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REVIEWS

Role of implantable cardioverter defibrillator in non-ischemic cardiomyopathy: a systematic review and meta-analysis of prospective randomized clinical trials

Jorge Romero[1] · Rahul Chaudhary[2] · Jalaj Garg[3] · Florentino Lupercio[1] · Neeraj Shah[3] · Rahul Gupta[4] · Talha Nazir[3] · Babak Bozorgnia[3] · Andrea Natale[1,5] · Luigi Di Biase[1,5]

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Abstract

Introduction A mortality benefit in patients with implantable cardioverter defibrillator (ICD) in ischemic cardiomyopathy is well established. However, the benefit of ICD implantation in non-ischemic cardiomyopathy (NICM) on total mortality remains uncertain. We performed a systematic review and meta-analysis of randomized controlled trials (RCT) evaluating the role of primary prevention ICD in NICM patients.

Methods We performed a systematic review on PubMed, The Cochrane Library, EMBASE, EBSCO, Web of Science, and CINAHL databases from the inception through February 2017 to identify RCT evaluating the role of ICD in NICM patients. Mantel-Haenszel risk ratio (RR) fixed effects model was used to summarize data across treatment arms. If heterogeneity (I^2) ≥25, random effects model was used instead.

Results We analyzed a total of 2573 patients from five RCTs comparing ICD with medical therapy in patients with NICM. The mean follow up for the trials was 48 ± 22 months. There was a significant reduction in (a) all-cause mortality (RR 0.84, 95% CI 0.71–0.99, $p = 0.03$) and (b) sudden cardiac death (RR 0.47, 95% CI 0.30–0.73, $p < 0.001$) in ICD group versus medical therapy.

Conclusion Our analysis demonstrates that the use of ICD for primary prevention is associated with a reduction in all-cause mortality and SCD in patients with NICM.

Keywords Implantable cardiac defibrillator · Sudden cardiac death · Non-ischemic cardiomyopathy

Abbreviations

ICD	Implantable cardioverter defibrillator
NICM	Non-ischemic cardiomyopathy
CI	Confidence interval
SCD	Sudden cardiac death
LVEF	Left ventricular ejection fraction
RCTs	Randomized controlled trials
SMD	Standard mean difference

1 Introduction

The survival benefit with primary prevention implantable cardioverter defibrillator (ICD) implantation is stronger for ischemic cardiomyopathy (ICM) patients [1] as compared to patients with non-ischemic cardiomyopathy (NICM). According to the current American College of Cardiology Foundation/American Heart Association and European Society of Cardiology guidelines for the management of heart

Jorge Romero, Rahul Chaudhary, and Jalaj Garg have contributed equally for the paper

✉ Jalaj Garg
garg.jalaj@yahoo.com

✉ Luigi Di Biase
dibbia@gmail.com

[1] Montefiore-Einstein Center for Heart and Vascular Care, Montefiore Medical Center, Albert Einstein College of Medicine, 111 East 210th Street, Bronx, NY 10467, USA

[2] Department of Medicine, Sinai Hospital of Baltimore, Johns Hopkins University, Baltimore, MD, USA

[3] Division of Cardiology, Lehigh Valley Health Network, 1250 S Cedar Crest Blvd, Allentown, PA 18103, USA

[4] Queens Cardiac Care, Queens Village, New York, NY, USA

[5] Texas Cardiac Arrhythmia Institute at St. David's Medical Center, Austin, TX, USA

failure, primary prevention ICD is considered a class IA recommendation for selected patients (both ischemic and non-ischemic) with heart failure and reduced left ventricular systolic function (LVEF) of ≤35% and New York Heart Failure (NYHA) class II or III symptoms on guideline-directed medical therapy, who have reasonable expectation of meaningful survival for more than 1 year [2, 3]. For NICM patients, this recommendation was based on the trend towards reduction in all-cause mortality observed in the sub-analysis of sudden cardiac death in heart failure trial (SCD-HeFT) and results of the meta-analysis by Desai et al. [2, 4]. Also, studies have shown that LVEF remain the most powerful predictor of sudden cardiac death (SCD) in heart failure patients. However, many patients with NICM who experience SCD do not have a severely reduced LVEF and, conversely, some patients are not at high risk for SCD despite having a depressed LVEF [5, 6]. Moreover, several patients who meet criteria for primary prevention ICD do not receive appropriate ICD shocks in their lifetime probably due to significant advances in heart failure medical therapy [7]. In addition, patients in SCD-HeFT trial were enrolled between 1997 and 2001.

