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Primary prevention implantable cardioverter defibrillator in patients with non-ischaemic cardiomyopathy: a meta-analysis of randomised controlled trials

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ABSTRACT

Objectives The objective of this meta-analysis of randomised controlled trials (RCTs) is to evaluate the role of primary prevention implantable cardioverter defibrillator (ICD) in patients with non-ischaemic cardiomyopathy (NICM).

Setting A meta-analysis of RCTs performed according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines.

Data sources The PubMed, MEDLINE, Embase and Cochrane Central Register of Controlled Trials databases were searched for relevant articles.

Participants A total of 5 RCTs with 2573 patients with NICM were included.

Intervention Primary prevention ICD, compared with medical therapy alone.

Primary and secondary outcome measures All-cause mortality (primary outcome) and sudden cardiac death (SCD, secondary outcome).

Data analysis Summary estimate HR were constructed using the random-effect DerSimonian and Laird's model. Multiple study-level subgroup analyses were performed, and interaction was tested using random-effect analysis.

Results Compared with medical therapy alone, ICD placement was associated with lower risk of all-cause mortality (HR 0.79; 95% CI 0.64 to 0.93; p<0.001; I^2=0%) at a mean follow-up of 4.2 years. The risk of SCD was also lower with ICD placement (RR 0.47; 95% CI 0.30 to 0.73; p=0.001; I^2=0%) compared with control. On subgroup analyses, there was a suggestion of possible effect modification by age, in which benefit was observed in age group <60 years (HR 0.64; 95% CI 0.47 to 0.89), but not with age ≥60 years (HR 0.82; 95% CI 0.65 to 1.03) ($P_{interaction}$=0.058), but not with other study-level variables.

Conclusions Compared with medical therapy alone, primary prevention ICD therapy in patients with NICM is associated with a significant reduction in all-cause mortality, especially in younger patients. Future dedicated studies are needed to investigate the role of primary prevention ICD in the elderly population.

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Strengths and limitations of this study

- Updated meta-analysis of five randomised trials comparing implantable cardioverter defibrillator versus medical therapy alone in patients with non-ischaemic cardiomyopathy.
- The quality of the included trials and the risk of bias were assessed using the components described by the Cochrane Collaboration.
- The overall quality of evidence for each outcome was further assessed using the Grades of Recommendation, Assessment, Development and Evaluation tool.
- Multiple sensitivity analyses were performed.
- Limitations include the lack of patient-level data and inability to assess other outcomes.

INTRODUCTION

In patients with symptomatic heart failure and reduced left ventricular systolic function, implantable cardioverter defibrillator (ICD) carries a class I recommendation, both by the European Society of Cardiology (ESC) and the American Heart Association (AHA), for primary prevention of sudden cardiac death (SCD) and reduction of mortality.[1 2] However, the evidence supporting the mortality benefit of primary prevention ICD was derived from studies that predominantly evaluated patients with ischaemic cardiomyopathy.[3–6]

For patients with non-ischaemic cardiomyopathy (NICM), data are less conclusive. While a prior meta-analysis of 1854 patients with NICM showed a 31% reduction in all-cause mortality with primary prevention ICD compared with medical therapy,[7] the most recent randomised controlled trial (RCT), the Danish Study to Assess the Efficacy of ICDs in Patients with Non-ischaemic Systolic Heart Failure on Mortality

(DANISH), failed to show such a survival benefit with ICD implantation in this patient population.[8] Thus, we aim to perform a meta-analysis of RCTs to evaluate the role of primary prevention ICD therapy in patients with NICM compared with medical therapy alone.

