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Response to letter regarding article “Implantable Cardioverter-Defibrillator for Non-Ischemic Cardiomyopathy: An Updated Meta-Analysis”

Harsh Golwala^{1,*}, Navkaranbir Singh Bajaj^{1,2,*}, Garima Arora², and Pankaj Arora^{2,3}

¹Brigham and Women’s Heart and Vascular Institute, Boston, MA, USA

²Division of Cardiovascular Diseases, University of Alabama, Birmingham, AL, USA

³Section of Cardiology, Birmingham Veterans Affairs Medical Center, Birmingham, AL, U.S.A

We thank *Nery et al* for their insightful letter to our article.¹ We alluded to the age and survival interaction with implantable cardioverter defibrillator (ICD) use in non-ischemic cardiomyopathy (NICM) patients noted in DANISH trial in our article.¹ We agree that similar trends have been observed in other trials.² However, only four out of six trials included in our meta-analysis (DEFINITE, COMPANION, SCD-HEFT, DANISH)¹ reported age stratified outcomes. Two of the four trials, SCD-HEFT³, and COMPANION⁴ had these outcomes reported for both ischemic and non-ischemic patients, making age stratified analysis in NICM patients difficult in absence of individual patient level data. Nonetheless, we do agree that this should be recognized as one of the key limitations of the currently available data we have from the randomized controlled trials (RCTs). In addition, all treatment decisions for ICD placement should be personalized and involve shared decision making with patients.

We agree with *Barakat et al* that the COMPANION⁴ trial did not directly report individual comparison of ICD plus cardiac resynchronization therapy (CRT-D) vs. CRT-pacemaker (CRT-P). Unfortunately, our efforts to obtain the relevant information from the trial authors⁴ were unsuccessful. Nevertheless, the trial⁴ reported treatment effects of (i) CRT-D vs. pharmacotherapy [Hazard Ratio (HR) 0.50; 95% Confidence interval (CI), 0.29–0.88] and (ii) CRT-P vs. pharmacotherapy [HR; 0.91 (95% CI, 0.55–1.49)]; indicating that treatment effect of CRT-P and pharmacotherapy is relatively similar in patients with NICM.⁴ For further confirmation, we estimated “indirect” treatment effect using Bucher method⁵ of CRT-D vs. CRT-P from these estimates. We found that the “indirect” HR was 0.55 (95% CI, 0.26–1.16) which was similar to treatment effect of COMPANION trial that we used in our primary and sub-group analysis [HR; 0.50 (95% CI, 0.29–0.88)].¹ Further analysis after inclusion of these indirect estimates did not affect our primary or sub-group summary estimates [summary HR reported in primary analysis using COMPANION⁴ trial HR; 0.77

Corresponding author: Pankaj Arora, MD, FAHA, Division of Cardiology, Department of Medicine 1670 University Blvd, Volker Hall B140, University of Alabama at Birmingham, Birmingham, AL 35294-0019, United States of America, Phone Number: 205-996-6630, Facsimile Exchange: 205-975-4720, parora@uabmc.edu.

* Contributed equally to the manuscript

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(95% CI, 0.64–0.91), whereas summary HR using “indirect” HR for COMPANION⁴ trial was 0.78 (95% CI, 0.66–0.93). Similarly, summary HR reported in our sub-group analysis; 0.70 (95% CI, 0.39–1.26), which was once again equivalent to summary HR using “indirect” HR for COMPANION⁴ trial; 0.79 (95% CI, 0.51–1.23).

Barakat et al also suggested that since CRT improves mortality independent of ICD, inclusion of COMPANION trial, which included patients with both ICD and CRT, could be misleading. We disagree with the authors in their viewpoint. Firstly, we presented in our article ICD only summary HR; 0.76 (95% CI, 0.62–0.94), after excluding both COMPANION and patients with CRT use in the DANISH trial which was similar to our primary analysis summary HR.¹ Further, when we performed one study omitted sensitivity analysis to assess the effect of exclusion of COMPANION⁴ trial on our primary analysis; the summary estimate did not change significantly [COMPANION included summary HR; 0.77 (95% CI, 0.64–0.91), COMPANION excluded summary HR; 0.80 (95% CI, 0.67–0.96)] (Figure 1). Similar results were also discussed by *Desai et al*⁶ in their prior meta-analysis suggesting that overall treatment effect remains robust by inclusion of the COMPANION⁴ trial. Finally, optimal medical therapy for heart failure has evolved over the last decade. Control arms in the included RCTs have ranged from placebo, amiodarone, to the state of the art medical therapy with CRT use in more than half of the patients in the recently concluded DANISH trial.¹ Despite the evolving comparator in control arm, given the fact that baseline characteristics were similar between treatment and control groups in all these trials, one could reason that the survival benefit in each trial was driven primarily by the ICD. Limitations of meta-analysis have been previously described.⁷ However, our sensitivity and heterogeneity analysis detected minimal statistical heterogeneity. The treatment effects were nearly similar in magnitude and concordant in direction across all RCTs. Hence we believe that treatment effects are accurately represented in our meta-analysis and can be used clinically while having individualized discussions with the patients about the need for ICD implantation. In an era of precision medicine, we believe that current focus to risk stratify NICM patients for sudden cardiac death solely on basis of ejection fraction falls short of perfect and future efforts should focus on improvement of risk stratification of NICM patients.

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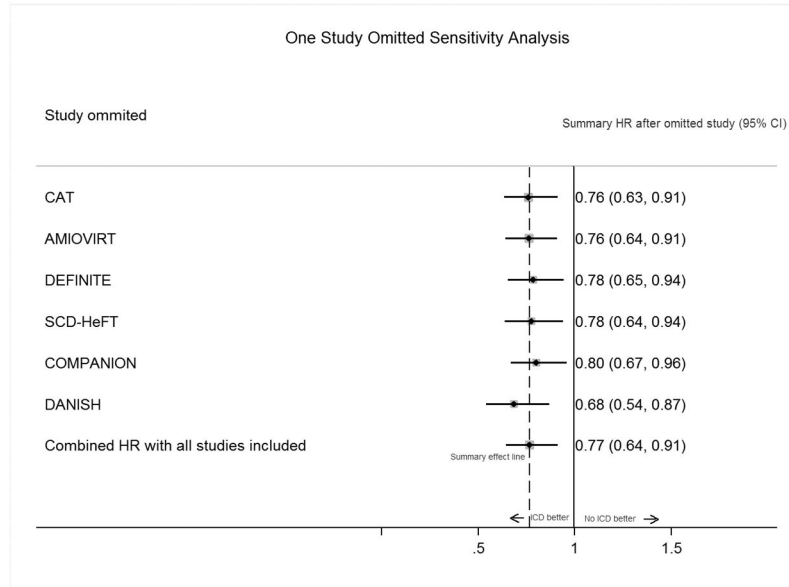


Figure 1. One Study Omitted Sensitivity Analysis to assess the effect of individual trials on summary treatment effect of implantable cardioverter-defibrillator on all-cause mortality

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; ICD= implantable cardioverter defibrillator.

Note: Black markers and solid lines around them represent summary HRs and 95% CI after excluding the study in the left column. The numerical estimates in the right column are pooled effects and 95% CI after excluding the trial in the left column from the meta-analysis. The direction and statistical significance of summary treatment effect remains similar after excluding any trial from meta-analysis indicating “robustness” of the estimated summary treatment effect.