Reviews

Prophylactic Implantation of Cardioverter Defibrillators in Idiopathic Nonischemic Cardiomyopathy for the Primary Prevention of Death: A Narrative Review

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ABSTRACT

Implantable cardioverter defibrillator (ICD) therapy reduces sudden cardiac death rates and reduces mortality in patients with ischemic heart disease and low ejection fractions. One-third of the deaths in patients with nonischemic cardiomyopathy are sudden. However, the efficacy of ICDs in the primary prevention of death in these patients is less clear. The most common cause of mortality in patients treated with ICDs is heart failure progression. ICD shocks can cause direct myocardial injury, fibrosis, inflammation, and adverse psychological outcomes, and these changes may contribute to the ventricular dysfunction in patients who already have a significantly depressed ejection fraction. We have reviewed the published randomized controlled trials and meta-analysis of prophylactic ICD therapy in the primary prevention of death in patients with nonischemic cardiomyopathy. The individual randomized controlled trials do not report a statistically significant reduction of mortality unless the ICD treatment is added to cardiac resynchronization therapy, but the meta-analysis did show a significant mortality reduction and favored ICD therapy in these patients. Medical management of many study participants was suboptimal, at least based on current guidelines. The patients with non-ischemic cardiomyopathy have good outcomes with medical therapy, and ICD therapy in this relatively low-risk population needs better selection criteria.

Introduction

Idiopathic nonischemic cardiomyopathy (NCM) is characterized by dilatation of both ventricles and impaired left ventricular contractility in the absence of coronary artery disease or disproportionate to the severity of coronary artery disease. It is a common cause of heart failure with an estimated 5-year mortality of 20%.[1,2] Approximately one-third of the deaths in NCM are sudden cardiac deaths secondary to bradycardia or ventricular tachycardia/fibrillation. The benefit of implantable cardioverter-defibrillators (ICDs) compared with medical therapy in the secondary prevention of sudden cardiac death is well established.[3] Whether or not to implant an ICD (especially without cardiac resynchronization therapy) in patients with NCM with no history of life-threatening arrhythmias is less clear, and individual randomized trials do not provide definitive evidence for choosing the best strategy in this population. Nevertheless, current guidelines state that ICDs may be considered (Class IIb, level of evidence B) for the primary prevention of the primary prevention of sudden cardiac death in patients with NCM who have a left ventricular ejection fraction (LVEF) $\leq$30%–35%, are New York Heart Association (NYHA) functional class II or III, are receiving chronic optimal medical therapy, and have reasonable expectation of survival with a good functional status for more than 1 year.[2] Information from an ICD registry indicates that approximately 31% of ICDs are placed in patients with NCM.[4] Because the evidence for mortality benefit from prophylactic ICDs in the primary prevention is less clear in these patients, we reviewed the major randomized controlled trials relevant to this guideline to determine the efficacy of ICDs in this population. We focused on medical management of the patients, outcomes, and complications of ICD treatment in these trials.

Data From CAT

The Cardiomyopathy Trial (CAT) enrolled 104 patients with recent-onset (<9 months) NCM and a LVEF <30% between 1991 and 1997.[5] The mean age was 52 $\pm$ 11 years, and all patients were in NYHA functional classes II and III. Baseline ECG revealed atrial fibrillation/flutter in approximately 16% of patients in the 2 groups. Angiotensin-converting enzyme (ACE) inhibitors were used in 96% of