METHODS

Search strategy and study selection

We searched electronic databases according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[9] Initially, a systematic review of PubMed, MEDLINE, Embase and Cochrane Central Register of Controlled Trials, without any language restriction, was performed from inception until November 2016. We used the following keywords: 'defibrillator', 'cardiomyopathy', 'heart failure' and 'non-ischaemic' (see online supplementary table 1). After eligible trials were retrieved, we screened their bibliographies for any potential missed trials through the initial search. Furthermore, prior meta-analyses were reviewed to ensure all eligible trials are included. This meta-analysis is registered with the International Prospective Register for Systematic Reviews or PROSPERO (CRD42016052010).[10]

To be eligible for inclusion, studies had to be RCTs; randomising NICM patients to either ICD placement or medical therapy alone (control group) and reporting outcomes of interest. We excluded trials if (1) ICD implantation was for secondary prevention of SCD[11–13]; (2) there was an unbalanced use of cardiac resynchronisation therapy (CRT) between both arms,[14] to avoid a possible confounding effect on outcomes.[15–17]

Data extraction

Two independent authors (AFB and AYE) extracted comprehensive data on study characteristics, patients' demographics and quality assessment data. The numbers of events for outcomes of interest in the two arms were tabulated. The extracted data were revised by a third author (MS). Discrepancies were resolved by consensus among all the authors.

Assessment of quality and bias

The quality of the included trials and the risk of bias were assessed by two independent reviewers (MS and ANM) using the components described by the Cochrane Collaboration,[18] including random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other sources of bias. Trials were considered low risk of bias if meeting less than two high-risk components, and high risk of bias if meeting more than four high-risk components. The overall quality of evidence for each outcome was further assessed using the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) tool recommended by the Cochrane Handbook for Systematic Reviews of Interventions.[19]

Outcomes

The main outcome assessed in this meta-analysis was all-cause mortality. We also assessed SCD as a secondary outcome. Outcomes were reported at the longest follow-up.

Statistical analysis

This meta-analysis was performed with an intention-to-treat approach. Descriptive analyses were conducted using weighted frequencies for categorical variables and weighted means with SD for continuous variables. The weighted mean follow-up duration of each outcome was calculated. The sample size of each trial was used as its weight.

To evaluate the outcome of all-cause mortality at the longest follow-up reported by all the trials, we calculated summary estimate HR using the reported HRs and 95% CIs in each trial through the random-effect DerSimonian and Laird's model.[20] We calculated estimate RRs for the outcome of SCD using the same model, since HRs were not uniformly reported by all trials for this outcome. Heterogeneity testing was performed by using Higgins I^2 test.[21] An I^2 <25% was considered indicative of low heterogeneity, while I^2 >50% was considered indicative of high heterogeneity. All the p values were two tailed with statistical significance level at 0.05. Publication bias was calculated using the Egger's method.[22] Random-effect inverse variance weighted incidence with 95% CI was calculated for each outcomes using STATA V.14 'Metaprop' software.

We performed a sensitivity analysis after exclusion of The Cardiomyopathy Trial (CAT),[23] since it is the only trial that included patients with recent-onset heart failure (<9 months) and had a low mortality rate in the control group at 1 year. Another sensitivity analysis was performed after excluding the DANISH trial, since it constitutes the largest patient cohort among all the trials. Furthermore, we performed multiple subgroup analyses for the following study-level variables: (a) male gender, (b) age, (c) New York Heart Association class III/IV, (d) beta-blocker use at follow-up, (e) ACE inhibitor use at follow-up, (f) left ventricular ejection fraction, (g) history of non-sustained ventricular tachycardia and (h) duration of heart failure. A test for interaction was performed by random-effect analysis to compare the effect size in each subgroup. All statistical analyses were conducted using STATA V.14.

RESULTS

As outlined in figure 1, our initial electronic database search yielded 413 articles. On further screening, six RCTs met our eligibility criteria.[6 8 14 23–25] On detailed review, one trial[14] was excluded because of unbalanced use of CRT between the intervention and control arms: the Cardiac-Resynchronisation Therapy with or without an Implantable Defibrillator in Advanced Chronic Heart Failure (COMPANION) trial randomised 1520 patients with New York Heart Association class III or IV heart failure secondary to ischaemic or NICM and QRS >120 ms to receive medical therapy alone or in combination with CRT-pacer (CRT-P) or CRT-defibrillator (CRT-D). However, the reported data comparing outcomes

