Received: 2 October 2017 | Accepted: 4 November 2017

DOI: 10.1002/joa3.12017

REVIEW ARTICLE

WILEY Journal of Arrhythmia Open Access

Implantable cardioverter defibrillator in nonischemic cardiomyopathy: A systematic review and meta-analysis

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Abstract

The evidence to support implantable cardioverter defibrillator (ICD) in subjects with nonischemic cardiomyopathy (NICM) for primary prevention of sudden cardiac death (SCD) is not robust. This meta-analysis intends to assess the impact of routine ICD implantation for primary prevention of mortality due to SCD in NICM based on all the published randomized clinical trials (RCTs). Six RCTs were selected using PubMed/Medline, EMBASE, and CENTRAL from inception to December 2016. Outcomes were calculated as random-effects relative risk (RR) and risk difference (RD) with 95% confidence interval (CI). Patients were randomized to ICD arm and control arm (usual care, medical treatment, and anti-arrhythmic drugs). ICD significantly reduced all-cause mortality in NICM patients (RR, 0.74, 95% CI, 0.56-0.97, $P = .03$, $I^2 = 40$). Mortality benefit was achieved due to a significant reduction in sudden cardiac death (SCD) (RR, 0.47, 95% CI, 0.30-0.73, $P < .001$, $I^2 = 0$). There were no statistical differences between two groups with regard to risk of noncardiac mortality, non-SCD, cardiac arrest, cardiac transplant, sustained ventricular tachycardia (VT), and VT requiring medical treatment. Our results support efficacy of ICDs at reducing all-cause mortality due to a reduction in SCD.

KEYWORDS

implantable cardioverter defibrillator, meta-analysis, mortality, nonischemic cardiomyopathy, sudden cardiac death

1 | INTRODUCTION

Sudden cardiac death (SCD) is one of the most common causes of death in general population and accounts for approximately 30% of mortality in patients with nonischemic cardiomyopathy (NICM).[1,2] Implantable cardioverter-defibrillator (ICD) implantation is class I indication for the primary prevention of SCD in patients with heart failure [New York Heart Association (NYHA) class II & III] and reduced left ventricular ejection fraction (LVEF) due to NICM.[3] These guidelines are mainly based on meta-analysis showing a significant reduction in all-cause mortality with ICD (relative risk (RR), 0.69, 95% confidence interval (CI), 0.55-0.87, $P = .02$).[4] The positive results in this meta-analysis were mainly driven by the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) and the Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) Trial.[5,6] However, conflicting data have emerged in the recent times that challenge the role of ICD in NICM. Danish Study to Assess the Efficacy of ICDs in Patients with Nonischemic Systolic Heart Failure (DANISH) trial showed a reduction in SCD by about 50% but no effect on long-term mortality in patients receiving ICD compared to usual care.[7]

Recent meta-analysis on this topic had excluded trials of cardiac resynchronization therapy (CRT) and those that used anti-arrhythmic therapy as control arm.[8] Furthermore, important endpoints such as cardiac mortality, noncardiac mortality, SCD, non-SCD, cardiac arrest, cardiac transplant, sustained ventricular tachycardia (VT), and VT requiring medical treatment remained unassessed. Consequently, to better comprehend the role of ICD in NICM, we conducted a meta-analysis of all the RCTs to investigate the effects of ICD in NICM.

2 | METHODS

2.1 | Data sources and searches

Two authors (MUK and FN) independently searched MEDLINE, EMBASE, and the Cochrane Library from inception to December 2016. The search terms used were as follows: "Implantable Cardioverter Defibrillator" OR "Internal Cardiac Defibrillator" OR "ICD", "AICD" OR "sudden cardiac death" OR "SCD", OR "mortality" OR "Cardiac Mortality" AND "Non-Ischemic Cardiomyopathy" OR "NICM." Duplicates were removed manually by hand and through EndNote ×7 (Philadelphia, PA, USA).