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patients. However, only 3.8% of patients received β-blocker therapy. Fifty patients were randomized to ICD treatment, and 54 patients were randomized to medical therapy. The mean follow-up was 22 ± 4 months. Despite the limited use of β-blockers, the survival was excellent in both groups at 2, 4, and 6 years (93%, 80%, and 68% in controls and 92%, 86%, and 73% in the ICD group, respectively). Therefore, the trial was stopped for futility, because all-cause mortality rates were not different between the ICD group and the control group in either short-term or long-term follow-up periods. The only predictor of death was an impaired LVEF. Twenty-two percent of the patients received appropriate shocks in the ICD group. Whether or not ICD shocks adversely affected prognosis is unclear.[6] This group of NCM patients had a favorable prognosis, and the overall mortality of the control group was very low even though these patients were suboptimally treated with minimal use of β-blockers. Consequently, this study suggests that the prognosis in NCM differs significantly from that of ischemic cardiomyopathy. In this study, 4 patients in the ICD group and 2 patients in the control group died during the first year, and 13 patients in the ICD group and 17 in the control group died after 5.5 ± 2.2 years follow-up (*P* value nonsignificant for all).

Data From AMIOVIRT

Amiodarone versus Implantable Cardioverter-Defibrillator: Randomized Trial in Patients with Nonischemic Dilated Cardiomyopathy and Asymptomatic Nonsustained Ventricular Tachycardia (AMIOVIRT) enrolled 103 patients with NCM and nonsustained ventricular tachycardia (NSVT).[7] All patients had LVEF <35% and were in NYHA functional classes I–III. After a mean follow-up period of 2.0 ± 1.3 years, the study was prematurely stopped secondary to the inability to demonstrate that ICD therapy is better than amiodarone in reducing mortality. Conversely, amiodarone was more cost effective (60% cost savings) and had a better arrhythmia-free survival rate at 3 years than ICDs (73% vs 63%, $P = 0.1$). During the follow-up, only 3.9% of the patients in the ICD group had syncope secondary to ventricular arrhythmia. Thirty-one percent of the patients with ICDs received an appropriate shock. The 1-year and 3-year survival rates of patients with ICD were 96% and 88%, respectively. Although 90% of the ICD patients were on ACE inhibitors, only 53% of the patients received β-blockers, and one-fifth received spironolactone. This study raises the question as to whether or not amiodarone therapy should be the initial choice before proceeding with ICDs in asymptomatic patients with NCM, especially in those with nonsustained ventricular tachycardia. Amiodarone treatment in NCM was previously associated with a trend toward reduced mortality.[8] Given the reports that shocks delivered by ICDs may possibly worsen heart failure, the further question is raised as to whether or not those NCM patients with relatively good prognosis should be first stratified by response to intensified drug therapy with or without amiodarone before device implantation.[5]

Data From DEFINITE

Patients in the Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation (DEFINITE) trial were in similar age, LVEF, and NYHA classes as patients in CAT and AMIOVIRT.[9] However, the study population (458 patients) was larger. All patients had NSVT (22%), frequent premature ventricular ectopy (9%), or both (68%). Twenty-four percent of the study patients had history of atrial fibrillation. Patients were treated optimally in their medical management strategy with β-blockers in 84% and ACE inhibitors in 86%. Amiodarone use was specifically discouraged, and only 5% of the study patients were on this drug. Spironolactone was also not used as a standard therapy. Mean follow-up was 29.0 ± 14.4 months. Annual mortality with this medication regimen was only 7%. Each arm included 229 patients; 28 patients in the ICD group and 40 patients in the medical treatment group died during the follow-up. Adding ICD therapy to the medical management was not statistically superior to the medical management alone in this study (hazard ratio [HR]: 0.65, 95% confidence interval [CI]: 0.40–1.06, $P = 0.08$). Although arrhythmic death was significantly reduced in the ICD group (HR: 0.2, $P = 0.006$), it should be recalled that the amiodarone use was negligible (6%) in the standard therapy group and that amiodarone produced better results than did ICDs in the AMIOVIRT trial. Eighteen percent of the patients received appropriate ICD shocks; 21% percent of the patients received inappropriate ICD shocks. This study also raises concerns about ICD implantation in NCM patients, because all-cause mortality benefit was not demonstrated, at least in patients who met the entry criteria for DEFINITE. Therefore, these investigators concluded that the routine implantation of an ICD cannot be recommended for all patients with NCM and severe left ventricular dysfunction.