No randomized controlled trial (RCT) has demonstrated a statistical significant mortality benefit with primary prevention ICD in NICM patients to date. Previously, two RCT [8, 9] demonstrated a trend towards mortality benefit in the subgroup analysis of NICM patients treated with primary prevention ICD versus medical therapy alone, but failed to achieve statistical significance. Additionally, two other small RCT [10, 11] failed to demonstrate any benefit over medical therapy plus antiarrhythmic drugs versus primary prevention ICD. Finally, the results from the recently published defibrillator implantation in patients with non-ischemic systolic heart failure (DANISH) trial [12] make the role of ICD in NICM even more controversial.

Given limited and conflicting evidence of benefit of primary prevention ICD in NICM patients, we performed a systematic review and meta-analysis of RCTs evaluating the role of primary prevention ICD in NICM patients.

2 Methods

The present meta-analysis was performed according to Cochrane Collaboration and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statements [13].

2.1 Search strategy

We performed a systematic review on PubMed, The Cochrane Library, EMBASE, EBSCO, Web of Science, and CINAHL databases from the inception through November 27, 2016 to identify trials evaluating use of ICD in patients with NICM. We combined the medical subject heading keywords including the following: non-ischemic cardiomyopathy or defibrillators or implantable or primary prevention ICD. The identified studies were systematically assessed using the inclusion and exclusion criteria described below.

2.2 Eligibility criteria

The eligibility criteria for our systematic review and meta-analysis included [1] human subjects with NICM, undergoing primary prevention ICD implantation and [2] reported clinical outcomes of all-cause mortality and/or SCD [3]. We included randomized trials comparing medical therapy to primary prevention implantation of an ICD without CRT capability, or which used CRT as a randomization stratification factor in order to avoid a differential impact of CRT across the device and medical therapy arms. In DANISH trial, subjects were randomized in a 1:1 ratio to receive an ICD or exclusively medical therapy. The randomization was stratified by whether the patient was scheduled to receive a CRT, which was intended to balance the impact of CRT between the two arms. Thus, DANISH met the inclusion criteria. The comparison of medical therapy, pacing and defibrillation in heart failure (COMPANION) trial, in contrast, randomized subjects to medical therapy, or cardiac resynchronization therapy with a pacemaker only (CRT-P) or with a pacemaker-defibrillator (CRT-D). Since CRT was not available in the medical therapy arm for COMPANION, the impact of the pacemaker cannot be isolated from the impact of the defibrillator. Thus, COMPANION did not meet the inclusion criteria. Retrospective studies, abstracts, case reports, conference presentations, editorials, reviews, and expert opinions were excluded from our analysis.

2.3 Data extractions and quality appraisal

Two investigators (RC and JG) independently screened all titles, abstracts and manually searched the full text versions of all relevant studies that fulfilled the inclusion criteria. References of the retrieved articles were independently reviewed for further identification of potentially relevant studies. Jadad score was independently calculated by two investigators (RC and JG). Any disparities between the two investigators were discussed with a third investigator (NJS) until consensus was reached. Final results were reviewed by senior investigators (AN and JR) (Fig. 1).

2.4 Outcomes

The outcomes for the study were “all-cause mortality” and “sudden cardiac death” at the longest follow-up period in patients with NICM.