2.2 | Study selection

Studies had to meet following inclusion criteria: (i) Only primary prevention RCTs where patients were randomized to either ICD group or control group (usual care, medical treatment, or amiodarone) and reporting outcomes of interest were selected. (ii) Full-text articles were included, and abstracts were not considered for final analysis. The initial search yielded 381 articles, and after diligent screening, 6 RCTs were included. Meta-analysis was carried out according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses. The study selection process is illustrated in Figure 1.

2.3 | Quality assessment and data extraction

Data extraction was carried out independently by two authors (ST and HR) using Microsoft EXCEL spreadsheets incorporating baseline characteristics, crude point estimates, events, and sample size. Estimates from intention to treat analysis were preferred. Data were appraised by SUK and MUK, and discrepancies were resolved by mutual consensus or by third-party review. Risk of bias assessment was performed at the study level, and methodological quality assessment was performed using the Cochrane bias risk assessment tool (Table S1).[9]

2.4 | Outcome measures

The primary focus was all-cause mortality. The secondary endpoints were cardiac mortality, noncardiac mortality, SCD, non-SCD, cardiac arrest, cardiac transplant, sustained ventricular tachycardia (VT), and VT requiring medical treatment.

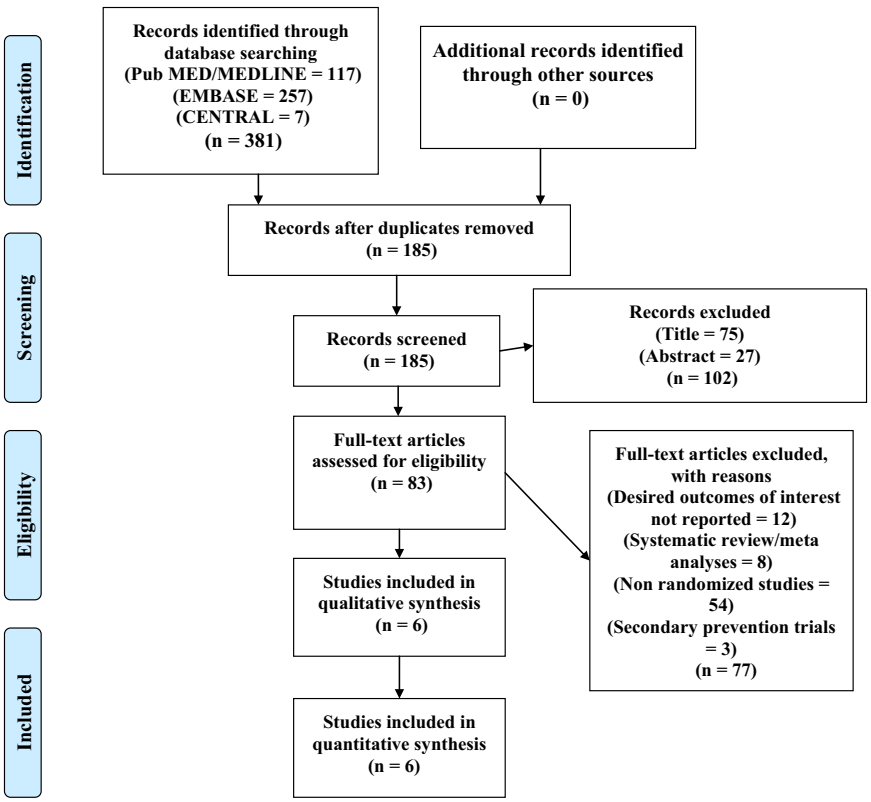

FIGURE 1 Search strategy: Study selection process through Preferred Reporting Items for Systematic Reviews and Meta-analyses

2.5 | Statistical analysis

Outcomes from all the studies were combined using the generic invariance method, and both fixed- and random-effects models were generated. Random-effects model was used for the final reporting of the estimates. Outcomes were expressed as RR and risk difference (RD) with corresponding 95% CI. As both the RR and RD represent the same data, we provide forest plots for RR estimates only. A *P* value of .05 was set as significant. Heterogeneity was assessed using Q statistics with I^2 with values >25, >50%, and >75% consistent with a mild, moderate, and severe heterogeneity, respectively.[10]

Publication bias was assessed using Funnel plot and Eggers regression test. Comprehensive Meta-analysis software version 2.2 (Biostat, Englewood, NJ, USA) was used for all the analyses.

