Mortality Effect of ICD in Primary Prevention of Nonischemic Cardiomyopathy: A Meta-Analysis of Randomized Controlled Trials

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ICD in Nonischemic Cardiomyopathy. Introduction: Implantation of an implantable cardioverter defibrillator (ICD) for primary prevention of sudden cardiac death (SCD) is controversial in view of the recent DANISH trial which suggested no benefit with ICD for primary prevention in patients with non-ischemic cardiomyopathy (NICMP).

Methods: We conducted a meta-analysis of randomized controlled trials studying the role of ICD in primary prevention of SCD in patients with NICMP. Only six studies were identified after the application of inclusion/exclusion criteria.

Results: Pooling of these randomized trials showed a statistically significant benefit of using ICDs in patients with NICMP [OR 0.76 (0.64 – 0.91), I² = 0%]. Sensitivity analysis did not show a statistically significant mortality benefit of ICD in NICMP in trials which had adequate beta blocker, ACE/ARB and aldosterone receptor blocker (ALD-RB) use [OR 0.70 (0.41, 1.19), I² = 70%].

Conclusion: The DANISH trial’s failure to show mortality benefit may be due to the significant number of patients who had CRT. Our meta-analysis studied the independent effect of ICDs and showed them to be associated with net mortality benefits in patients who are not on optimal guideline directed medical therapy; especially the patients not on ALD-RB. (J Cardiovasc Electrophysiol, Vol. pp. 1-6)

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

Introduction

Implantation of an implantable cardioverter defibrillator (ICD) for primary prevention of sudden cardiac death (SCD) is a class 1 indication in the current clinical practice guidelines for patients with heart failure and a low ejection fraction. Although commonly used in clinical practice, acquisition of ICDs in the United States range from approximately $18,000 for the simplest devices to over $35,000 for ICDs with biventricular pacing capabilities. This has led to significant strain on the budgets of many healthcare systems leading to the importance of identifying and preventing implanting ICD in populations who would not benefit.

There is strong evidence supporting the mortality benefit of ICD in primary prevention of SCD in ischemic cardiomyopathy. However, the evidence supporting the use of ICD in primary prevention of SCD with nonischemic cardiomyopathy (NICMP) is not very robust. The current guidelines are based on a meta-analysis of five RCTs which were limited by their conflicting results with the positive results driven mainly by the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) and Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) trial. The negative trials exclusively enrolled patients with NICMP, while the positive trials (SCD-HeFT trial and COMPANION) also included patients with ischemic cardiomyopathy and studied the effect of NICMP in its subanalysis. The COMPANION trial did not study the role of ICD independently as these patients also had cardiac resynchronization therapy (CRT), which had independent mortality benefits. Recently the Danish Study to Assess the Efficacy of ICDs in Patients with Non-Ischemic Systolic Heart Failure on Mortality (DANISH) reported the lack of any survival benefit of ICD in patients with NICMP. However, 58% of the patients in the DANISH study had CRT implantation and thus the study did not address the mortality effects in NICMP patients who only had ICDs. In light of the recent results from the DANISH trial along with the importance of ICDs from a clinical and a public health perspective, we conducted a meta-analysis of the randomized controlled trials to evaluate the efficacy of primary prevention ICDs in NICMP. The meta-analysis aims to help us to better understand the differences in the results of these trials and the applicability of these different trials to the current patient population in view of the changes in guideline directed medical therapy over the years.
Methods

We conducted a meta-analysis of randomized control trials studying the role of ICD in primary prevention of SCD in patients with NICMP. The initial search was performed in MEDLINE, Embase, Web of Science, Cochrane Library, and ProQuest Dissertations and Theses from database inception to September 8, 2016. The systematic review was carried out in accordance to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines.

