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Use of Traditional and Biventricular Implantable Cardiac Devices for Primary and Secondary Prevention of Sudden Death

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Sudden cardiac death (SCD) accounts for 450,000 deaths yearly in the United States and remains a major public health problem [1]. There is a dismal survival rate following such an event [2–4], with only 3% to 28% of patients who experience SCD surviving to hospital discharge [5]. Therapy for survivors of SCD and sustained ventricular tachycardia (VT) focused initially on types 1 and 3 antiarrhythmic drugs. The results of these trials were disappointing, which led to the development of the implantable cardioverter defibrillator (ICD). Multiple randomized clinical trials have shown a significant mortality benefit of defibrillator therapy compared with antiarrhythmic drug therapy for secondary prevention of SCD [6–10], and ICDs long have been considered the standard of care in this group. Furthermore, clinical trials of antiarrhythmic drugs for the primary prevention of sudden death have failed to show consistent benefit [11]. Paradoxically, other drug classes, such as β-blockers, angiotensin-converting enzyme (ACE) inhibitors, aldosterone antagonists, and statins appear to have moderate efficacy for preventing SCD in high-risk cohorts. Multiple trials completed over the past decade have documented the effectiveness of the ICD for primary prevention to reduce the risk of SCD and overall mortality in patients at high risk for lethal arrhythmias [12]. Because ventricular tachyarrhythmias are considered the underlying cause of SCD in most subjects, most cardiac rhythm device studies designed to reduce mortality have focused on ICD technology with or without pacing.

Cardiac resynchronization therapy (CRT) using biventricular pacing has emerged as an important adjunctive therapy for patients who have systolic heart failure and intraventricular conduction delay. Several large multicenter trials of CRT have shown an improvement in exercise capacity and quality of life with a reduction in hospitalizations among subjects who have advanced heart failure, QRS prolongation and a reduced left ventricular ejection fraction (LVEF). A reduction of sudden death and all-cause mortality also has been demonstrated with CRT, with or without ICD backup. In addition, bradycardia initiates some sudden death episodes, and pacing may be effective to reduce sudden death by preventing asystole or affecting repolarization. This article reviews the clinical trials evaluating the effects of ICD and pacing therapy on SCD.

Secondary prevention implantable cardioverter defibrillator trials

Several prospective, randomized trials evaluated the role of the ICD in secondary prevention of SCD [6–10], defined as those patients who previously experienced an episode of sustained ventricular tachyarrhythmia. The first and largest published study was the Antiarrhythmics versus Implantable Defibrillators (AVID) trial in 1997, which enrolled 1016 patients who had survived one or more episodes of ventricular fibrillation

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(VF) or had symptomatic, sustained VT and a reduced LVEF [6]. The study patients were randomized to either ICD or antiarrhythmic drug therapy, which was primarily amiodarone. Patients assigned to the defibrillator group were found to have a 31% relative reduction in mortality, leading the data safety monitoring board to terminate the trial prematurely. This translated into an average improvement in life expectancy of 2.7 months, although this is likely an underestimate of the benefit of this therapy, because median follow-up was only 18 months. Additionally, the AVID investigators performed a prospective cost-effectiveness analysis and found that the cost of an ICD compared with antiarrhythmic therapy was approximately $67,000 per year of life saved [13].

The Canadian Implantable Defibrillator Study (CIDS) [7] reported on 659 patients who had a history of cardiac arrest, sustained VT, or syncope with a depressed ejection fraction (EF) and inducible sustained ventricular arrhythmia. Subjects were randomized to treatment with an ICD or amiodarone. A 20% relative decrease in mortality from all causes was observed in the defibrillator group, which did not reach statistical significance.

The Cardiac Arrest Study Hamburg (CASH) [8] included 346 patients who survived a cardiac arrest and randomly were assigned to receive an ICD or antiarrhythmic drug therapy (amiodarone, metoprolol, or propafenone). Relative to the patients in AVID and CIDS, the subjects enrolled in CASH were healthier, with a higher mean LVEF. The propafenone arm had a 61% excess total mortality during the first year of follow-up and was stopped early. The final analysis included the 288 remaining patients, and compared the defibrillator group versus the metoprolol and amiodarone groups at 57 months mean follow-up. As with CIDS, CASH showed a trend toward decreased total mortality in the ICD group (23% relative risk reduction), which did not reach statistical significance.

Connolly and colleagues [14] performed a meta-analysis of the AVID, CIDS, and CASH trials and found that ICD therapy, compared with amiodarone, resulted in significant relative reductions in total mortality (28%) and arrhythmic death (50%) (Fig. 1). The mean survival benefit of an ICD, as compared with drug therapy, was estimated to be 4.4 months over a follow-up period of 6 years. Furthermore, defibrillator therapy improved mortality outcomes regardless of the presence of structural heart disease, use of β-blockers, prior surgical revascularization, or presenting arrhythmia (VT or VF). This analysis also showed that patients who had LVEF greater than 35% derived significantly less benefit from ICD therapy than those who had more significant LV dysfunction. A second meta-analysis, which separately compared the effectiveness of ICD therapy versus medical therapy for both primary and secondary prevention of arrhythmic events, found a significant decrease in all-cause mortality in the ICD group in the secondary prevention trials [15].