3 | RESULTS

In six RCTs (n = 5, 822), 2, 332 patients were randomized to the ICD group and 3490 patients to the control arm. The mean age of study participants was 60 years, 72% were male, 50% had hypertension, and 30% had diabetes mellitus. Mean LVEF was 23%, about 62% were in NYHA class II, and 39% were in class III. Baseline characteristics of the participants are reported in Table 1. RD estimates with corresponding numbers needed to treat (NNT) or harm (NNH) are provided in Table 2.

ICD significantly reduced all-cause mortality in NICM patients (RR, 0.74, 95% CI, 0.56-0.97, $P = .03$, $I^2 = 40$; Figure 2). Five RCTs reported outcomes for cardiac mortality, three trials for noncardiac mortality, three trials for SCD, and four trials for non-SCD. Estimates for cardiac arrest, cardiac transplant, and sustained VT were pooled from two RCTs each, while three studies provided outcomes for VT requiring medical treatment. ICD significantly reduced the risk of SCD (RR, 0.47, 95% CI, 0.30-0.73, $P < .001$, $I^2 = 0$). Noncardiac mortality and non-SCD were not affected by ICD (Figure 2). There was no statistical difference between two groups with regard to risk of cardiac arrest, cardiac transplant, sustained VT, and VT requiring medical treatment (Figures 2 and 3). Funnel plot and Eggers regression test could not highlight publication bias ($P = .44$; Figure 4).

TABLE 1 Baseline characteristics of the patient

	CAT [12]	AMIOVIRT [13]	DEFINITE [14]	SCD-HeFT [5]	COMPANION [6]	DANISH [7]
Mean follow-up duration (months)	66	29	26	45.5	Range 14.8-16.5 months	67.6
Location	Germany	USA	USA	USA, Australia, and New Zealand	USA	Denmark
Control	MT	AMIO	MT	MT/MT +AMIO	MT/MT+ CRT	MT
Participants	104	103	458	792	397	1116
Participants with NICM No. (%)	104 (100)	103 (100)	458 (100)	1210 (48)	397 (44)	1116 (100)

Patients (n)	ICD (50)	Control (54)	ICD (51)	Control (52)	ICD (229)	Control (229)	ICD (829)	Control (845/847)	ICD (617)	Control (308/595)	ICD (556)	Control (560)
Age-mean (years)	52	52	58	60	58	58	60.1	60.4/59.7	67	68/66	64	63
Male sex (%)	86	74	67	74	72	69	77	76/77	67	69/67	73	72
BMI—mean (Kg/m2)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	26.8	26.8
White (%)	NR	NR	NR	NR	67	67	77	77/76	NR	NR	NR	NR
Others (%)	NR	NR	NR	NR	33	33	33	33/34	NR	NR	NR	NR
NYHA class II	66.7	64.1	64	63	54.2	60.7	70	70	NR	NR	53	54
NYHA class III	34.6	33.3	16	24	20.5	21.4	30	30	87	82/86	45	45
LVEF (%)	24	24	22	23	20.9	21.8	24	25/25	20	22/22	25	25
Left bundle branch block (%)	84.6	81.8	42	53	19	19	NR	NR	69	70/73	NR	NR
Right bundle branch block (%)	7.7	0	16	8	3.5	3.1	NR	NR	12	9/10	NR	NR
Diabetes mellitus (%)	NR	NR	31	36	22.7	23.1	31	29/32	39	45/41	18	20
Hypertension (%)	NR	NR	58	67	NR	NR	55	56/56	NR	NR	33	30
Atrial fibrillation (%)	NR	NR	NR	NR	22.7	26.2	17	16/14	NR	NR	24	20
Beta blocker (%)	3.8	4.0	53	50	85.6	84.3	69	69/69	68	66/68	92	92
ACE inhibitors (%)	94	98.1	90	81	83.8	87.3	83	87/85	70	69/69	96	97
Mineralocorticoid receptor blocker (%)	NR	NR	20	19	NR	NR	20	21/19	53	55/55	59	57
Renal insufficiency (%)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR

