelines extrapolate beyond the RCTs, however, these may be difficult because of perceptions of the lack of equipoise in a “no-ICD arm.” Advances in medical therapy, ICD technology and programming strategies, and structural heart disease are likely to have a significant impact among patients who are candidates for secondary prevention ICD.

To date, few observational studies have examined patterns in survival, ICD therapies, and other healthcare outcomes in contemporary practice. Future investigations are needed to help inform shared decision making around ICD implantation in patients with multiple comorbidities who have survived a cardiac arrest (Table 3): examining outcomes in populations not represented in the trial, including the elderly, those with advanced-class heart failure, patients with chronic kidney disease, and women; assessing the impact of contemporary care strategies including ICD programming and use of goal-directed medical therapy; developing risk models for competing outcomes of arrhythmic vs nonarrhythmic death; and assessing outcomes beyond death including ICD therapies, quality of life, and physical function and independence. Although guidelines provide fairly clear direction about the use of ICDs for secondary prevention indications, refined studies are needed to better understand outcomes in a contemporary population.

Table 3. Future Investigations Into Patients With Secondary Prevention ICDs

Future Investigations
Outcomes in populations not represented in trials
Elderly (>70 years old)
Women
Severely symptomatic heart failure (e.g. NYHA class IV symptoms)
Chronic kidney disease
Severely depressed LVEF
Nonwhite race
Impact of care strategies
ICD programming
Goal-directed medical therapy (BB, ACE-I, MRA) and shock risk
Risk models
Device-related complications
Competing outcomes of arrhythmic vs nonarrhythmic death
Outcomes beyond death
ICD therapies (shocks, antitachycardia pacing)
Quality of life
Physical function/independence

ACE-I indicates angiotensin-converting enzyme inhibitor; BB, β -blockers; ICD, implantable cardioverter defibrillator; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist, NYHA, New York Heart Association.

Conclusion

Based on RCTs performed on relatively few patients over two decades ago, secondary prevention ICDs reduce the risk of death (as compared with antiarrhythmic medications) and are indicated for patients who have survived SCA who have a reasonable expectation of survival for at least a year with good functional status. However, in contemporary practice, patients who receive secondary prevention ICDs do not resemble those enrolled in the trials. Further, advances in medical therapy for left ventricular systolic dysfunction and coronary artery disease are likely to attenuate the risk of subsequent SCA in this population, potentially attenuating the benefits of ICD therapy. Observational studies of this population are relatively few compared with those focusing on primary prevention, despite the fact that a substantial proportion (nearly 25%) of ICDs implanted are for secondary prevention.³ Future investigations are needed to improve the quality of care provided to this large population of patients.

Disclosures

Dr Masoudi has a contract with the American College of Cardiology for his role as Chief Science Officer of the National Cardiovascular Registry programs. The other authors have no disclosures.

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Key Words: implantable cardioverter-defibrillator • secondary prevention • sudden cardiac arrest