Both the AVID and CIDS investigators performed subgroup analyses to determine the benefit of ICD therapy based on LVEF [16,17]. In the AVID trial, patients who had LVEF less than

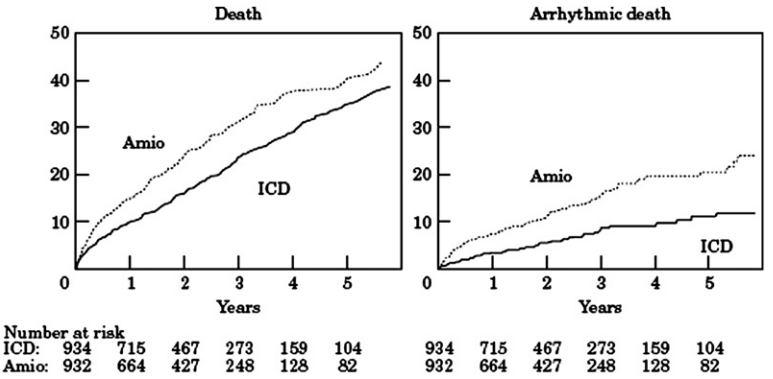

Fig. 1. Cumulative risk of total mortality and arrhythmic death with implantable cardioverter–defibrillator (ICD) versus amiodarone from secondary prevention trials (*Reproduced from* Connolly SJ, Hallstrom AP, Cappato R, et al. Meta-analysis of the implantable cardioverter defibrillator secondary prevention trials: AVID, CASH, and CIDS studies. Eur Heart J 2000;21(24):2074; with permission.)

35% showed a 40% relative mortality reduction with an ICD versus drug therapy, whereas those who had an LVEF greater than 35% did not benefit significantly [16]. Likewise, the subgroup analysis from CIDS found that patients who had more severe LV dysfunction (LVEF less than 35%) gained a greater mortality benefit from defibrillator therapy than those who had a more preserved LVEF [17]. A separate investigation from the AVID population compared survival rates across different quintiles of LVEF. In the antiarrhythmic drug group but not the ICD group, survival was associated strongly with left ventricular (LV) systolic function. The authors concluded that this effect likely was related to the superiority of the ICD in treating malignant ventricular arrhythmias [18].

Substudies from the CIDS and AVID trials were designed to uncover additional baseline characteristics that would predict benefit of ICD therapy. In the CIDS trial, high-risk patients (defined by two or more of the following: LVEF less than or equal to 35%, age greater than or equal to 70, and New York Heart Association class 3 or 4), were found to have a 50% relative risk reduction for total mortality, whereas patients who had one or no risk factors derived no benefit [17]. In separate substudies that included patients in the other secondary prevention trials, however, LVEF remained the only risk factor predictive of ICD efficacy [15,19]. A retrospective substudy from AVID sought to identify baseline variables that were predictive of low arrhythmia recurrence based on a review of stored ICD event data [20]. Factors that significantly predicted low arrhythmia recurrence rate were VF as the index arrhythmia, no history of cerebrovascular disease, higher LVEF, no tachyarrhythmia history, and need for revascularization [20]. Raitt and colleagues [21] examined spontaneous arrhythmias occurring in AVID patients randomized to an ICD. Those patients who had VT as their index arrhythmia were significantly more likely to have appropriate therapy than those who presented initially with VF. These findings suggest that there are important differences in the electrophysiologic characteristics between these two patient populations [21].

Another substudy from the AVID registry involved patients with life-threatening ventricular arrhythmias thought to be secondary to a reversible cause, a group that was not eligible for randomization [22]. Compared with patients who had a primary ventricular arrhythmia (no reversible cause identified), mortality for patients who had a transient or identifiable cause was equally high [23]. It was also noteworthy that patients who had hemodynamically stable VT had a similar prognosis as those who had unstable VT [24]. These results call into question the previously held beliefs that patients who have stable VT and those who have a potentially reversible cause have a good prognosis and are not candidates for an ICD. Rather, it may be that other nonarrhythmic clinical characteristics, such as ischemia, heart failure, or LV dysfunction, may be more important for determining sudden and all-cause mortality. This finding has led to an increase in the practice of ICD implantation for patients who have documented sustained ventricular arrhythmias and concurrent electrolyte abnormalities, heart failure exacerbations, or ischemia (in the absence of an ST elevation myocardial infarction).