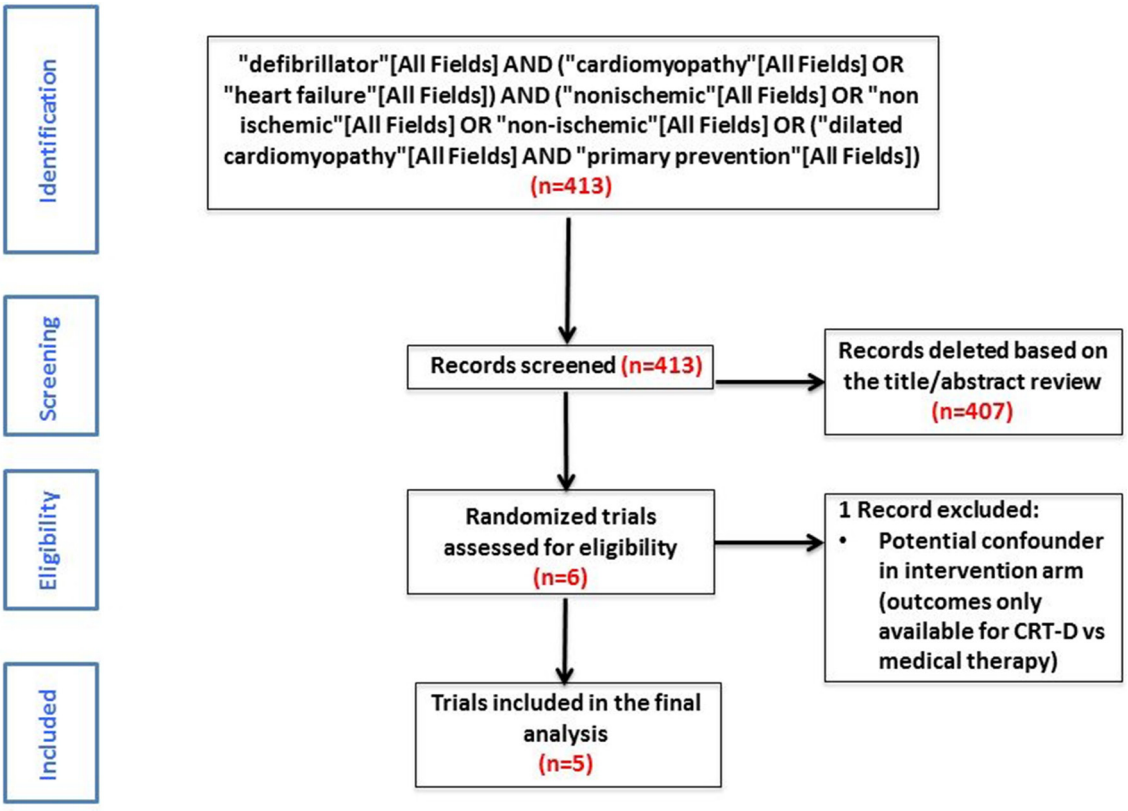

Figure 1 A flow diagram of the search strategy conducted. CRT-D, cardiac resynchronisation therapy-defibrillator.

in patients with NICM was only available for CRT-D versus medical therapy alone.[14] Therefore, five RCTs with a total of 2573 patients with NICM (1284 patients in the ICD arm, and 1289 patients in the control arm) were included in our analysis.[6 8 23–25] All trials enrolled exclusively patients with NICM except Sudden Cardiac Death in Heart Failure Trial which enrolled both ischaemic and NICM patients and reported outcomes for both groups. The primary outcome in all trials was all-cause mortality. The weighted mean age was 61±1.7 years, and 74.3% were men. The weighted mean heart failure duration was 1.9±0.4 years, and the weighted mean ejection fraction was 23.9%±1.1%. Details about the trials' characteristics and patients' baseline demographics are summarised in table 1.