AMIO, Amiodarone; AMIOVIRT, Amiodarone vs Implantable Cardioverter-Defibrillator Randomized Trial; CAT, Cardiomyopathy Trial; CRT, cardiac resynchronization therapy; COMPANION, Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure Trial; DEFINITE, Defibrillators in Nonischemic Cardiomyopathy Treatment Evaluation Trial; DANISH, Danish Study to Assess the Efficacy of ICDs in Patients with Nonischemic Systolic Heart Failure trial; LVEF, left ventricular ejection fraction; ICD, implantable cardioverter defibrillator; MT, medical therapy; NR, Not reported; NYHA, New York Heart Association; NICM, nonischemic cardiomyopathy; SCD-HeFT, Sudden Cardiac Death in Heart Failure Trial.

TABLE 2 Absolute risk difference with the corresponding number needed to treat (NNT) or harm (NNH)

Outcome	Absolute Difference (95% CI)	NNT	NNH	*P*- Value
All-cause mortality	−0.024 (−0.061, 0.014)	41	–	.22
Cardiac mortality	−0.000 (−0.004, 0.003)	–	–	.81
Noncardiac mortality	0.000 (−0.002, 0.002)	–	–	.98
Sudden cardiac death	−0.002 (−0.008, 0.003)	500	–	.36
Non-sudden cardiac death	0.000 (−0.002, 0.002)	–	–	.97
Cardiac arrest	−0.001 (−0.009, 0.006)	1000	–	.69
Need for cardiac transplant	0.001 (−0.045, 0.047)	–	1000	.96
Sustained ventricular tachycardia	−0.000 (−0.002, 0.001)	–	–	.98
Ventricular tachycardia requiring medical treatment	0.000 (−0.001, 0.002)	–	–	.98