One criticism of the AVID results was related to an imbalance between β-blocker usage observed between the study groups (40% of patients received β-blockers in the ICD arm versus 11% in the antiarrhythmic drug arm of the trial), which could modify the observed benefits of ICD therapy [6,25]. An AVID substudy evaluated the effects of β-blockade in both the randomized and nonrandomized populations followed in the trial [25]. In patients treated with either an ICD or amiodarone, β-blocker use did not alter survival. AVID-eligible patients who were not randomized to either amiodarone or ICD therapy, however, experienced a 53% mortality reduction with β-blockers compared with those who did not receive β-blockers. The authors postulated that β-blocker use led to a reduction in SCD, but this survival benefit was no longer prominent when patients also were receiving specific antiarrhythmic therapy with amiodarone or a defibrillator [25].

An AVID substudy collected quality of life data on 800 trial participants surviving to at least 1 year of follow-up [26]. Similar alterations in self-perceived quality of life were observed among participants treated with antiarrhythmic drugs and those treated with ICDs. The development of sporadic shocks was associated with a reduction in physical functioning and mental well-being among ICD recipients. Among patients treated with antiarrhythmic drugs, a similar reduction in both physical functioning and mental well-being occurred in those who developed adverse symptoms related to therapy [26]. Quality-of-life

outcomes from the CIDS trial were somewhat different from those observed in AVID. In a post-hoc analysis, emotional and physical health scores improved significantly in the ICD group and were either unchanged or deteriorated in the amiodarone group. The investigators noted, however, that quality of life did not improve in the subgroup of ICD patients who received five or more shocks from their device during the 12-month follow-up period [27].

Brodsky and colleagues [28] investigated the utility of electrophysiologic (EP) studies in AVID patients following VT, VT with syncope, or sustained VT in the setting of LV dysfunction. In this setting, the EP study did not predict death or recurrent arrhythmias accurately during follow-up. Another potential predictor evaluated by the AVID group was electrical storm, defined as multiple temporally related episodes of VT or VF. Electrical storm was found to be a significant risk factor for overall mortality within the 3 months following its occurrence, and to a lesser extent beyond that time [29].

Although the aforementioned secondary prevention trials generally followed patients for a limited time, long-term outcomes were assessed in a subset of VT/VF survivors from the CIDS trial. Patients were followed for a mean duration of 5.6 years. The all-cause annual mortality rate in the amiodarone group was found to be 5.5% versus 2.8% in the ICD group [30]. Although the initial CIDS trial only showed a modest mortality advantage of ICD therapy over amiodarone, the CIDS long-term substudy investigators found a progressive increase in the benefits of defibrillator therapy over time [31]. In addition, 82% of patients receiving amiodarone experienced drug-related adverse effects, and 50% of patients on amiodarone required dose reduction or discontinuation [30]. This highlights some of the problems interpreting the relatively short-term follow-up of most ICD trials. The efficacy of ICDs does not appear to wane over time, whereas drug therapy may become less effective or lead to increased intolerance as the cardiac substrate changes or systemic accumulation progresses. Therefore, the benefit of ICD therapy compared with antiarrhythmic drugs may continue to increase with longer follow-up. Moreover, the duration of median follow-up is much shorter than battery longevity, so the cost of ICD therapy likely is overestimated, and the prolongation of life likely is underestimated.

Primary prevention trials

Clinical trials of antiarrhythmic drug therapy for the primary prevention of sudden death had variable results, showing harm, no effect, or an inconsistent benefit [11]. Given the high morality rate associated with an out-of-hospital cardiac arrest and the disappointing results of antiarrhythmic drugs, multiple trials were undertaken to examine the efficacy of defibrillator therapy in high-risk cohorts (Table 1). The first of these trials to be published was the Multicenter Automatic Defibrillator Implantation Trial (MADIT-I) [32], which enrolled 196 patients who had coronary artery disease (CAD), spontaneous nonsustained ventricular tachycardia (NSVT), LVEF less than or equal to 35%, and inducible VT that was not suppressed with the use of intravenous procainamide. The investigators found a 54% relative reduction in all-cause mortality over a mean follow-up period of 27 months in the defibrillator group compared with the group assigned to conventional medical therapy. This mortality reduction translated into a number needed-to-treat (NNT) of 3 over 36 months. The cost of ICD therapy compared with conventional care was $27,000 per life-year gained in MADIT, which compares favorably with other cardiac interventions [33].