The keywords and phrases used in the search strategy were: SCD OR sudden cardiac arrest OR sudden heart death; primary prevention OR primordial prevention; implantable cardioverter defibrillator OR ICD OR AICD OR internal cardiac defibrillator OR implantable defibrillators OR implantable defibrillator OR implantable heart defibrillator; AND nonischemic OR nonischemic; cardiomyopathy OR dilated cardiomyopathy OR hypertrophic cardiomyopathy OR congestive cardiomyopathy OR alcoholic myopathy OR restrictive cardiomyopathy OR arrhythmogenic right ventricular dysplasia OR ARVD OR heart right ventricle dysplasia.

Only randomized control trials that studied adults >18 years and reported mortality in their endpoints were included. Studies that did not mention all-cause mortality in their endpoint were excluded. The data were extracted in an Excel sheet. Discrepancies in data extraction and assessing bias in individual studies were resolved through mutual discussion and consensus formulation. The abstracted information included the year of publication, study design, sample size, duration of follow-up, mean age of the patients, patient characteristics, and the treatments the patients were receiving. Hazard ratios reported by individual studies for relevant outcomes were used in the analyses. Odds ratios were calculated by the raw data provided in those studies where the effect estimate was not reported. Review Manager 5.3 was used to analyze the data that are represented as a forest plot. The Generic inverse variance method was used to pool the outcomes taking into consideration the associated heterogeneity. This method is recommended to be used when the effect estimate has been provided by the individual studies along with the standard error. Heterogeneity was measured by the I² statistic with values greater than 25%, 50%, and 75% used to signify mild, moderate, and severe heterogeneity. Fixed effects were used for mild heterogeneity and random effects were used for moderate to severe heterogeneity in the analysis. Two reviewers independently assessed the methodological quality of selected studies and the risk of bias using the Cochrane Collaboration’s tool for randomized trials.

Sensitivity and subgroup analysis were performed to study the effects of different variables on outcomes like age and location. Effects of treatments were analyzed in the subgroup analysis including CRT. Differences in the use of different heart failure medication were also analyzed. Usage of a drug was defined as adequate if more than 50% of the study cohort was on that drug.

Results

We identified 106 PubMed, 253 Embase, 10 Cochrane, 171 Web of Science, and 1 ProQuest Dissertations and Thesis records by using the search strategy mentioned above that is outlined in Figure 1. There were a total of 541 papers out of which 386 were duplicates. Only six studies were identified after the application of inclusion/exclusion criteria. The number of participants in the trials ranged from 103 to 2,521. Majority of patients in the included studies were NYHA class 2 heart failure followed by class 3 heart failure patients. Some studies included NYHA class 1 and class 4 patients. The duration of heart failure also varied in between the trials. Amiodarone Versus Implantable Cardioverter-Defibrillator: Randomized Trial in Patients With Nonischemic Dilated Cardiomyopathy and Asymptomatic Nonsustained Ventricular Tachycardia (AMIOVIRT), Defibrillators in Nonischemic Cardiomyopathy Treatment Evaluation (DEFINITE), COMPANION, and DANISH trials enrolled patients with heart failure of at least 2–3 years’ duration while the Cardiomyopathy Trial (CAT) trial enrolled patients with heart failure of short duration of less than 9 months. The trials were mostly conducted in the United States and Denmark.

Only two of the randomized control trials studying the role of ICD in NICMP that compared standard medical therapy with patients having an ICD were included. The SCD-HeFT trial with 68 months and SCD-HeFT trial with 46 months. The details of the studies with their baselines characteristics are further described in Tables 1 and 2.