Quality and risk of bias of the included trials

The risk of bias was performed using the Cochrane Collaboration tool. All trials were deemed at low risk of bias. Furthermore, the quality of the body of evidence for the outcomes was evaluated using the GRADE assessment tool, and both reached the level of high quality of evidence. No publication bias was seen for either all-cause mortality (p=0.30) or SCD (p=0.62) (see online supplementary tables 2 and 3).

Outcomes

The weighted incidence of mortality was 15% (95% CI 8 to 22) in the ICD group versus 18% (95% CI 11 to 25) in the control group. At weighted mean follow-up duration of 4.2 years, ICD placement was associated with lower risk of all-cause mortality (HR 0.79; 95% CI 0.64 to 0.93; p<0.001; I^2=0%) compared with the control group (figure 2). The risk of SCD was also lower with ICD placement (RR 0.47; 95% CI 0.30 to 0.73; p=0.001; I^2=0%) (figure 3).

The results of the sensitivity analyses were similar to the main analysis: (1) after exclusion of the CAT trial (HR 0.78; 95% CI 0.63 to 0.94; p<0.001; I^2=0%) and (2) after exclusion of the DANISH trial (HR 0.71; 95% CI 0.51 to 0.92; p<0.001; I^2=0%) (see online supplementary figures 1 and 2, respectively).

Subgroup analysis showed that ICD placement is beneficial across various study-level variables such as gender, New York Heart Association class III/IV, beta-blocker or ACE inhibitor use at follow-up, left ventricular ejection fraction, history of non-sustained ventricular tachycardia and duration of heart failure. Subgroup analysis by age showed possible effect modification, in which benefit was observed in age group <60 years (HR 0.64; 95% CI 0.47 to 0.89) but might be less beneficial in those aged ≥60 years (HR 0.82; 95% CI 0.65 to 1.03) ($P_{interaction}$=0.058) (figure 4).

DISCUSSION

In this meta-analysis of five multicentre RCTs with 2573 patients, we demonstrated that primary prevention ICD therapy in patients with NICM was associated with 21% relative risk reduction and 3% absolute risk reduction in all-cause mortality (number needed to treat=33)

Table 1 Baseline characteristics of the included trials

	CAT[24]	AMIOVIRT[23]	DEFINITE[25]	SCD-HeFT[6]	DANISH[8]
Study characteristics					
Patients (n)	50/54	51/52	229/229	398/394*	556/560
Enrolment period	1991–1997	1996–2000	1998–2002	1997–2001	2008–2014
Year of publication	2002	2003	2004	2005	2016
Single/multicentre	Multicentre	Multicentre	Multicentre	Multicentre	Multicentre
Inclusion criteria	Recent-onset Idiopathic DCM EF≤30% NYHA II–III	NIDCM EF≤35% NYHA I–III NSVT	NIDCM EF≤35% NYHA I–III PVC's or NSVT	EF≤35% NYHA II,III	NICM EF≤35% NYHA II–IV† NT-BNP>200
Follow-up (years)	1.9	2	2.4	3.8	5.6
Completion of follow-up (%)	100	100	100	100	100
Crossovers	NR/NR	15/22	10/2	NR/6	5/8
Patients' characteristics					
Mean age (years)	52/52	58/60	58/58	60/60	64/63
Male (%)	86/74	67/74	73/70	77/77	73/72
Hypertension (%)	NR	58/67	NR	55/56	33/30
Diabetes mellitus (%)	NR	31/36	23/23	31/32	18/20
Atrial fibrillation (%)	20/11	NR	23/26	17/14	24/20
NSVT (%)	53/58	100/100	22/23	25/21	NR
QRS duration (ms)	102/144	NR	115/116	NR	146/145
NYHA III/IV (%)	33/36	16/24	21/21	32/30	46/46
EF (mean %)	24/25	22/23	21/22	24/25	25/25
Duration of HF (years)	0.3/0.2	2.9/3.5	2.4/3.3	NR	1.7/1.5
Medications at baseline (%)					
Beta-blockers	4/4	NR	NR	69/69	92/92
ACEI/ARB	94/98	NR	NR	94/98	96/97
Amiodarone	NR	NR	NR	0/0	6/6
Aldosterone antagonist	NR	NR	NR	NR	59/57
Medications at follow-up (%)					
Beta-blockers	NR	53/50	86/84	82/79	98 ‡
ACEI/ARB	NR	90/81	97/96	86/88	99 ‡
Amiodarone	NR	22/52	4/7	14/7	NR
Aldosterone antagonist	NR	20/19	NR	NR	79 ‡