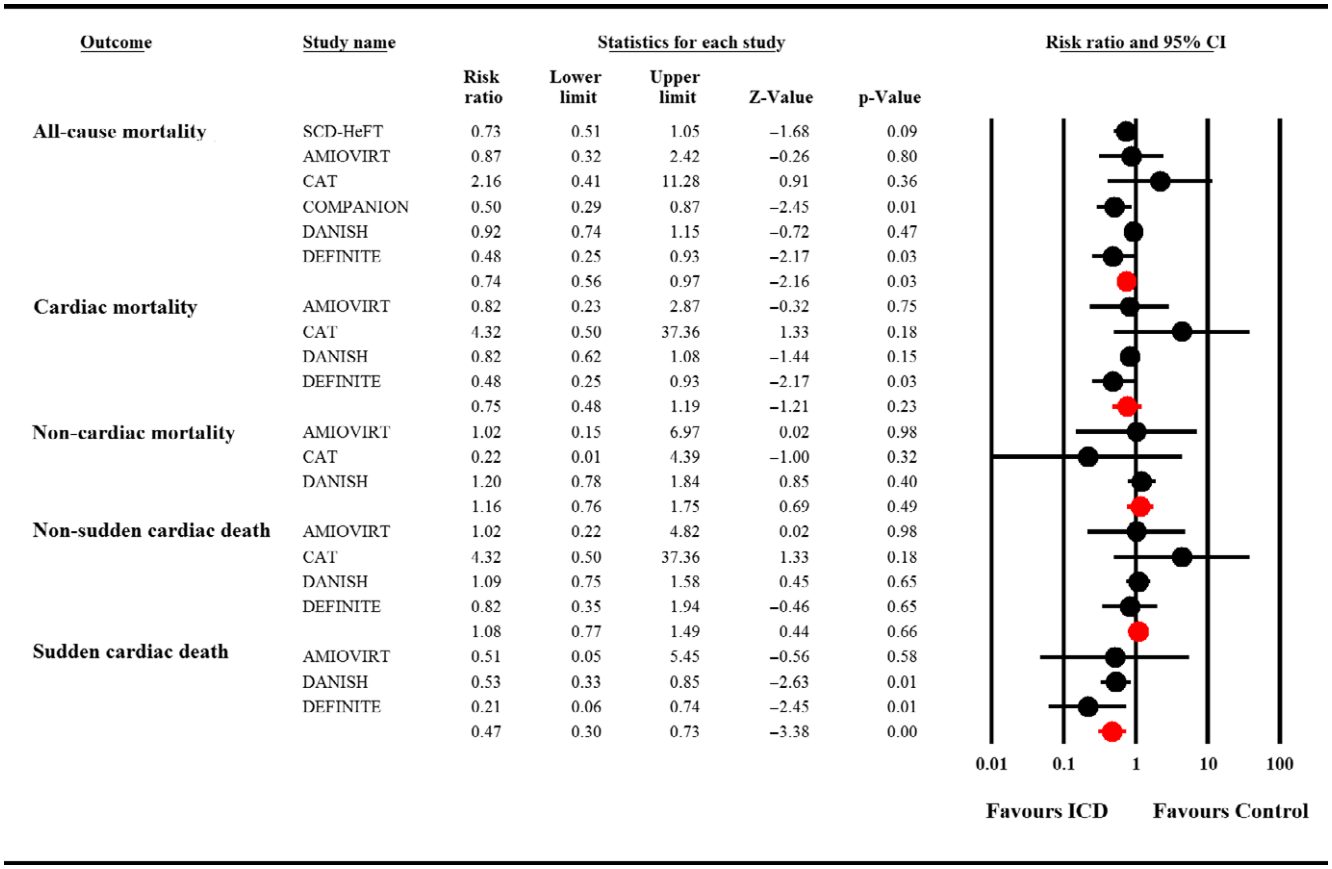

FIGURE 2 Forest plot showing effects of primary prevention implantable cardioverter defibrillator vs control on mortality

4 | DISCUSSION

The medical community should continue to engage in efforts to delineate which of the NICM patients will benefit the most and harmed minimally by this costly life-saving therapy. At the same time, we are obligated to continue tracking how frequently appropriate and inappropriate electrical therapy is delivered in the era of quality heart failure medical therapy and what is the frequency and impact of ICD-related complications.

Our results showed that in patients with NICM, ICD significantly reduced all-cause mortality due to a reduction in SCD. ICD had no protective role in noncardiac mortality, non-SCD, cardiac arrest, cardiac transplant, sustained VT, and VT requiring medical treatment. These outcomes are identical to prior published meta-analyses. Desai et al performed meta-analysis prior to publication of DANISH and noticed a significant reduction in all-cause mortality.[4,7] Luni et al[11] showed consistent favorable outcomes with primary prevention ICD (odds ratio (OR), 0.86, 95% CI, 0.64-0.91, $P = .002$, $I^2=0$). The more recent meta-analysis by Al-Khatib et al[8] excluded studies with antiarrhythmic control arm and showed 25% improvement in survival (Hazard ratio (HR), 0.75, 95% CI, 0.61-0.93, $P = .008$). Compared to these meta-analyses, our study is more comprehensive and