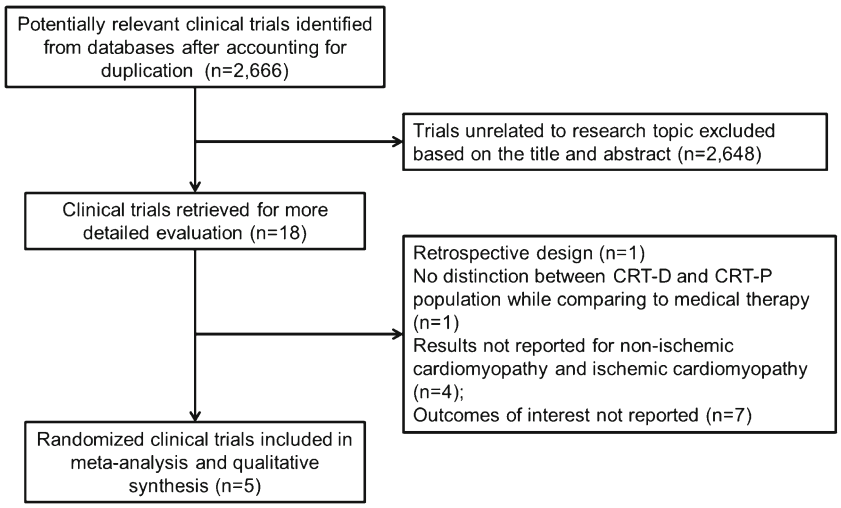

Fig. 1 Process of study selection for randomized and prospective trials (PRISMA statement). *CRT-D* cardiac resynchronization therapy-defibrillator, *CRT-P* cardiac resynchronization therapy with pacemaker

2.5 Statistical analysis

We conducted a meta-analysis of summary statistics from the individual trials because detailed, patient-level data were not available for all trials. Summary estimates and 95% CI were reported for continuous variables as difference in means (DM). Mantel-Haenszel risk ratio (RR) fixed effects model was used to summarize data across treatment arms. We evaluated heterogeneity of effects using the Higgins I-squared (I^2) statistic [14]. In cases of heterogeneity (defined as $I^2 > 25\%$), random effects models of DerSimonian and Laird [15] were used, otherwise analyses were performed by fixed effect models. Publication bias was estimated visually by funnel plots [16, 17]. If any bias was observed, further bias quantification was measured using the Begg-Mazumdar test [18], and Egger test [16]. Sensitivity analyses were performed to assess the contribution of each study to the pooled estimate by excluding individual trials one at a time and recalculating the pooled RR estimates for the remaining studies. All analyses were conducted using Comprehensive Meta-Analysis 2.0 software (Biostat, Inc., Englewood, NJ).

3 Results

A total of 2666 studies were identified after exclusion of duplicate or irrelevant references (Fig. 1). After a detailed evaluation of these studies, five relevant studies were included that incorporated a total of 2573 participants [8–12]. Although COMPANION trial evaluated the use of cardiac resynchronization therapy (CRT) with or without ICD in patients with advanced heart failure, the trial was not included in our analysis as data comparing CRT-defibrillator (CRT-D) versus CRT-pacemaker (CRT-P) were not available [19. Moreover, it was not statistically feasible to compare the CRT-D group vs. the medical therapy group since it would be impossible to know if patients in the CRT-D group had better survival due to either defibrillator or due primarily to CRT. The characteristics of these trials, mean follow-up periods, and patient characteristics are described in Tables 1 and 2.

3.1 Quality assessment and publication bias

The most notable difference between the trials was the severity of illness in the enrolled patients. The amiodarone versus implantable cardioverter-defibrillator: randomized trial (AMIOVIRT), defibrillators in non-ischemic cardiomyopathy treatment evaluation (DEFINITE), and SCD-HeFT trials enrolled comparable number of patients with NYHA class III or IV heart failure of at least 3-year duration. In contrast, the cardiomyopathy trial (CAT) and DANISH trials enrolled patients with NYHA class II or III heart failure of short duration (less than 3 years). Despite the differences in design of these five primary prevention trials, a sufficient similarity between the included populations and the testing hypothesis merited their inclusion in the quantitative meta-analysis.

Overall, there were clear definitions of the study population, outcomes, and assessment in most component studies, but blinded assessment of outcomes was not reported in all studies resulting in potential bias. Jadad score was calculated for all RCTs with a mean Jadad score of 3 indicating that the studies involved were of high quality (Table 1).