Values are reported as ICD/control arm.
*Only placebo arm data are included as the control arm of SCD-HeFT.
†NYHA IV was included if CRT was planned.
‡Total percentage in both arms.
ACEI, ACE inhibitors; AMIOVIRT, Amiodarone Versus Implantable Defibrillator Trial; ARB, angiotensin receptor blockers; DANISH, Danish Study to Assess the Efficacy of ICDs in Patients with Non-ischaemic Systolic Heart Failure on Mortality; DCM, dilated cardiomyopathy; DEFINITE, Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation; EF, ejection fraction; HF, heart failure; ICD, implantable cardioverter defibrillator; NIDCM, non-ischaemic dilated cardiomyopathy; NICM, non-ischaemic cardiomyopathy; NR, not reported; NSVT, non-sustained ventricular tachycardia; NT-BNP, N-terminal probrain natriuretic peptide; NYHA, New York Heart Association; PVC, premature ventricular contractions; SCD-HeFT, Sudden Cardiac Death in Heart Failure Trial.

compared with medical therapy alone, at a mean follow-up of ~4 years. Subgroup analysis demonstrated the benefit of ICD placement across variable study-level variables, however; there was a suggestion of possible effect modification by age, with more benefit in patients <60 years of age compared with older patients (ie, ≥60 years). Other subgroup analyses did not reveal significant effect modification, indicating that the mortality benefit with primary prevention ICD therapy could be achieved on a wide spectrum of NICM patients, with diverse demographics and clinical presentations. Using the Cochrane Collaboration tool and GRADE assessment, all trials were deemed at low risk of bias and the quality of the body of evidence for the outcomes reached the level of high

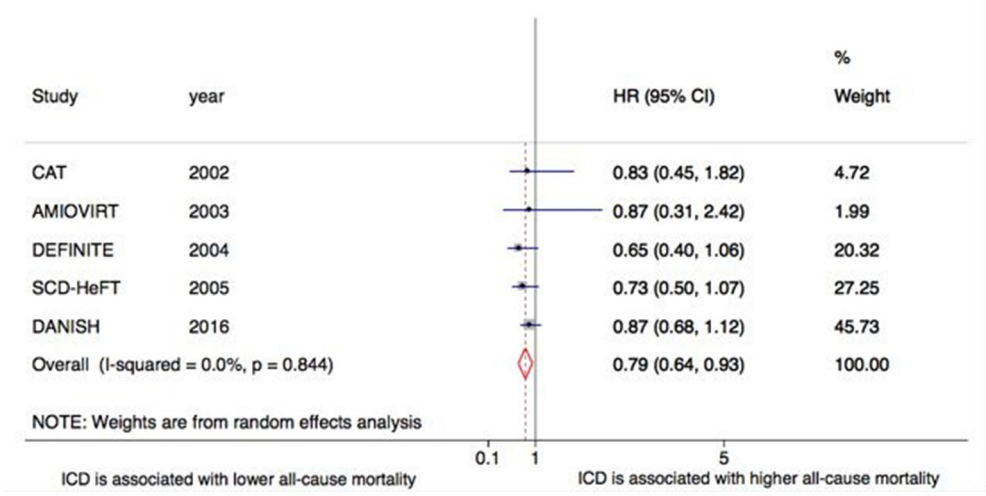

Figure 2 Summary forest plot of all-cause mortality. The relative size of the data markers indicates the weight of the sample size from each study. AMIOVIRT, Amiodarone Versus Implantable Defibrillator Trial; CAT, The Cardiomyopathy Trial; DANISH, Danish Study to Assess the Efficacy of ICDs in Patients with Non-ischaemic Systolic Heart Failure on Mortality; DEFINITE, Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation; ICD, implantable cardioverter defibrillator; SCD-HeFT, Sudden Cardiac Death in Heart Failure Trial.

quality of evidence. No publication bias was noted for the assessed outcomes.