Outcome	Study name	Risk ratio	Lower limit	Upper limit	Z-Value	p-Value
Cardiac arrest	AMIOVIRT	0.20	0.01	4.14	−1.03	0.30
	DANISH	0.79	0.36	1.73	−0.59	0.56
		0.73	0.34	1.55	−0.83	0.41
Cardiac transplant	CAT	2.16	0.20	23.09	0.64	0.52
	AMIOVIRT	0.51	0.05	5.45	−0.56	0.58
		1.05	0.20	5.60	0.06	0.96
Sustained VT	AMIOVIRT	0.20	0.01	4.14	−1.03	0.30
	DANISH	1.05	0.61	1.79	0.17	0.87
		0.93	0.40	2.14	−0.17	0.86
VT requiring medical treatment	CAT	0.22	0.01	4.39	−1.00	0.32
	AMIOVIRT	3.06	0.13	73.36	0.69	0.49
	DANISH	1.15	0.57	2.34	0.39	0.70
		1.11	0.56	2.17	0.29	0.77

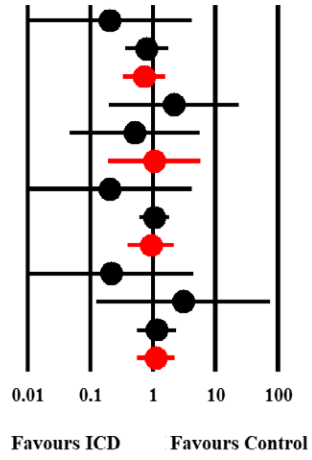

FIGURE 3 Forest plot showing effects of implantable cardioverter defibrillator on nonmortality outcomes

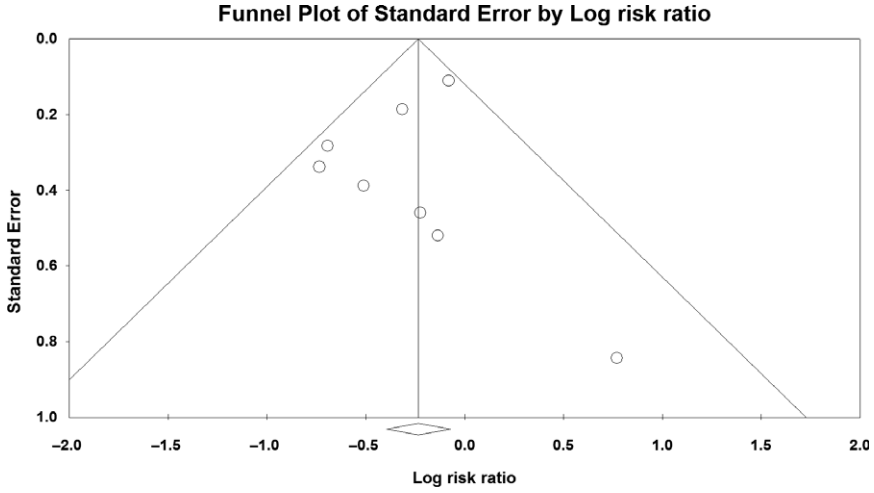

FIGURE 4 Funnel plot depicting publication bias for all-cause mortality

unique based on the inclusion of important and more elaborated endpoints.

The role of ICD in NICM has been addressed in six primary prevention trials and three secondary prevention trials. The six primary prevention trials were the Cardiomyopathy Trial (CAT); the Amiodarone vs Implantable Cardioverter-Defibrillator Randomized Trial (AMIOVIRT); the Defibrillators in Nonischemic Cardiomyopathy Treatment Evaluation (DEFINITE) Trial; the SCD-HeFT trial; the Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) Trial; and, more recently, the DANISH trial.[5-7,12-14] These trials display noticeable qualitative heterogeneities with regard to study design, comorbidity burden, and follow-up duration. Among primary prevention trials, the CAT, AMIOVIRT, DEFINITE, and DANISH trials exclusively enrolled patients with NICM, while SCD-HeFT and COMPANION comprised patients with both ICM and NICM. CAT, AMIOVIRT, and DEFINITE randomized patients to ICD or medical therapy, while in DANISH, patients were randomized to ICD and usual care and about 58% of patients in both the groups received CRT device.[7,12-14] Furthermore, DANISH trial utilized maximum medical therapy in both groups and so far is the only trial which included NT pro-BNP levels for enrollment.[7] On the other hand, the designs of the SCD-HeFT trial and COMPANION trial were more complex.[5,6] In the SCD-HeFT, patients with left ventricular systolic dysfunction (LVEF ≤35%) and congestive heart failure were randomized to ICD, amiodarone, or placebo and only 47.3% had NICM,[5] whereas in the COMPANION trial, the heart failure patients (both ICM and NICM), and QRS duration > 120 milliseconds were randomized to optimal pharmacologic therapy alone or in combination with CRT using either a pacemaker or pacemaker-defibrillator, and 44% of the enrolled participants had NICM.[6]