Funnel plots did not reveal publication bias for comparison of all-cause mortality and sudden cardiac death between ICD group as compared to medical therapy group (Figs. 2 and 3). Likewise, other methods such as Begg-Mazumdar test and Egger test, did not suggest the presence of publication bias (Table 3).

Table 1 Characteristics of the included studies

Name of study	CAT trial (10)	AMIOVIRT[a] (11)	DEFINITE (9)	SCD-HeFT (8)	DANISH[b] (12)
Year of publication	2002	2003	2004	2005	2016
Type of trial	RCT	RCT	RCT	RCT	RCT
ICD/medical therapy group, *n*	50/54	51/52	229/229	Total=1676; 792 (47.3%) with NICM	556/560
Follow-up duration (median, months)	66	24	24	45.5	66
Patients with CRT-D (%)	N/A	No	No	No	58
Total complications	10	N/A	9	N/A	27
Breakdown of complications	7 electrode dislodgements + 2 device infections + 1 perforation	N/A	6 electrode dislodgements + 1 device infection + 1 venous thrombosis and 1 perforation	N/A	27 device infections
Shocks received (appropriate/inappropriate, no. of pts)	11/NA	N/A	41/49	N/A	64/33
Jadad score	3	1	3	5	3

CAT the cardiomyopathy trial, *AMIOVIRT* amiodarone versus implantable cardioverter-defibrillator: randomized trial in patients with non-ischemic dilated cardiomyopathy and asymptomatic non-sustained ventricular tachycardia, *DEFINITE* defibrillators in non-ischemic cardiomyopathy treatment evaluation, *SCD-HeFT* sudden cardiac death in heart failure trial, *DANISH* defibrillator implantation in patients with non-ischemic systolic heart failure, *NICM* non-ischemic cardiomyopathy, *RCT* randomized controlled trial

[a] AMIOVIRT trial compared amiodarone as a part of medical therapy with ICD

[b] DANISH study included patients receiving cardiac resynchronization therapy (CRT) with 322 and 323 in ICD and medical therapy groups, respectively

3.2 Baseline characteristics

In the participant studies, the mean follow-up period was 48 ± 22 months. There were no significant differences between the two groups in terms of age, gender, New York Heart Failure (NYHA) class II and III, diabetes, use of beta-blockers, angiotensin converting enzyme inhibitors, or angiotensin receptor blockers. There was a higher number of patients with NYHA class I heart failure in the ICD group versus medical therapy group (30 versus 21%, respectively, $p = 0.02$) (Table 2).

3.3 Assessment of all-cause mortality

There was a statistical significant reduction of all-cause mortality in the ICD group as compared to medical therapy group (RR 0.84, 95% CI 0.71–0.99, $p = 0.03$) (Fig. 2). The relative and the absolute reduction in total mortality obtained by implanting ICD for primary prevention in NICM was 16 and 3.8%, respectively. No significant heterogeneity was observed between trials.

3.4 Assessment of sudden cardiac death

A significant reduction in SCD was also observed with the use of ICD in patients with NICM (RR 0.47, 95% CI 0.30–0.73, $p < 0.001$) (Fig. 3). No significant heterogeneity was observed between trials.

4 Discussion

To our knowledge, this is the largest meta-analysis of RCTs evaluating the role of primary prevention ICD in NICM patients compared to medical therapy. The main findings in our study was (1) significant reduction in all-cause mortality and sudden cardiac death with primary prevention ICD versus medical therapy in patients with NICM. The results from the primary prevention trials are convincing, with data from 2573 NICM patients from five RCTs demonstrating a 16% reduction in all-cause mortality with primary prevention ICD therapy versus medical therapy alone despite negative results from individual primary prevention trials. Although results of our study corroborate with the prior meta-analysis by Desai et al., yet their study demonstrated higher mortality reduction benefit of primary prevention ICD implantation for NICM than our current meta-analysis (31% vs. 16%, respectively) [4]. NICM patients constitute one-third of heart failure patients with 5-year mortality as high as 20% and SCD accounting for 30% (8 to 50%) deaths [20–22]. Approximately, 154,659 ICDs were implanted between the years 2005–2010 according to National Cardiovascular Data Registry [23], on the basis of trends towards all-cause mortality reduction observed in the sub-analysis of SCD-HeFT trial and meta-