The DANISH trial[8] randomised 1116 patients to receive either primary prevention ICD or usual clinical care. It did not show a difference in all-cause mortality between both groups in the overall population, even though it showed about 50% reduction in SCD. A plausible explanation for the attenuated mortality benefit in this trial is the increased age of the study population, with one-third of the patients being 68 years of age or older. Importantly, on subgroup analysis, the DANISH trial demonstrated that all-cause mortality was improved with ICD implantation among younger patients (age <59 years (lowest tertile), HR 0.51, 95% CI 0.29 to 0.92, p=0.02 and age <68 years (lowest two tertiles), HR 0.64, 95% CI 0.45 to 0.90, p=0.01).[8] This is further supported by the fact that about one-third of the deaths in the DANISH study was attributed to non-cardiovascular aetiology. In our analysis, a possible effect modification by age was noted. In addition, despite a striking reduction in SCD in all

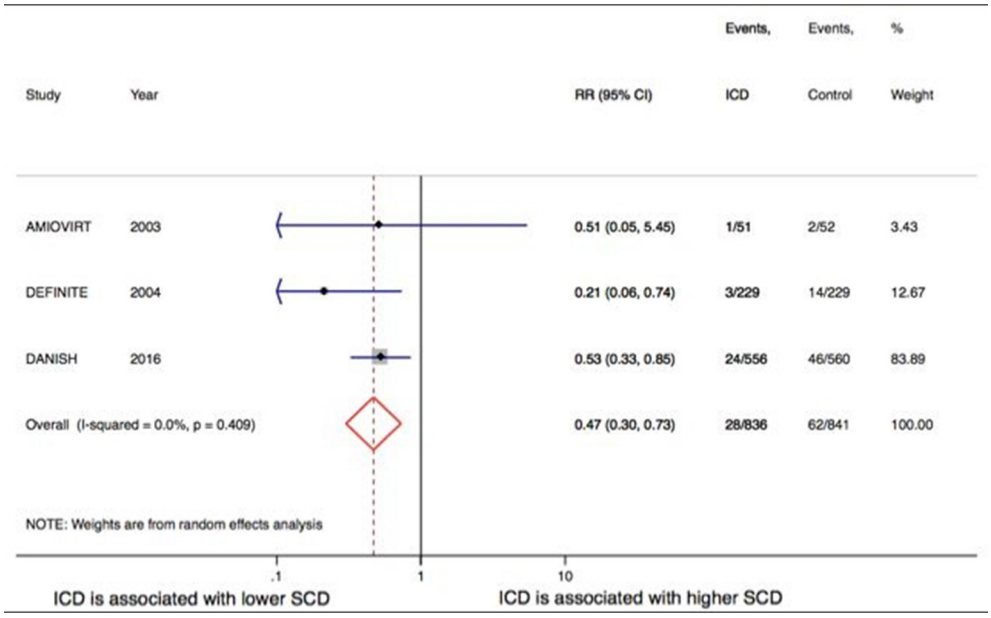

Figure 3 Summary forest plot of sudden cardiac death. CAT trial was excluded since it reported zero events. SCD-HeFT trial was excluded due to lack of reporting of sudden cardiac death events in the non-ischemic heart failure subgroup. The relative size of the data markers indicates the weight of the sample size from each study. AMIOVIRT, Amiodarone Versus Implantable Defibrillator Trial; DANISH, Danish Study to Assess the Efficacy of ICDs in Patients with Non-ischaemic Systolic Heart Failure on Mortality; DEFINITE, Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation; ICD, implantable cardioverter defibrillator.