Data From SCD-HeFT

The 3 trials discussed above did not provide definitive evidence that ICDs reduced mortality in patients with NCM. The Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) results changed the applicability of ICD treatment enormously and refined our understanding of its benefits in congestive heart failure.[10] SCD-HeFT enrolled both ischemic cardiomyopathy and NCM patients between 1997 and 2001. All patients were NYHA class II or III, and the LVEF was <35% before enrollment. Patients were randomized into placebo, amiodarone, or single-lead ICD groups. ICD testing was limited to no more than 2 inductions of ventricular fibrillation. Similar to CAT, approximately 16% of the patients had atrial fibrillation/flutter with no difference between groups. The total study population was

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2521 patients, and 48% had NCM. The baseline medications of the patients were similar (β-blockers 72% and ACE inhibitors 71% in the amiodarone group at the last follow-up). However, the ICD group was treated more frequently with β-blockers at the last follow-up than the amiodarone arm (87% vs 72%, $P < 0.001$). The median follow-up was 45.5 months. Amiodarone did not improve survival when compared with placebo; ICD therapy reduced the overall mortality by 23%. Subgroup analysis revealed that ICD therapy reduced the mortality rate compared with placebo in NCM patients, but this reduction was not statistically significant (HR: 0.73, 95% CI: 0.50–1.07, $P = 0.06$). Therefore, this study did provide more evidence about the possibility of limited benefit of ICD therapy in primary prevention in NCM patients compared with the patients with ischemic cardiomyopathy or in secondary prevention trials. The 2-year survival of NCM patients enrolled in SCD-HeFT was high, even better than the patients in the DEFINITE trial (90% vs 86%). The SCD-HeFT patients included 23% women, and the ICD benefit among women was less than among men.[11] The etiology of heart failure in the SCD-HeFT was more frequently nonischemic dilated cardiomyopathy (NCM) in women than in men (66% vs 43%). Therefore, the smaller ICD benefit in women in this trial might be explained by the higher prevalence of NCM, as the amount of fixed scar is less and the chance of reverse remodeling following heart failure treatment is higher than in ischemic cardiomyopathy. Therefore, these patients do well with medical therapy.

Data From COMPANION

One of the largest heart failure device trials, Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION), enrolled 1520 patients between 2000 and 2002.[12] These patients with advanced heart failure (NYHA class III or IV) and a QRS interval of >120 milliseconds were randomized to compare the efficacy of cardiac resynchronization therapy (CRT), with or without ICD, against medical therapy. The primary endpoint was all-cause mortality or hospitalization. The patient population was older (66 years in the CRT+ICD arm) than in the previous trials. Ninety percent of the patients were on an ACE inhibitor or angiotensin receptor blocker, and 68% of the patients were on β-blockers in the CRT+ICD group. Approximately half of the patients were on aldosterone receptor antagonists. Fifteen percent of the patients in the CRT+ICD arm received appropriate shocks. There was a significant mortality benefit with CRT and medical therapy compared with medical therapy alone (HR, 0.81, 95% CI: 0.69–0.96, $P = 0.014$). This benefit was slightly higher when ICD therapy was added to CRT (HR: 0.80, 95% CI: 0.68–0.95, $P = 0.01$), but the survival curves in the 2 device groups largely overlap. This trial included patients with heart failure from any cause and confirmed the benefit of CRT in advanced heart failure patients with prolonged QRS intervals.

Of the patients enrolled in the COMPANION trial, 682 had NDCM. Subgroup analysis revealed that patients with NCM had significant benefit from CRT+ICD compared with medical therapy. All-cause mortality was lower in the CRT+ICD group than in the pharmacologic therapy group (HR: 0.50, 95% CI: 0.29–0.88, $P = 0.015$), but at a cost of significantly increased number of moderate or severe adverse events from any cause (61% in the pharmacologic therapy group vs 69% in the CRT+ICD group, $P = 0.03$). Eight percent of patients with CRT+ICD had moderate or severe adverse events related to the implantation procedure (coronary venous dissection, perforation, or tamponade). Finally, how much of this mortality benefit results from resynchronization and how much results from lethal arrhythmia treatment is uncertain, because CRT alone clearly reduced mortality in this population.[2,12] Nevertheless, COMPANION provides evidence for the mortality reduction with ICDs in the NCM population, although its main study objective was to test CRT in patients with advanced heart failure and intraventricular conduction delay.