Table 2 Baseline demographics of study population

Baseline characteristics	ICD	Medical therapy	Number	Studies (*n*)	*p* value
Age (year)	58.5	58.7	207	2	0.53
Males (%)	74	72	1781	4	0.49
Heat failure, NYHA I (%)	30%	21%	561	2	*0.02*
Heat failure, NYHA II (%)	60%	61%	1781	4	0.48
Heat failure, NYHA III (%)	33%	37%	1781	4	0.86
Diabetes (%)	24%	27%	1677	3	0.33
On beta-blockers (%)	59%	58%	1781	4	0.97
On ACEI (%)	91%	91%	1781	4	0.23
On ARBs (%)	31%	28%	1677	3	0.28

ICD implantable cardioverter-defibrillator, *NYHA* New York Heart Association, *ACEI* angiotensin converting enzyme inhibitor, *ARBs* angiotensin II receptor blockers

analysis by Desai et al. [2, 24]. However, none of the primary prevention trials have demonstrated a significant benefit of ICD over medical therapy for all-cause mortality in patients with NICM, likely due to lower than predicted medical group mortality and probably because these trials have been underpowered to show a statistical difference. Hence, it is possible that individual trials are un underrepresentation of real-world NICM patients. The cardiomyopathy trial (CAT) and amiodarone versus implantable cardioverter-defibrillator: randomized trial (AMIOVIRT) trials were underpowered to detect a difference between ICD and medical therapy. In addition, with inclusion of recently published DANISH trial that enrolled relatively stable heart failure (NYHA II or III) patients on goal directed medical therapy (>90% medication compliance with beta-blocker and angiotensin converting enzyme inhibitor) as compared to AMIOVIRT, DEFINITE, and SCD-HeFT trials (NYHA III or IV), could possibly account for attenuated mortality benefit with primary prevention ICD as compared to the prior meta-analysis. In addition, we did not include the results of COMPANION trial in our analysis as compared to prior meta-analysis as data-comparing CRT-D versus CRT-P was not available [19]. Importantly, prior meta-analyses [4, 25] have included the COMPANION trial, which showed a stronger effect than all other studies assessing the benefit of ICD in NICM patients. The relative reduction in all-cause mortality in the COMPANION trial was 50% while in all the other studies it was not greater than 30%. Since the data extracted from the COMPANION trial in prior meta-analyses are from the group treated with medical therapy vs. the group who received ICD and CRT, these meta-analyses may have overstated the benefit of ICDs in this patient population due to the simultaneous benefit obtained by biventricular pacing in heart failure patients, particularly in NICM. Also, studies have also demonstrated unclear mortality benefit in patients who are eligible for CRT to receive defibrillator additionally [25, 26].

Ventricular arrhythmias, both symptomatic and asymptomatic are common in patients with NICM. Non-sustained VT can be observed in 30–50% of the patients, with a significant decrease on goal directed optimal medical therapy [27]. The relationship between SCD and ICD remains controversial in NICM patients. Our analysis demonstrated a significant reduction in SCD of 53% with primary prevention ICD in NICM patients versus medical therapy alone. It is conceivable to speculate that ICD indeed protect patients from dying from ventricular arrhythmias in the short term but given the fact that only a limited percentage of these patients undergo radiofrequency ablation for ventricular tachycardia and more importantly because of the modest success rate of ablative procedure in NICM, these patients will eventually pass away from repetitive ICD shocks or advanced heart failure. In fact, studies have shown that increased ICD shocks (both appropriate and inappropriate) are associated with increased myocardial damage and hence increased mortality [28, 29]. Increasing myocardial damage and subsequent scar formation may form a substrate for episodes of recurrent ventricular tachycardia