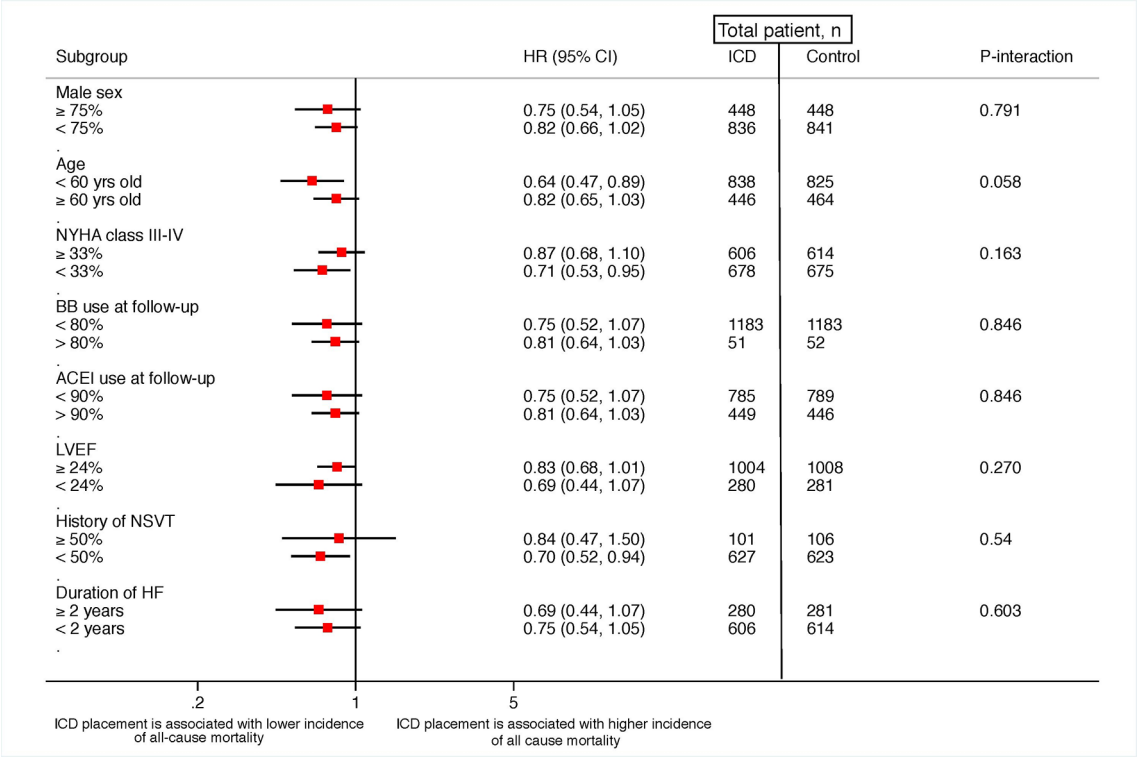

Figure 4 Summary forest plot of subgroup analyses for all-cause mortality. The relative size of the data markers indicates the weight of the sample size from each study. Age subgroups represent the mean age reported in each trial except DANISH trial, in which the hazard ratios were directly extracted from the published data. For the remainder of the subgroup analyses, the mean for each characteristic was used. ICD, implantable cardioverter defibrillator; NYHA, New York Heart Association; BB, beta-blocker; ACEI, ACE inhibitor; HF, heart failure; LVEF, left ventricular ejection fraction; NSVT, non-sustained ventricular tachycardia.

the analysed trials, the reduction in all-cause mortality was less evident in some trials. This appropriately highlights the fact that ICD is potent in reducing SCD, but it cannot modify other competing non-cardiac death events. Another possible explanation for the attenuated mortality benefit in DANISH trial is the increased use of CRT in the study population (58% in each arm), which is well known to significantly improve the left ventricular ejection fraction, and subsequently might reduce the risk of ventricular arrhythmias and SCD. The evaluation of the mortality benefit of CRT-D versus CRT-P is beyond the scope of this analysis and needs to be assessed in dedicated large prospective trials.