Data From Meta-analysis

These individual randomized controlled trials have not demonstrated a statistically significant benefit of prophylactic ICD implantation in NCM patients for primary prevention of sudden cardiac death. Desai and coworkers did a meta-analysis of the pooled data from the 5 primary-prevention trials (1854 NCM patients total).[13] Although a significant reduction in mortality was not achieved in the CAT, AMIOVIRT, DEFINITE, and SCD-HeFT trials, the meta-analysis of the 5 trials (including COMPANION) revealed a 31% reduction in all-cause mortality with ICD relative to medical therapy (relative risk [RR]: 0.69, 95% CI: 0.55–0.87, $P = 0.002$). Not surprisingly, exclusion of COMPANION attenuated the benefit of ICDs to some degree, but statistically significant benefit still persisted in ICD-treated NCM patients compared with the medical therapy group (RR: 0.74, 95% CI: 0.58–0.96, $P = 0.02$). Therefore, ICDs reduce all-cause mortality by 4% to 42%. Based on these results, the number of NCM patients needed to treat to prevent 1 death at 2 years was 25 (vs 18 in ischemic cardiomyopathy). Although this meta-analysis favors ICDs in patients with NCM, meta-analysis articles are always vulnerable to publication bias, especially when the number of studies included is limited.

Complications of ICD Treatment

ICD therapy has potential complications that may increase its total costs. CAT reported 10 complications among 50 patients with ICDs (7 incidences of electrode dislocation and sensing/isolation defects, 2 incidences of infection with total device replacement, and 1 perforation). Three

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(1.3%) patients in DEFINITE had acute implantation-related complications (hemothorax, pneumothorax, and cardiac tamponade), but none died. During follow-up the total complication rate was 4.4%, including lead dislodgements or fractures, venous thrombosis, and infection. Acute events were also significant in SCD-HeFT participants (2% declined to undergo ICD placement, implantation was unsuccessful in <1% of the patients, and significant ICD complications occurred in 5% at the time of implantation). In addition, 9% of the patients developed ICD complications later in the course of the trial. Similar complication rates were observed in COMPANION trial. Implantation was not successful in 9% of patients in the CRT+ICD group. Three (0.5%) deaths occurred in the CRT+ICD group; 5 (0.8%) additional patients died in the CRT group. Moderate or severe adverse events occurred in 8% of CRT+ICD group and 10% of the CRT group; these included coronary venous dissection, perforation, and tamponade. The recent report from the ICD registry indicates that the overall complication rate is 3.7%, and that 1.5% of these were classified as major.[4]

Cost Analysis of ICD Treatment

There is limited information on the cost-effectiveness of ICD therapy specific to the NCM population. Formal cost-effectiveness analysis is reported in the original publications of these trials only in AMIOVIRT (as a secondary endpoint). In this study there was no statistically significant difference between the amiodarone group and the ICD group in the total cost of medical care in the first year after entry into the study ($8879 \pm $27 614 in the amiodarone group vs $22 079 ± $22 039 in the ICD group, $P = 0.1$). A cost-effectiveness ratio is defined as the difference in the total cost of patients receiving an ICD and patients receiving alternative therapy divided by the additional life years of survival provided by an ICD compared with the alternative therapy.[14] Mark and coworkers investigated the long-term economic implications of the SCD-HeFT trial.[15] The lifetime cost-effectiveness ratio was calculated at $38 389 for ICDs relative to medical therapy alone per life year saved. They concluded that ICD therapy is economically "attractive" for NYHA class II patients but not for NYHA class III patients, as long as the benefits of ICD therapy persist for at least 8 years. However, because the data for ICD benefits at the 8-year follow-up are not available, the analysis will need revalidation in the future. Sanders and colleagues calculated the cost-effectiveness of the ICDs in the populations represented in 8 primary prevention trials (including SCD-HeFT, DEFINITE, and COMPANION).[16] Their analysis did not include CAT and AMIOVIRT. This study reported that the prophylactic implantation of an ICD had a cost-effectiveness ratio below $100 000 per quality-adjusted life years gained in populations with a significant device-related reduction in mortality, provided that the mortality benefit of the ICD lasts 7 years. Because long term follow-up results of these trials are not available, this conclusion has the same limitation as Mark's analysis.