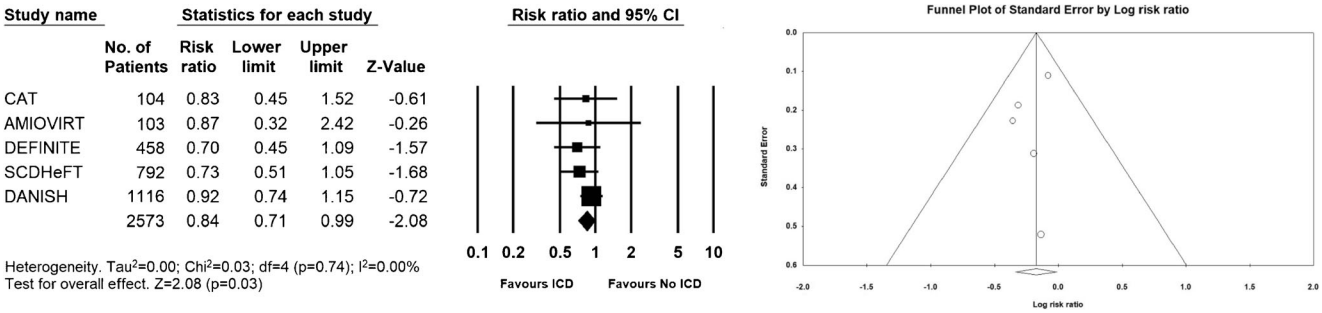

Fig. 2 Forest plot demonstrating all-cause mortality in patients with NICM undergoing ICD implantation versus medical therapy

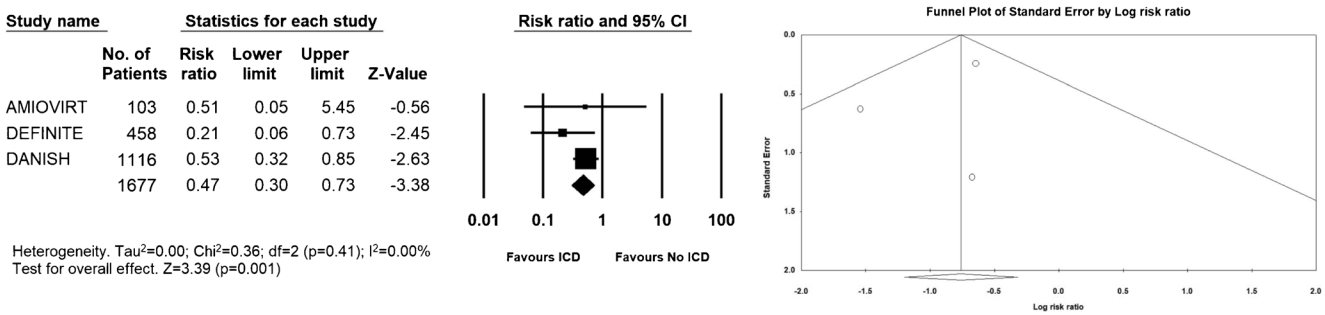

Fig. 3 Forest plot demonstrating sudden cardiac death in patients with NICM undergoing ICD implantation versus medical therapy

(VT). A recurrent VT itself may change the electrophysiological properties of the myocardium, predisposing to new VT reentry circuits in the tissue thus forming a vicious cycle [30]. Hence, changes in device programming parameters, i.e., high rate zone (therapy delivered for heart rate >199 beats per minute) and delay therapy zone (heart rate >169 beats per minute with longer tachyarrhythmia monitoring), as studied in MADIT RIT trial, might help in the reduction of inappropriate ICD shock and all-cause mortality as compared to conventional programming parameters (heart rate >169 beats per minute) [31]. Hence, we think that although in our study, primary prevention ICDs are associated with reduction in SCD, patients who suffer from initial ventricular arrhythmias are at increased risk of subsequent ventricular arrhythmias, and might benefit from early VT ablation [32, 33]. Catheter ablation for VT has emerged as an important therapeutic intervention to control VT and reduce recurrent episodes of sustained VT, and with endocardial and/or epicardial VT ablation patients might have a complete different clinical course. Several studies have shown that non-inducibility of VT after catheter ablation is an independent predictor of long-term VT-free survival and reduced mortality [34, 35]. In a recent meta-analysis, combined endo–epicardial ablation was significantly associated with reduced of VT recurrence compared to endocardial ablation alone (OR = 2.02, 95% CI 1.19–3.44), suggesting that a combined endo–epicardial ablation strategy might be necessary to improve the long-term outcome in NICM patients with recurrent VT [36]. Therefore, electrophysiologists should have a lower threshold to perform catheter ablation for VT once the patient has experienced ICD shock or anti tachycardia pacing.