The Multicenter Unsustained Tachycardia Trial (MUSTT) [34] was a randomized trial that enrolled a similar population to that of MADIT-I. Patients who had a history of myocardial infarction (MI), LVEF less than or equal to 40%, and spontaneous NSVT underwent an EP study. Those patients who had inducible VT ($n = 704$) were assigned randomly to either no therapy or antiarrhythmic therapy, while patients who did not have inducible VT were followed in a registry. The patients who randomly were assigned to EP-guided therapy underwent serial drug testing followed by random assignment of an antiarrhythmic drug. The most common drugs prescribed were class 1 antiarrhythmics (26%), followed by amiodarone (10%) and sotalol (9%). ICD therapy could be used only after failure of at least one antiarrhythmic drug. Although MUSTT frequently has been considered to be a defibrillator trial, it may be described better as a test of an EP-guided treatment strategy in which an ICD could be prescribed at an investigator's discretion [35]. Of note, the frequency of defibrillator prescription varied among the trial centers and over time. Despite these limitations, the 5-year all-cause mortality among the 161 patients

Table 1
Selected clinical trials of implantable cardioverter defibrillator therapy for primary prevention of sudden cardiac death

Trial	Number of patients	Inclusion criteria	Mean follow-up (months)	Control therapy	Relative risk reduction (%)	Absolute risk reduction (%)	P value
MADIT-I [32]	196	Nonrecent MI (>3 wks) or CABG (>3 mos), EF ≤35%, spontaneous NSVT, and inducible VT	27	Medical therapy	54	22.8	0.009
MUSTT [34]	704	Nonrecent MI (≥4 days), EF ≤40%, spontaneous NSVT, and inducible VT	39	Medical therapy	51	23	<.001 (ICD versus medical therapy)
MADIT-II [40]	1232	EF ≤30%, remote MI (>1 mo)	20	Medical therapy	31	5.4	0.02
AMIOVIRT [51]	103	EF ≤35%, NICM, NSVT	24	Medical therapy	13	1.7	0.8
Cardiomyopathy Trial (CAT) [52]	104	NYHA II-III, EF ≤30%, NICM, recent-onset heart failure (≤9 mos)	23	Medical therapy	17	5.4	0.6
DEFINITE [53]	458	NICM, EF <35%, NSVT, or ≥10 PVCs/hr	29	Medical therapy	35	5.2	0.08
SCD-HeFT [54]	1676	NYHA II-III, nonrecent MI or revascularization (>30 days), nonrecent heart failure onset (>3 mos)	46	Placebo	23	6.8	<0.01

Abbreviations: CABG, coronary artery bypass graft surgery; EF, ejection fraction; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NICM, nonischemic cardiomyopathy; NSVT, nonsustained ventricular tachycardia; NYHA, New York Heart Association functional class; PVC, premature ventricular complex; VT, ventricular tachycardia.

who received ICD therapy during the initial hospitalization was 24%, which was significantly lower than the 171 patients treated with antiarrhythmic drugs (55% mortality) and the 353 patients who received no therapy (48% mortality). This translated into a 49% relative risk reduction for defibrillators as compared with drug therapy. Antiarrhythmic therapy was associated with a nonsignificant worsening of survival compared with standard medical therapy.

The MUSTT investigators also examined the prognostic significance of inducible VT during EP testing by comparing the long-term outcomes of patients who did not receive therapy [36]. Over a 5-year follow-up period, patients in whom sustained VT could not be induced had a significantly lower risk of sudden death or cardiac arrest than similar patients who had inducible VT. The overall mortality was also significantly lower in patients without inducible VT; however, the absolute difference in mortality between the patients who were inducible at the time of study and those who were noninducible was only 4% (48% versus 44%, respectively). These data suggest that the group of noninducible patients also might benefit from a primary prevention strategy, and that an EP study may be an inadequate risk stratification tool [37].

Multiple substudies from MUSTT sought to identify clinical risk factors that would predict increased risk of SCD. For the patients enrolled in MUSTT who did not receive antiarrhythmic therapy, the risk of total mortality and arrhythmic death was significantly greater among patients who had LVEF less than 30%, compared with patients who had LVEF 30% to 40% [38]. A recently published multivariate analysis from MUSTT, however, showed that EF alone may not be an adequate assessment of risk. Multiple other clinical factors, including functional class, history of heart failure, NSVT not related to bypass surgery, age, LV conduction abnormalities,

and atrial fibrillation, were found to influence total mortality and arrhythmic death. In addition, patients who have LVEF greater than 30% and other risk factors may be at higher risk for events than patients who have LVEF less than or equal to 30% but no other risk factors [12].

A MUSTT substudy compared the outcomes of enrolled patients based on race, and found multiple differences between blacks and whites [39]. These differences included a higher ICD implantation rate in whites versus blacks (50% versus 28%, respectively) and higher probability of inducible sustained VT on serial EP testing in whites, making whites more likely to be eligible for ICD implantation. Whites assigned to EP-guided therapy had a lower risk of arrhythmic death and overall mortality compared with blacks. Beyond the discrepancy in ICD implantation, there may be differences in arrhythmic substrates and proarrhythmic responses to antiarrhythmic drugs between the two races that partially explain these outcomes [39].