Summary

The mortality benefit of ICDs in ischemic cardiomyopathy and in secondary prevention of sudden cardiac death has been well established. However, the benefit of ICD treatment for the primary prevention of death in NCM is still uncertain, as NCM patients have a better prognosis and a lower mortality rate than patients with ischemic cardiomyopathy (Table 1). The Marburg Cardiomyopathy Study revealed that a low LVEF and the lack of β-blocker use predicted arrhythmia in patients with NCM.[17] Other studies have demonstrated that ventricular arrhythmias are associated with myocardial scar tissue in NCM patients, and this is present in almost 50% of the patients with premature ventricular complexes or monomorphic ventricular tachycardia.[18] Aldosterone antagonists may reduce arrhythmic foci because of their potential to inhibit myocardial fibrosis and need more study in these patients. The addition of aldosterone antagonists is "recommended" in patients with symptoms of moderately severe to severe heart failure and reduced ejection fraction who can be carefully monitored for preserved renal function and normal potassium concentration.[19] In addition, better understanding of left ventricular dyssynchrony in heart failure and introducing CRT as an adjuvant therapy to pharmacologic treatment have improved survival significantly in these patients. It is clear that the clinical practice will always remain "suboptimal," as 100% therapy penetration cannot be realistically expected in this population, mainly due to side effects and drug intolerance. However, these results all indicate that medical management with ACE inhibitors and β-blockers with or without aldosterone antagonists reduces mortality in these patients and should be optimized as much as possible before ICD placement.

ICDs can have a negative effect on heart failure progression.[6] Shock therapy has been associated with worse outcomes in SCD-HeFT, though this may represent ascertainment bias wherein those with more advanced disease were more likely to suffer ICD discharges.[20] Saxon and coworkers analyzed the COMPANION trial and demonstrated that shock therapy increases the risk of hospitalization and death from sudden cardiac events.[21] In this study, appropriate shocks were reduced with the use of ACE inhibitors (HR: 0.44, 95% CI: 0.26–0.75, $P < 0.01$), β-blockers (HR: 0.63, 95% CI: 0.41–0.97, $P = 0.04$), and angiotensin receptor blockers (HR: 0.53, 95% CI: 0.28–0.99, $P = 0.05$). In addition, sudden cardiac death was significantly reduced when LVEF was >20% (HR: 0.55, 95% CI: 0.35–0.87, $P = 0.01$). Sudden cardiac death occurred twice as often in NYHA class IV patients compared with NYHA class III patients. These findings underscore the importance

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Table 1. Benefit of ICD Treatment for the Primary Prevention of Death in NCM

Randomized Controlled Trial	N	EF	NYHA	Baseline Heart Failure Drugs	Randomization Groups	Primary Outcome	All-Cause Mortality at 1 y	Grant Support
CAT	104	24	II–III	β-Blocker: 3%	ICD vs medical	All-cause mortality	ICD (8%)	Guidant
				ACE: 96%			Control (3.7%)	
				Spironolactone: NR				
AMIOVIRT	103	23	I–III	β-Blocker: 51%	ICD vs amiodarone	All-cause mortality	ICD (4%)	Guidant
				ACE: 85%			Amiodarone (10%)	
				Spironolactone:20%				
DEFINITE	458	21	I–III	β-Blocker: 84%	ICD vs medical	All-cause mortality	ICD (2.6%)	St. Jude Medical
				ACE: 96%			Control (6.2%)	
				Spironolactone:NR				
SCD-HeFT	792	25	II–III	β-Blocker: 69%	ICD vs amiodarone vs placebo	All-cause mortality	ICD (3%)	Medtronic, NHLBI, NIH, Wyeth-Ayerst, Knoll
				ACE: 96%			Control (3%)	
				Spironolactone 20%				
COMPANION	682	22	III–IV	β-Blocker: 67%	Medical vs CRT vs CRT+ICD	All-cause mortality or hospitalization	CRT+ICD (12%)	Guidant
				ACE: 89%			Control (19%)*	
				Spironolactone:55%				