Pooling of these randomized trials showed a statistically significant benefit of using ICDs in patients with NICMP with an odds ratio of 0.76 (0.64–0.91) and I² of 0% (Fig. 2). Sensitivity analysis did not show a statistically significant benefit of ICD in NICMP in trials that had adequate beta-blocker, angiotensin converting enzyme/angiotensin receptor blocker (ACE/ARB) and aldosterone receptor blocker (ALD-RB) use (OR 0.70 [0.41, 1.19], I² = 70%). There was still a statistically significant mortality benefit of ICD on excluding the COMPANION trial (OR 0.80 [0.66–0.96], I² = 0%), which compared patients with CRT defibrillator (CRT-D) with controls having no CRT. Pooling of the two studies that compared CRT-D with controls showed mortality benefit. (OR 0.79 [0.63–0.99], I² = 70%). The effect of age on mortality with ICD use could not be ascertained as the data was either not present in the studies, or was presented in a manner that could not be analyzed in the meta-analysis.

Publication bias was not assessed as there were only six studies.

Discussion

There have been six randomized trials to date studying the role of ICD in NICMP. The CAT trial and DEFINITE compared patients with ICDs with controls on standard medical therapy, while the AMIOVIRT compared patients with ICDs with patients on amiodarone. The SCD-HeFT trial had three study groups on standard medical therapy, amiodarone, and with ICD implantation. The COMPANION trial compared standard medical therapy with CRT pacemaker (CRT-P) and CRT-D. The DANISH trial is the latest trial that compared standard medical therapy with patients having ICD or CRT-D.

Only two of the randomized control trials studying the role of ICD in NICMP have demonstrated a mortality benefit. Although the DANISH trial did not show an overall
Records identified through database searching
PubMed = 106
Embase = 253
Cochrane = 10
Web of Science = 171
ProQuest Dissertations & Theses = 1
(n = 541)

Additional records identified through other sources
(n = 0)

Records after duplicates removed
(n = 386)

Records screened
(n = 207)

Records excluded
(n = 179)

Full-text articles assessed for eligibility
(n = 25)

Full-text articles excluded, with reasons
(n = 19)

Studies included in qualitative synthesis
(n = 6)

Studies included in quantitative synthesis (meta-analysis)
(n = 6)


<table>
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<tr>
<th>Publication</th>
<th>Country</th>
<th>Study Name</th>
<th>Study Size</th>
<th>Age Range (Years)</th>
<th>Mean/Median Duration of Follow-Up Period (Months)</th>
<th>NYHA Functional Class</th>
</tr>
</thead>
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<tr>
<td>Bansch</td>
<td>Germany</td>
<td>The Cardiomyopathy Trial</td>
<td>104</td>
<td>41–63</td>
<td>22.8</td>
<td>NYHA II–III</td>
</tr>
<tr>
<td>Bardy</td>
<td>USA</td>
<td>SCD-HeFT Trial</td>
<td>2521</td>
<td>51.2–69.2</td>
<td>45.5</td>
<td>NYHA II–III</td>
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<tr>
<td>Bristow</td>
<td>USA</td>
<td>COMPANION Trial</td>
<td>1520</td>
<td>66–68</td>
<td>12.0</td>
<td>NYHA II–IV</td>
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<tr>
<td>Kadish</td>
<td>USA</td>
<td>DEFINITE Trial</td>
<td>458</td>
<td>20.3–83.9</td>
<td>29</td>
<td>NYHA I–III</td>
</tr>
<tr>
<td>Kober</td>
<td>Denmark</td>
<td>DANISH Trial</td>
<td>1,116</td>
<td>56–72</td>
<td>67.6</td>
<td>NYHA II–IV</td>
</tr>
<tr>
<td>Strickberger</td>
<td>USA</td>
<td>AMIOVIRT Trial</td>
<td>103</td>
<td>58–72</td>
<td>24</td>
<td>NYHA I–III</td>
</tr>
</tbody>
</table>

Baseline Characteristics of Studies Included in Meta-Analysis

mortality benefit, the subanalysis from the trial did show that younger patients may have a survival benefit in association with ICD implantation. However, the overall pooling of studies in our meta-analysis did show a mortality benefit with ICD.