The second Multicenter Automatic Defibrillator Implantation Trial (MADIT II) [40] evaluated patients who had CAD, a history of MI, and LVEF less than or equal to 30%, and compared ICD therapy with standard medical care. This allowed for a larger segment of the population at risk for SCD to be included compared with MADIT (subsequently referred to as MADIT I), as patients were not required to have spontaneous or inducible arrhythmias. Patients treated with an ICD had a 31% relative reduction in mortality compared with standard medical therapy (14.2% versus 19.8%, respectively) during an average follow-up of 20 months. Antiarrhythmic drugs (primarily amiodarone) were used in less than 20% of subjects in both groups.

The MADIT-II investigators performed a subsequent analysis of defibrillator benefit as a function of time from MI to enrollment [41]. A mortality benefit was found among patients who had a remote MI (18 months or greater), but not in patients who had a more recent MI (less than 18 months). Furthermore, the mortality risk increased as a function of time from MI, and remained substantial for up to 15 years. This is contrary to older data suggesting that the highest risk period for SCD after MI was in the first year. This likely reflects a change in the management of these patients with aggressive use of reperfusion strategies and medical therapy to block neurohormonal activation, including β-blockers, ACE inhibitors and aldosterone antagonists. ICD benefit also was analyzed retrospectively based on time from last coronary revascularization [42]. Patients implanted more than 6 months after coronary revascularization received significant benefit from an ICD, whereas patients implanted less than 6 months following revascularization showed no benefit. This difference may be because of a relatively low risk for SCD in the early period following revascularization [42].

The benefit of ICD therapy in patients who were enrolled in MADIT-II was evaluated based on various clinical risk factors. In subjects randomized to treatment with a defibrillator, there was no significant difference in outcomes across New York Heart Association class or across varying degrees of LV dysfunction [43]. In a separate post-hoc analysis, all-cause mortality and SCD were increased across progressive degrees of renal dysfunction. Patients who had severe renal dysfunction, however, had no mortality benefit from ICD therapy, whereas patients who had no renal disease or mild to moderate disease had a significant survival benefit [44]. The MADIT-II investigators also assessed obesity as a risk factor for arrhythmic events [45]. In obese patients, there was a 64% increase in the risk of appropriate ICD therapy compared with nonobese patients over a follow-up period of 2 years.

Another intriguing analysis from the MADIT-II database examined the clinical course and subsequent mortality risk to patients following successful termination of a ventricular tachyarrhythmia by an ICD [46]. Patients who received successful appropriate ICD therapy had an 80% 1-year survival rate. Compared with MADIT-II patients not receiving therapy, patients receiving successful ICD therapy were at higher risk for heart failure and nonsudden cardiac death, suggesting that this group may require special attention during follow-up. A further evaluation examined factors that predict increased risk of ICD-appropriate therapy or death. In a multivariate analysis, interim hospitalizations for heart failure and coronary events subsequently were associated with an increased risk of ICD therapy for ventricular tachyarrhythmias and death [47].

Outcomes and effectiveness data were gathered based on race and gender differences in two separate MADIT-II substudies [48,49]. ICD therapy was associated with a reduction in mortality and SCD in whites; in contrast, there was no significant outcomes benefit for blacks [48]. Women enrolled in MADIT-II had similar mortality and

ICD effectiveness, but fewer episodes of ventricular arrhythmias, compared with men [49].

A cost-effectiveness analysis also was performed based on the results of MADIT-II [50]. The estimated cost per life-year saved was $235,000 for the 3.5-year follow-up, a relatively high value. Projections out to 12 years follow-up, however, were substantially lower, ranging from $78,600 to $114,000 per year-of-life saved.

Several randomized primary prevention trials have been published comparing antiarrhythmic drugs with ICD therapy in patients with nonischemic cardiomyopathy (NICM). The Amiodarone versus Implantable Cardioverter–Defibrillator Trial (AMIOVIRT) [51] was a small study (n=103) of patients who had nonischemic LV dysfunction and asymptomatic NSVT. To be included in the trial, patients had to have a chronic (longer than 6 months) diagnosis of LV dysfunction. Over a 2-year average follow-up period, there was no statistically significant mortality difference between the group treated with an ICD versus the group treated with amiodarone.

The Cardiomyopathy Trial (CAT) [52] evaluated 104 patients who had NICM and LVEF less than 30% with recent onset heart failure (less than or equal to 9 months from enrollment). The trial compared ICD implantation with standard medical therapy. At a mean follow-up of 5.5 years, survival was not significantly different between the two groups.

The next trial to evaluate ICD therapy in this patient population was the Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation (DEFINITE) [53]. There were 488 patients who had NICM, LVEF less than or equal to 35%, and frequent premature ventricular beats or NSVT randomized to standard medical care or standard care plus an ICD. There was a trend toward improved overall mortality, the primary endpoint, at 2-year follow-up in the ICD group (14.1% versus 7.9%), but this did not reach statistical significance ($P = .08$). For sudden death, a secondary endpoint of the trial, a significant reduction in the ICD group was observed (3 in the ICD group versus 14 in the standard care group, $P = .006$).