Currently, primary prevention ICD therapy in patients with symptomatic heart failure of non-ischaemic aetiology has a class I B recommendation in the ESC guidelines[1] and a class I A recommendation in the AHA guidelines.[2] Importantly, primary prevention ICD in patients with ischaemic and NICM has been shown to be cost effective in a prior meta-analysis using a HR of 0.72 for all-cause mortality (comparable with our study results).[26] Thus, our meta-analysis adds to the current evidence which supports prophylactic ICD placement in patients with NICM. However, in light of the DANISH trial[8] results that demonstrated a mortality benefit only in patients that are less than 68 years of age, and the possible effect modification by age in this analysis, a patient-level meta-analysis of the available trials would provide further evidence regarding the utility of primary prevention ICD therapy in elderly frail NICM patients. Further, an ongoing clinical trial (ClinicalTrials.gov number, NCT02121158) is currently evaluating the safety and efficacy of primary prevention ICD implantation in patients who are 70 years of age or older, who are eligible for ICD therapy according to current Centres for Medicare and Medicaid Services criteria. In addition, with the increased use of CRT in the heart failure population, the mortality benefit of CRT-D compared with CRT-P in non-ischaemic systolic heart failure is an important area of future research.

A recent meta-analysis aimed to assess the benefits of ICD for primary prevention of mortality in patients with NICM.[27] The authors used a summary estimate (ie, HR and 95% CI) for the COMPANION trial[14] which compared CRT-D versus medical therapy, whereas the trial did not report a summary estimate between CRT-D and CRT-P in NICM patients. Therefore, the overall summary estimate for the benefit from ICD placement could have been biased by including the COMPANION trial as a result of the imbalance use of CRT, which in turn has been shown to improve mortality in heart failure patients irrespective of ICD placement.[15–17] Furthermore, the authors performed a subgroup analysis of two trials (COMPANION[14] and DANISH[8]) to compare CRT-D versus CRT-P using this same summary estimate for the COMPANION trial which again could lead to a misleading conclusion. In the current study, we aimed to perform

a robust analysis by using the GRADE methodology to ascertain the high-quality evidence of the included trials. Moreover, by excluding the COMPANION trial, we aimed to avoid the possible confounding benefit of CRT implantation proven by prior studies.[14–17]

The present analysis has some limitations. First, there is a considerable variation in the weights of the included trials; however, the heterogeneity in all the outcomes was zero. We further performed multiple sensitivity analyses through the exclusion of two trials, one at a time, and the results of these sensitivity analyses showed consistent benefit. Second, we focused on all-cause mortality as the main outcome, rather than cardiovascular mortality, since cardiovascular mortality was not consistently reported among the studies. In addition, some consider all-cause mortality as a preferred in the evaluation of cardiovascular disease.[28] Third, we included some old studies (ie, conducted >10 years ago). Moreover, the duration of follow-up was variable among the included studies. However, we aimed to include all the available data to minimise the risk of publication bias. Moreover, the medical therapy for systolic heart failure has not remarkably changed over these years. Fourth, we could not comment on the risk of device-related infections; however, we noted that the risk of all-cause mortality was even reduced with ICD therapy. Finally, lack of patient-level data precluded a full evaluation for the differences in patient-level covariates across comparisons. We conducted multiple study-level subgroup analyses and demonstrated a consistent benefit for ICD therapy.

CONCLUSIONS

Primary prevention ICD therapy in patients with NICM is associated with a significant reduction in the risk of all-cause mortality and SCD compared with medical therapy alone. This mortality benefit seems to be more evident in younger patients. Thus, patient-level meta-analysis of the available trials might further elaborate on the role of primary prevention ICD in the elderly population.

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Contributors AFB conceived the idea, performed data extraction and drafted the manuscript. MS contributed to data extraction, performed data analysis and contributed to manuscript drafting. AYE contributed to data extraction. AM and AA revised the intellectual content of the manuscript. ANM contributed to data analysis and revised the intellectual content of the manuscript. IYE revised the intellectual content and was responsible for the final version of the manuscript.

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