The difference in the effects of ICDs amongst different trials can be explained by the difference of treatment used in the trials. Most of the studies in our analysis were initiated before 2001\(^6,7,11,12,14\) during which time medical treatment was significantly different than the current standard of care. ACE/ARB were widely used in all studies. Beta-blockers was commonly utilized in all studies except two,\(^11,14\) while only two studies\(^7,13\) utilized ALD-RB in more than half the study population. No study utilized the newer angiotensin–neprylisin inhibitors, which is the latest heart failure medication with mortality benefits.\(^15\)
## TABLE 2
Baseline Characteristics at Baseline

<table>
<thead>
<tr>
<th>Study/Year</th>
<th>N</th>
<th>Study Cohorts (n)</th>
<th>Duration of Heart Failure</th>
<th>Mortality (n)</th>
<th>Age (Year)</th>
<th>Male (%)</th>
<th>DM (%)</th>
<th>HTN (%)</th>
<th>LV EF (%)</th>
<th>CRT (%)</th>
<th>Atrial Fib. (%)</th>
<th>BB (%)</th>
<th>ACE-I (%)</th>
<th>ALD-RB (%)</th>
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</thead>
<tbody>
<tr>
<td>Bansch(^1)</td>
<td>104</td>
<td>ICD (n = 50)</td>
<td>3 m</td>
<td>13(26%)</td>
<td>52</td>
<td>43</td>
<td>–</td>
<td>–</td>
<td>24</td>
<td>–</td>
<td>20.4</td>
<td>4</td>
<td>94</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Control (n = 54)</td>
<td>2.5 m</td>
<td>17(31%)</td>
<td>52</td>
<td>37</td>
<td>40</td>
<td>–</td>
<td>24</td>
<td>–</td>
<td>20.4</td>
<td>4</td>
<td>94</td>
<td>NA</td>
</tr>
<tr>
<td>Bardy H(^6)</td>
<td>2,521</td>
<td>Amio (n = 845)</td>
<td>–</td>
<td>240 (28%)</td>
<td>60.4</td>
<td>76</td>
<td>29</td>
<td>56</td>
<td>25</td>
<td>11</td>
<td>3.7</td>
<td>98.1</td>
<td>14</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Placebo (n = 847)</td>
<td>–</td>
<td>244 (29%)</td>
<td>59.7</td>
<td>77</td>
<td>32</td>
<td>56</td>
<td>25</td>
<td>14</td>
<td>69</td>
<td>87</td>
<td>14</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ICD (n = 829)</td>
<td>–</td>
<td>182 (22%)</td>
<td>60.1</td>
<td>77</td>
<td>31</td>
<td>55</td>
<td>24</td>
<td>17</td>
<td>69</td>
<td>83</td>
<td>14</td>
<td>14</td>
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<tr>
<td>Bristow(^7)</td>
<td>1,520</td>
<td>OMT (n = 308)</td>
<td>3.6 yr</td>
<td>77(25%)</td>
<td>68</td>
<td>69</td>
<td>45</td>
<td>–</td>
<td>22</td>
<td>–</td>
<td>66</td>
<td>69</td>
<td>55</td>
<td>55</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pacer (n = 617)</td>
<td>3.7 yr</td>
<td>131(21%)</td>
<td>67</td>
<td>67</td>
<td>39</td>
<td>–</td>
<td>20</td>
<td>67</td>
<td>68</td>
<td>70</td>
<td>53</td>
<td>53</td>
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<tr>
<td></td>
<td></td>
<td>Pacer-D (n = 595)</td>
<td>3.5 yr</td>
<td>105(18%)</td>
<td>66</td>
<td>67</td>
<td>41</td>
<td>22</td>
<td>66</td>
<td>–</td>
<td>68</td>
<td>69</td>
<td>55</td>
<td>55</td>
</tr>
<tr>
<td>Kadish(^12)</td>
<td>458</td>
<td>Standard (n = 229)</td>
<td>3.27 yr</td>
<td>40(17%)</td>
<td>58.1</td>
<td>69.9</td>
<td>23.1</td>
<td>–</td>
<td>21.8</td>
<td>–</td>
<td>26.2</td>
<td>84.3</td>
<td>87.3</td>
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<tr>
<td></td>
<td></td>
<td>ICD (n = 229)</td>
<td>3.27 yr</td>
<td>28(12%)</td>
<td>58.4</td>
<td>72.5</td>
<td>22.7</td>
<td>22.9</td>
<td>109</td>
<td>–</td>
<td>2.27</td>
<td>85.6</td>
<td>83.8</td>
<td>NA</td>
</tr>
<tr>
<td>Kobel(^13)</td>
<td>1,116</td>
<td>ICD (n = 556)</td>
<td>20 m</td>
<td>120(22%)</td>
<td>64</td>
<td>27</td>
<td>18</td>
<td>33</td>
<td>25</td>
<td>38</td>
<td>24</td>
<td>92</td>
<td>96</td>
<td>59</td>
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<tr>
<td></td>
<td></td>
<td>Control (n = 560)</td>
<td>20 m</td>
<td>131(23%)</td>
<td>63</td>
<td>28</td>
<td>20</td>
<td>30</td>
<td>25</td>
<td>38</td>
<td>20</td>
<td>92</td>
<td>97</td>
<td>57</td>
</tr>
<tr>
<td>Strickberger(^14)</td>
<td>103</td>
<td>Amio (n = 52)</td>
<td>3.5 yr</td>
<td>7(13%)</td>
<td>60</td>
<td>74</td>
<td>36</td>
<td>67</td>
<td>23</td>
<td>–</td>
<td>–</td>
<td>50</td>
<td>81</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ICD (n = 51)</td>
<td>2.9 yr</td>
<td>6(12%)</td>
<td>58</td>
<td>67</td>
<td>31</td>
<td>58</td>
<td>22</td>
<td>–</td>
<td>–</td>
<td>53</td>
<td>90</td>
<td>20</td>
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</table>