These relatively small studies showed at best a trend for mortality reduction among patients who have NICM. This is in contrast to the large benefit noted in most studies involving patients with known ischemic heart disease. Many of these studies were underpowered to address the issue of mortality benefit in this population. To help evaluate this issue more definitively, the National Institutes of Health (NIH) helped sponsor a large landmark trial. The Sudden Cardiac Death–Heart Failure Trial (SCD-HeFT) [54] evaluated 2521 patients who had ischemic and nonischemic cardiomyopathy, symptomatic heart failure, and LVEF less than or equal to 35%. The cohort included 70% who had NYHA class 2 functional status and 30% who had class 3. There were three arms to the trial: ICD therapy, amiodarone, and placebo. The defibrillators used in this trial were simple single-lead, programmed as shock-only devices. Medical management of heart failure patients in SCD-HeFT was exceptional, with 96% of patients on an ACE inhibitor or angiotensin receptor blocker at baseline, and 69% of patients on β-blockers. The primary end-point was all-cause mortality. At 5 years follow-up, patients randomly assigned to receive an ICD had a 23% relative risk reduction in mortality (7% absolute risk reduction) compared with placebo, and this benefit was similar in patients who had both ischemic and non-ischemic cardiomyopathy. Amiodarone therapy had a similar risk of death compared with placebo.

Mark and colleagues [55] published a cost-effectiveness analysis from SCD-HeFT. For an assumed pulse generator longevity of 5 years, there was a calculated cost- effectiveness of $33,192 per life-year saved for ICD therapy compared with amiodarone. This number compares favorably with the cost-effectiveness data presented from MADIT-II and AVID, perhaps because of the longer duration of follow-up in the SCD-HeFT trial. Similar cost-effectiveness data from SCD-HeFT were projected between etiologies of heart failure, whether ischemic or nonischemic in origin.

A recent substudy from SCD-HeFT specifically evaluated the population enrolled in the trial with atrial fibrillation (AF). In those randomized to ICD therapy, patients who had AF on baseline electrocardiogram were more likely to receive both appropriate and inappropriate shocks than patients in sinus rhythm at baseline. Total mortality rates were found to be similar between the two groups [56].

Nanthakumar and colleagues [57] performed a pooled analysis of treatment with and without ICDs in 10 trials for primary prevention of SCD, and included results of the AMIOVIRT, CAT, MADIT-I, MADIT-II, Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION), DEFINITE,

and SCD-HeFT trials (Fig. 2). ICD therapy provided between a 5.8% and 7.9% absolute mortality reduction ($P = .003$) compared with optimal medical management in patients who had LV systolic dysfunction, regardless of etiology. This translates into an NNT of 13 to 17 for ICD therapy over a period of approximately 34 months, depending on which trials were included in the analysis. This finding remains statistically significant regardless of the exclusion of any one trial.

Several older trials evaluated the efficacy of prophylactic ICD therapy in specific circumstances. The Coronary Artery Bypass Graft Patch (CABG Patch) trial compared treatment with an ICD versus standard care in 900 patients undergoing elective coronary bypass surgery with EF less than or equal to 35% and abnormal signal-averaged electrocardiograms (SAECG) [58]. Over a mean follow-up period of 32 months, there was no statistical difference in all-cause mortality between the two groups (hazard ratio for ICD group 1.07, $P = .64$). One plausible explanation for the lack of benefit observed with ICD therapy in this trial is the independent reduction in mortality associated with coronary bypass surgery alone. A subgroup analysis from the Studies of Left Ventricular Dysfunction (SOLVD) trials evaluated outcomes of patients who had prior history of coronary artery bypass surgery [59]. Prior coronary artery bypass surgery was associated with a 25% reduction in risk of death and a 46% reduction in risk of SCD compared with patients not undergoing surgery, both statistically significant. Thus, the prophylactic benefit of ICD implantation may not exist in this relatively protected population. Alternatively, the use of older thoracotomy ICD systems, the limited value of SAECG for risk stratification, or an improvement in systolic function following bypass surgery may have contributed to the lack of benefit of ICD therapy in this cohort.