The Antiarrhythmics vs Implantable Defibrillators (AVID), Canadian Implantable Defibrillators Study (CIDS), and Cardiac Arrest

Study Hamburg (CASH) were three secondary prevention trials.[15-17] None of these trials exclusively analyzed patients with NICM, and across all these trials, only 15% of patients had NICM. The control arms in these trials were anti-arrhythmic agents. Amiodarone was used as a control agent in AVID and CIDS, while in the CASH trial; subjects were initially randomized to 1 of 3 control arms: amiodarone, metoprolol, or propafenone.[15-17] Due to increased mortality in the propafenone arm, the arm was terminated early and ultimately the outcomes were based on a comparison between the amiodarone, metoprolol, and ICD.[16] While both AVIDS and CIDS were almost comparable with regard to baseline characteristics and study design, the CASH trial was substantially different in design. The data on secondary prevention ICD are comparatively well established, and hence, these trials were not included in final analysis.

Of all the RCTs, only SCD-HeFT and COMPANION showed mortality benefit.[5,6] However, DANISH did not show a survival benefit for the entire study population, but their subgroup analysis reported survival benefit among younger participants.[7] These differences in outcomes can be explained by certain reasons. First, most of the earlier trials were published during the period of evolving medical therapy; therefore, most of the heart failure patients in different studies were not optimally treated according to the current standards. For instance, the use of beta-blockers was low in CAT and AMIOVIRT and only DANISH and COMPANION used aldosterone receptor blockers in approximately half of the study population.[6,7,12,13] Similarly, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers were not used uniformly across all the studies. Furthermore, neither of the studies utilized contemporary angiotensin-neprilysin inhibitors. Second, in DANISH, more than half of the patients in both control and ICD arms had received CRT device.[7] This might have reduced the mortality in both the groups and minimized the incremental death reduction of ICD. Third, in the DANISH trial, mean age was 64 years, older than the mean age in most of the other studies.[7]

This meta-analysis has limitations inherent to any meta-analysis. First, there is a considerable degree of heterogeneity with regard to the study designs, demographics, burden of comorbidities, baseline medical therapy, and follow-up duration. This lack of qualitative homogeneity poses difficulty in the true interpretation of ICD benefits, which perhaps is the trigger point for ongoing discussion regarding the use of ICD in this subset of patients. Second, not all the studies reported data for most of the secondary outcomes. Third, ICD devices, software, and electrodes are constantly improving their accuracy, functional diversity, and durability. As medical devices and therapy improve, many landmark studies become irrelevant and contaminate the results of a meta-analysis. Finally, this current meta-analysis has assessed outcome at study level and results were not adjusted for patient-level information.

In conclusion, our findings endorse current professional guidelines and support the efficacy of ICDs in reducing all-cause mortality due to a reduction in SCD. The earlier studies could not demonstrate mortality benefit due to lack of optimal medical therapy, while the recent DANISH trial had various confounders that could bias the outcomes.[7] Well-designed RCTs are required to reassess our findings.

CONFLICT OF INTEREST

Authors declare no conflict of interests for this article.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

How to cite this article: Khan SU, Ghimire S, Talluri S, et al. Implantable cardioverter defibrillator in nonischemic cardiomyopathy: A systematic review and meta-analysis. *J Arrhythmia*. 2018;34:4–10. https://doi.org/10.1002/joa3.12017