ACE-I = angiotensin converting enzyme inhibitor; ALD-RB = aldosterone receptor blockers; Amio = amiodarone; BB = beta-blockers; CRT = cardiac resynchronization therapy; DM = diabetes mellitus; HTN = hypertension; ICD = implantable cardioverter defibrillator; LVEF = left ventricular ejection fraction; m = months; yr = years.
ICD implantation did not show a statistically significant effect when the trials with significant aldosterone antagonist usage were pooled. This highlights the mortality benefit of optimal medical therapy, especially the beneficial effects of (ALD-RB) in addition to beta-blocker and ACE/ARB. Only two trials utilized CRT and pooling of these studies showed a mortality benefit.

Our analysis demonstrates a mortality benefit with ICD in patients with NICMP. However, the limitations of our meta-analysis are that it only includes randomized control trials and the trial population may not be representative of the real-world population. Also, most of the trials in the meta-analysis utilized therapy, which is different than the current medical treatment. In addition, CRT was also not utilized in most of the studies. Thus, the results of our meta-analysis should be interpreted in the correct clinical scenario. This scenario is not uncommon as some patients with heart failure cannot tolerate guideline directed medical therapy due to side effects like hypotension. Studies have shown that many patients with heart failure are not on guideline-directed medical therapy for various reasons, and this patient population would likely benefit from implantation of ICDs. Although the DANISH trial showed no mortality benefit in patients on optimal medical therapy, our meta-analysis demonstrates that there is still a role of ICD in patients with NICMP who are not on optimal medical therapy, especially ALB-RB.

Conclusions

The DANISH trial’s failure to show mortality benefit may be due to the significant number of patients who had CRT. Our meta-analysis studied the independent effect of ICDs and showed them to be associated with net mortality benefits in patients who are not on optimal guideline directed medical therapy, especially the patients not on ALD-RB.

References