The Defibrillators in Acute Myocardial Infarction Trial (DINAMIT) was a primary prevention trial enrolling patients who had recent MI (within 6 to 40 days of enrollment) [60]. Additional inclusion criteria included LV systolic dysfunction (EF less than or equal to 35%) and impaired cardiac autonomic function, as manifested by low heart rate variability or high 24-hour resting heart rate. There was no statistical benefit in all-cause mortality for the ICD group at a mean follow-up of 30 months (hazard ratio for ICD group 1.08, $P = .66$). Although ICD therapy was associated with a significant reduction in death from arrhythmic causes, this was offset by an increase risk of death from nonarrhythmic causes in this group. As previously discussed in a subgroup analysis from MADIT-II, this lack of benefit may be related to improved medical therapies and more aggressive reperfusion strategies after MI in the present era. [41] Additionally, although impaired heart rate variability likely identifies a group of patients at high risk for arrhythmic death following MI, this marker also identifies patients who have LV dysfunction at high risk for progressive pump failure [61], which

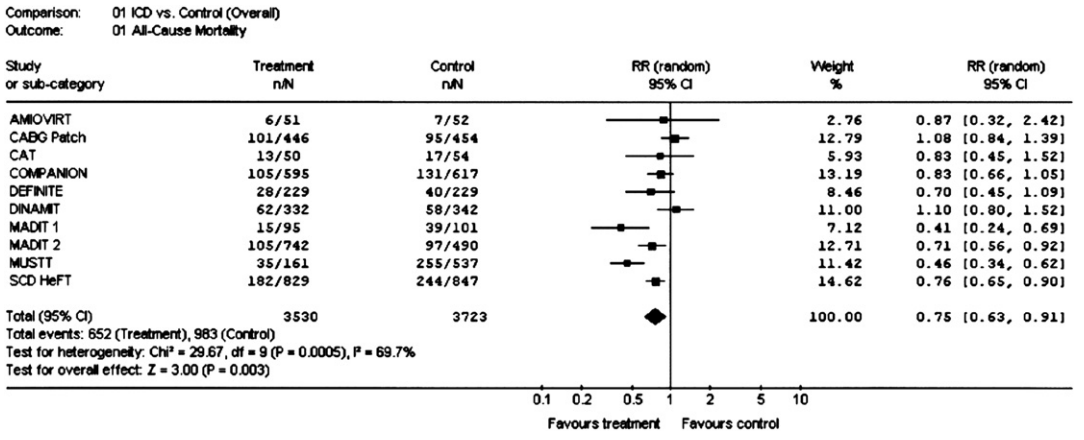

Fig. 2. Summary of implantable cardioverter–defibrillator (ICD) primary prevention trials (*Reproduced from* Nanthakumar K, Epstein AE, Kay GN, et al. Prophylactic implantable cardioverter–defibrillator therapy in patients with left ventricular systolic dysfunction: a pooled analysis of 10 primary prevention trials. J Am Coll Cardiol 2004;44(11):2170; with permission.)

defibrillators are incapable of treating. Finally, there may be a higher competing risk of fatal heart failure and recurrent ischemic events early post-MI that precludes demonstration of ICD benefit.

Pacemaker trials

Bradycardia and asystole represent additional mechanisms by which SCD may occur. Although intracardiac pacing is clearly efficacious for treating bradyarrhythmias, the mortality benefit in prevention of SCD is difficult to establish or quantify. There is little doubt that pacing prevents mortality in the setting of acquired complete heart block, although this observation never was subjected to prospective study. Multiple randomized trials have evaluated atrial-based (dual-chamber or atrial) pacing versus ventricular pacing in bradycardic patients; none of these trials have shown a reduction in mortality [62]. Additionally, a recent meta-analysis by Healey and colleagues, [62] while finding a reduction in the incidence of AF with atrial-based pacing, found no improvement in mortality, heart failure outcomes, or cardiovascular death compared with ventricular pacing.

Cardiac resynchronization therapy

The two large long-term randomized trials that have assessed the role of cardiac resynchronization therapy (CRT) on mortality are the COMPANION [63] and the Effect of Cardiac Resynchronization on Morbidity and Mortality in Heart Failure (CARE-HF) [64] trials. The COMPANION study, comprised of 1520 patients who had NYHA class 3 or 4 symptoms and QRS duration greater than 120 milliseconds, had three treatment arms: CRT with ICD, CRT alone, and optimal medical therapy. Patients who had LV dysfunction from both ischemic and nonischemic causes were included. The composite primary endpoint was death or hospitalization from any cause. There was a 40% relative risk reduction ($P<.001$) in the composite primary endpoint for the CRT with ICD group and a 34% relative risk reduction ($P<.002$) in the CRT alone group compared with medical therapy. With respect to all-cause mortality, a prespecified secondary endpoint, there was a 36% relative risk reduction ($P = .003$) in the CRT with ICD group and a 24% relative risk reduction ($P = .059$) in the CRT alone group compared with medical therapy. This translates into a NNT of only approximately 14 patients for the CRT with ICD group to prevent one death over a 1-year period, a large mortality reduction. This benefit remained consistent across multiple clinical and demographic variables including patient age, gender, QRS duration, cause of LV dysfunction, LVEF, blood pressure, and medication use.