Abbreviations: ACE, angiotensin-converting enzyme inhibitor; AMIOVIRT, Amiodarone versus Implantable Cardioverter-Defibrillator: Randomized Trial in Patients with Nonischemic Dilated Cardiomyopathy and Asymptomatic Nonsustained Ventricular Tachycardia; CAT, the Cardiomyopathy Trial; COMPANION, Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure; CRT, cardiac resynchronization therapy; CRT-ICD, cardiac resynchronization therapy with implantable cardioverter-defibrillator; DEFINITE, Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation; EF, left ventricular ejection fraction; n, number of patients; ICD, implantable cardioverter-defibrillator; NCM, idiopathic nonischemic cardiomyopathy; NHLBI, National Heart, Lung, and Blood Institute; NIH, National Institutes of Health; NR, not reported; NYHA, New York Heart Association class; SCD-HeFT, Sudden Cardiac Death in Heart Failure Trial; y, year.

[a] Data for ischemic and nonischemic cardiomyopathy.

of medical management with neurohormonal antagonists in the treatment of NCM patients.

Device therapy for ischemic and nonischemic cardiomyopathy represents a breakthrough in the management of heart failure, and ICD implantation is the mainstay of this treatment. None of the ICD therapy trials in patients with NCM have shown evidence of harm. Our literature review is subject to limitations and should not be interpreted as asserting that ICD treatment is "harmful" in the primary prevention of mortality in NCM. It is crucial to know that the initial randomized controlled trials, including CAT and AMIOVIRT, were underpowered to detect a clinically meaningful difference. The lack of treatment effect is difficult to interpret in the setting of an underpowered trial. This was also the case in the DEFINITE trial, where the overall mortality rate was lower than anticipated pretrial power calculations. Therefore, the results of the Desai meta-analysis might reflect the clinical equipoise of ICD studies. This is clearly a controversial area, and more longitudinal studies would clarify which patients benefit most with ICD treatment. In addition, in ICD trials complications are front-loaded and benefit often takes several years to appear. We should be using longer (eg, 5-year) interim ICD treatment outcome data to assess clinical benefit, even if the studies only ran for short times. Finally, the association of shocks and prognosis has always remained uncertain. It is very difficult to conclude whether or not the ICD shocks worsen the prognosis or simply reflect worse myocardium.

In summary, ICD implantation will be most cost-effective when used for patients at high risk for arrhythmic death and at low risk for nonarrhythmic causes of death.[22] NCM patients may represent a low arrhythmic death risk subgroup among all cardiomyopathy patients. Longitudinal studies of clinically relevant subgroups and risk stratification models for these patients are necessary to select appropriate patients for ICD implantation for optimal benefit. Although a causal relation is difficult to establish, there are reports demonstrating that ICD treatment with either appropriate or inappropriate shocks may increase heart failure progression.[6,20,23] Stable NCM patients with low arrhythmic death risk may be vulnerable to this effect of ICD treatment. Therefore, ICD treatment for primary prevention of mortality in patients with NCM who are free of symptomatic arrhythmia may either be unnecessary (compared with optimal medical management and possibly antiarrhythmic drugs) or could possibly be harmful. Primary prevention with these devices needs careful justification on a case-by-case basis in NCM patients, with particular attention to NYHA class, gender, and medical management.

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