Furthermore, data from real-world studies have shown that the compliance with beta-blockers is approximately 85% mainly due to side effects or drug intolerance [3]. In our pooled analysis, the compliance with beta-blockers was approximately 59%, which could have been one of the reasons for observed significant reduction in SCD with the use of primary prevention ICD in NICM patients.

It is important to notice that in clinical practice, once coronary artery disease has been ruled out as the cause of cardiomyopathy and patients are "labeled" with the term NICM, the etiology of heart failure in those patients is rarely found. Efforts must be made to find a specific diagnosis of the cardiomyopathy since there are several reversible and/or treatable causes of NICM such as PVC or tachycardia-induced cardiomyopathy, high hyperthyroidism, anemia, alcohol- and cocaine-induced cardiomyopathy, cardiac sarcoidosis, and amyloidosis among others.

Risk stratification in NICM patients therefore constitutes a crucial part in patient management. Currently, LVEF remains the most powerful predictor for prevention of SCD in heart failure patients. However, it lacks sensitivity for prediction of SCD. Even a low LVEF (<20%) may not have high positive predictive value for SCD. In fact, patients with LVEF >30% and risk factors (NYHA functional class, non-sustained VT, age, LV conduction abnormalities, atrial fibrillation) are at increased mortality risk as compared to patients with LVEF <30% and no risk factors [37]. Several other factors have been recognized for risk stratification that includes a history of unexplained syncope [38, 39], abnormal signal averaged ECG [40], fragmented QRS [41], QRS-T angle, T-wave alternans [42], and myocardial scintigraphy [43]. Additionally, there has been recent literature supporting use of cardiac MRI [44, 45] to detect and quantify the extent of myocardial fibrosis. Studies have shown the late gadolinium enhancement in NICM patients is the strongest independent predictor of ventricular arrhythmias (independent of LVEF) [46, 47]. Thus, it is also possible that increased prevalence of these unaccounted prognostic markers in our pooled analysis could have accounted reduction in SCD with primary prevention ICD. However, it is also evident that studies looking at the relationship between SCD and primary prevention ICD in NICM patients are limited, and with small sample sizes.

Since no single marker individually presents with high positive and negative predictive value for risk stratification, combination of different test should be employed. Combination of numerous risk markers for risk stratification in systolic heart failure patients has been studied in the past [48]. Given relatively low event rates in this selected cardiomyopathy patients, high costs, device-related complications, and inappropriate shocks [49, 50] demand a risk stratification score with better patient selection who are at increased mortality risk and would benefit from ICD the most.

Table 3 Summary of Egger and Begg's Mazumdar test for publication bias

	Egger test *p* value	Begg's Mazumdar test *p* value
All-cause mortality	0.25	1.00
Sudden cardiac death	1.00	0.63

P value of <0.05 indicates publication bias

4.1 Study limitations

This systematic review and meta-analysis has several important limitations that should be acknowledged. First, there was a lack of uniformity in the participant trials for optimization of study participants on goal directed medical therapy (with ACE inhibitors and beta-blockers). Second, the overall results could have been driven from the data from CAT trial, DEFINITE trial and SCD-HeFT as observed with sensitivity analysis (Table 3). Also, we included clinical trials that enrolled patients during a period of rapid evolution in the efficacy of medical therapy in improving survival among patients with NICM. With varying compliance rates to medical therapy between trials, this may have led to overestimate the benefit of ICD therapy.

5 Conclusion

ICD implantation for primary prevention in NICM patients was associated with reduction in all-cause mortality and SCD in our meta-analysis.

Compliance with ethical standards

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Conflict of interest The authors declare that they have no conflicts of interest.

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