CARE-HF was the second large randomized trial (n = 813) to evaluate the role of CRT in patients who had advanced heart failure (NYHA Class III-IV), cardiomyopathy, and LV dyssynchrony. Patients were randomly assigned to CRT (without ICD function) or medical therapy. The primary endpoint was death from any cause or unplanned cardiovascular hospitalization. Over a mean follow-up of 29 months, there was a 16% absolute risk reduction in the primary endpoint ($P<.001$) and a 10% absolute risk reduction ($P<.002$) in the secondary endpoint of all-cause mortality. There was also a significant benefit in multiple hemodynamic and echocardiographic parameters with CRT including improvement in LVEF and reductions in interventricular mechanical delay, end–systolic volume index, and area of the mitral regurgitant jet. CRT also provided better quality of life and symptomatic outcomes compared with medical therapy alone ($P<.01$).

A recent meta-analysis reviewed the outcomes from COMPANION, CARE-HF, and several smaller randomized trials of CRT versus medical therapy only [65–71]. All patients enrolled in the studies were characterized by symptomatic heart failure, LV systolic dysfunction, and cardiac dyssynchrony. Overall mortality (fixed effects odds ratio 0.72, 95% CI 0.59 to 0.88) and heart failure hospitalizations (fixed effects odds ratio 0.55, 95% CI 0.44 to 0.68) were reduced markedly with CRT (Fig. 3).

Summary

Over the past two decades, the indications for ICD use have broadened based on a series of landmark clinical trials. The ICD consistently has shown a reduction in SCD and overall mortality in the treatment of patients with prior symptomatic ventricular arrhythmias. A series of primary prevention trials demonstrated a significant benefit of prophylactic ICD therapy versus antiarrhythmic drugs for the treatment of high-risk ischemic and nonischemic cardiomyopathy patients. Currently, LVEF remains the best

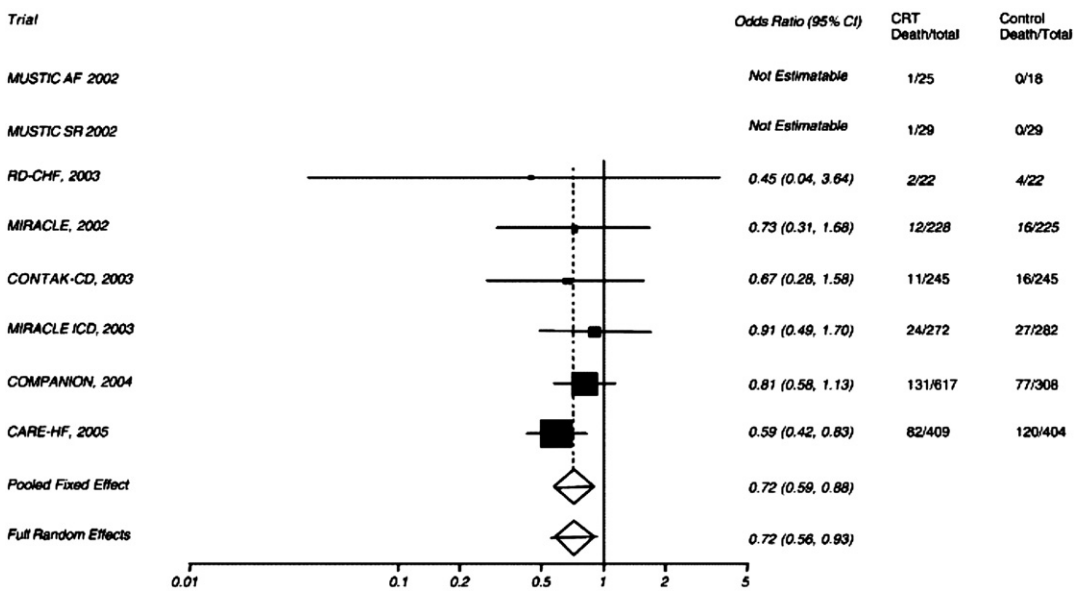

Fig. 3. Summary of cardiac resynchronization trials on mortality (*Reproduced from* Freemantle N, Tharmanathan P, Calvert MJ, et al. Cardiac resynchronisation for patients with heart failure due to left ventricular systolic dysfunction—a systematic review and meta-analysis. Eur J Heart Fail 2006;8(4):438; with permission.)

predictor of benefit in these populations. Recent clinical trials also provide evidence for the morbidity and mortality benefit of CRT using biventricular pacing in advanced heart failure patients who have a prolonged QRS duration.

Despite the aforementioned primary prevention trials that defined a subset of patients at high risk for SCD, most patients who present with SCD would not meet present criteria for prophylactic ICD implantation before their sudden death event. Thus, there remains a large cohort of patients at risk for SCD presently not well identified. Conversely, most patients who receive ICDs based on current guidelines do not require device therapy for ventricular tachyarrhythmias over the first 3 to 5 years of follow-up. Thus, further studies to improve risk stratification are needed.

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