Implantable Cardioverter-Defibrillator for Non Ischemic Cardiomyopathy:  
An Updated Meta-Analysis

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Use of Implantable cardioverter-defibrillators (ICD) have been a major advancement in patients with ischemic cardiomyopathy (ICM) with reduced ejection fraction <35%. While the data supporting the use of ICDs are robust in patients with ICM, limited randomized controlled clinical trial (RCT) data exist for similar benefit in patients with non-ischemic cardiomyopathy (NICM). A prior meta-analysis that included both primary and secondary prevention ICD trials in 2004 by Desai et al. demonstrated a 31% reduction in all-cause mortality with ICD use in patients with NICM. The data became the backbone of the current American College of Cardiology/American Heart Association (ACC/AHA) guidelines for ICD implantation in patients with NICM. However, recently, the DANISH trial which randomized more than 1,100 patients with NICM on optimal medical therapy (OMT) and/or cardiac resynchronization therapy (CRT) to ICD vs. no ICD for primary prevention of sudden cardiac death (SCD) revealed no difference in all-cause mortality between the two groups at 5 year follow up. Although the primary results of DANISH were neutral, the ICD group showed reduction in incidence of sudden cardiac death by half and there was an interaction of survival benefit with ICD use in younger patients with NICM. In light of the recent data, we sought to update the meta-analysis of RCTs assessing the utility of ICD for primary prevention in patients with NICM.

We searched MEDLINE, PUBMED and SCOPUS databases using keywords: implantable cardioverter defibrillator, ICD, cardiac resynchronization therapy, CRT, heart failure, cardiomyopathy and randomized controlled trials from their inception to October 20, 2016. After examining 773 relevant studies, we included 6 RCTs that assessed the efficacy of ICD for primary prevention in patients with NICM. Two authors (H.G. N.B) independently extracted data from each individual study. We calculated risk ratios/hazard ratios (HR) and 95%
confidence intervals (CIs) using the available event rate data from individual trials when these measures were not reported in the individual trial. The risk measures and 95% CIs were log transformed and combined using random effects model. Data were analyzed for heterogeneity using the I^2 statistic. We also performed a separate analysis of trials with/without CRT use to assess the differential effect of CRT on efficacy of ICD. Analyses were performed using Stata V14.1 (College Station TX, USA) statistical software.

We identified 6 RCTs enrolling 2,970 patients with NICM to study the efficacy of ICD for primary prevention. Pooled analysis of the 6 RCTs (including those with CRT-D) demonstrated a statistically significant 23% risk reduction in all cause mortality in favor of ICD therapy [HR 0.77, 95% CI (0.64, 0.91)] (Figure). In addition, when we performed separate analysis of trials that assessed ICD plus OMT vs. OMT alone (after exclusion of trials that involved patients with CRT-D); we found a statistically significant 24% reduction in all cause mortality with ICD [HR 0.76, 95% CI (0.62, 0.94)]. When we compared the two trials (COMPANION and DANISH-CRT subgroup) with ICD plus CRT plus OMT vs. CRT plus OMT alone, we found a trend towards benefit in terms of all cause mortality in the ICD group, although it did not meet statistical significance [HR 0.70, 95% CI (0.39, 1.26)] (Figure).

Newly diagnosed NICM is a heterogeneous group of HF patients, and prior studies demonstrate that despite OMT, a subset of these patients remains at risk of sudden cardiac death.\(^5\) Our updated meta-analysis combining all available RCTs including the recently published DANISH trial demonstrates that ICDs reduce all-cause mortality by 23% in patients with NICM. This incremental reduction of all cause mortality with ICD is substantial and provides support to the existing ACC/AHA guidelines until we acquire additional data.\(^3\) In addition, despite the individual subgroup analysis of COMPANION and DANISH trials
demonstrating no incremental benefit of ICD in patients with CRT; when we combined the two
trials, we found that ICD may still reduce all cause mortality in patients who are also candidates of CRT therapy, although the results did not meet statistical significance. It may be plausible that due to high use of CRT in the DANISH trial (60% in each arm), ICD failed to demonstrate statistically significant effect on all-cause mortality in patients with NICM.

Taken collectively, despite the neutral results of the recently published DANISH trial, our meta-analysis of all the published RCTs till date, demonstrate significant clinical benefit on all-cause mortality in favor of ICD use for primary prevention in patients with NICM. Improvement in risk prediction models can help overcome the traditional reliance on ejection fraction for risk stratification of sudden cardiac death in NICM patients. Furthermore, adequately powered randomized studies are needed prior to recommending any change in existing guidelines and clinical judgment should prevail while assessing risk of sudden cardiac death in NICM patients with reduced EF.

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None.
References


Figure. Forest plot of all-cause mortality among patients with Non-ischemic cardiomyopathy randomized to ICD and/or CRT-D vs. optimal medical therapy for primary prevention of sudden cardiac death.

**Abbreviations:** HR= Hazard ratio, CI= Confidence Interval; CAT= Cardiomyopathy trial; AMIOVIRT= Amiodarone vs Implantable Cardioverter-Defibrillator Randomized Trial; DEFINITE= Defibrillator in Nonischemic Cardiomyopathy Treatment Evaluation; SCD-HeFT= Sudden Cardiac Death in Heart Failure Trial; COMPANION= Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure; DANISH= Defibrillator Implantation in Patients with Nonischemic Systolic Heart Failure; CRT= cardiac resynchronization therapy, ICD= implantable cardioverter defibrillator.

**Note:** Black marker represents hazard ratio estimate for the study. The grey box around the marker corresponds to the weight of study in the random effects model. The diamond shaped box is the summary estimate from random effects model. The horizontal black lines denote 95% confidence intervals of hazard ratio of each study. Black vertical line is line of no effect difference.