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Medical therapy versus implantable cardioverter -defibrillator in preventing sudden cardiac death in patients with left ventricular systolic dysfunction and heart failure: A meta-analysis of >35,000 patients

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ABSTRACT

Background: Patients with left ventricular systolic dysfunction (LVSD) are at high risk of sudden cardiac death (SCD). Implantable cardioverter defibrillators (ICDs) have an important role in preventing SCD in selected patients with LVSD and chronic heart failure (CHF). Drug therapies for LVSD and CHF also appear to also be useful in reducing SCD. However, the magnitude of benefit of these approaches on SCD is uncertain. We therefore conducted a meta-analysis comparing the effect on SCD achieved by ICDs versus medical therapies, additional to standard background medical therapies including ACE inhibitors and/or beta-blockers (BBs).
Methods: Our meta-analysis included trials of >100 patients with reduced left ventricular ejection fraction (LVEF), i.e., <40%. Fourteen randomized controlled trials met the criteria for meta-analysis, 10 involving medical therapies (angiotensin receptor blockers [ARBs], mineralocorticoid receptor antagonists [MRAs], ivabradine, n3-polyunsaturated fatty acid [PUFA], ferric carboxymaltose and aliskiren) and four involving ICDs. Results were pooled using the Mantel–Haenszel random effects method.
Results: Drug therapy ($n = 36{,}172$) reduced the risk of SCD overall (risk ratio (RR) = 0.89, 95% confidence interval (CI) = 0.82–0.98, $p = 0.02$) when compared to placebo. MRAs alone were most effective in reducing SCD ($n = 11{,}032$, RR = 0.79 [0.68–0.91], $p = 0.001$). ICD insertion greatly reduced SCD ($n = 4{,}269$, RR = 0.39 [0.30–0.51], $p < 0.00001$) compared with placebo. The difference in treatment effect between the ICD and drug therapy was significant ($p < 0.002$), and between ICD and MRAs ($p < 0.002$).
Conclusions: Drug therapies when added to a standard background regimen comprising ACE inhibitor and/or BB reduced SCD overall and MRAs alone were most effective in this regard. ICDs were more effective than drugs in SCD abrogation. However, the added procedural morbidity and the cost of ICD need to be considered in decision-making re-approach to SCD reduction in the individual patient.

1. Introduction

Heart failure is a common clinical syndrome resulting in high levels of morbidity and mortality despite best current management strategies for the condition [1]. Effective pharmacological therapies for patients with systolic heart failure include ACE inhibitors and beta-blockers (BB) [1]. It has been proven to be relatively difficult to demonstrate morbidity and mortality benefits in addition to these background agents in improving outcomes in this setting. This is particularly true of sudden cardiac death (SCD), a mode of death that affects approximately 50% of all systolic heart failure patients [2]. The recent use of implantable cardioverter defibrillators (ICDs) has provided substantial benefit in this regard. As SCD is often, but not always, related to a ventricular tachyarrhythmia, ICDs are particularly effective at circumventing this problem [3–5]. What is unclear is whether more recently studied pharmacological therapies may also have beneficial effects on SCD and how this may compare to the implantation of ICDs. In contrast to drug therapies, ICDs have expensive up-front cost and come with their own morbidity related to insertion as well as potential for long-term complications of having hardware reside within the body [6,7].

The purpose of this study was therefore to meta-analyze the impact of medical therapies in addition to background ACE inhibitor and/or BB on SCD and all-cause mortality in participants with left ventricular systolic dysfunction (LVSD) and to compare these with the beneficial effects of ICDs in this regard.

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2. Methods

2.1. Search strategy

A comprehensive search of English-language publications was conducted in Medline (1946 to May 2013) and Embase (1974 to May 2013). The following keywords were used: systolic heart failure, cardiomyopathy, angiotensin inhibitors, beta-blockers, aldosterone antagonist, defibrillator, sudden cardiac death, and mortality. Manual reference checking of the bibliographies of all retrieved articles was also conducted.

2.2. Selection criteria

Studies were eligible if they were randomized placebo-controlled trials examining the effects of medical therapy (in addition to background ACE inhibitors and/or BB) or ICD on SCD in patients with left ventricular ejection fraction (LVEF) of less than 40%. Studies had to have minimum of 100 patients, and there was no minimum duration of time for the trial. Only studies published in English were considered.

2.3. Data extraction

Two independent reviewers (KYP and YL) assessed and selected the studies. We aimed to extract data on sudden death and all-cause mortality. All data were reported on intention-to-treat analysis. Unpublished data were not sought.

2.4. Assessment of the risk of bias

The assessment of the risk of bias was performed in accordance with the Cochrane Collaboration's handbook [8]. We assessed three aspects of trial quality relevant to this analysis: random sequence generation, degree of blinding, and losses to follow-up. Studies with high or unclear risk of bias for any of the three criteria were considered to be low quality.

2.5. Statistical analysis

Statistical analysis was performed using Review Manager (RevMan) Version 5.2.5 (Cochrane Collaboration) and the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines [9,10]. The results were pooled using Mantel–Haenszel random effects model given the clinical heterogeneity of the studies included. Risk Ratio (RRs) with 95% confidence interval (CI) were derived from each individual study and determined for overall outcome, and the significance of risk ratio (RR) was performed using Z-test. A weighting was calculated based on the number of events that occurred in each study. Sensitivity analyses were performed excluding post-myocardial infarction (MI) studies to determine whether there was a differential effect versus non-ischemic heart failure and heart failure remote from an MI. A further sensitivity analysis was performed excluding trials of low quality. A test for interaction was used to estimate differences between the subgroups [11]. Potential publication bias was estimated visually by funnel plots which plot the trials' effect estimates against sample size [12]. Precision in estimating the underlying treatment effect increases as the sample size of individual studies increases, with small studies scattering widely at the bottom and larger studies with greater precision scattering more narrowly at the top. The plot will take on the appearance of a symmetrical inverted funnel with all studies falling within the triangle (2 standard deviations of the effect estimate) if bias is not present. An Egger regression asymmetry test was applied [12].

3. Results

3.1. Search results

The search (Fig. 1) revealed 753 potentially relevant articles through the search engine. In addition, 5 articles were found from hand searches following manual reference checking. Six hundred and eighty of these articles were excluded based on title, and a further 55 were excluded based on abstract. Twenty-three studies remained for detailed review. Of these, six were excluded because they did not meet the search criteria with two of these including active comparators. In addition, three studies were excluded because they did not provide data on SCD. Thus, a total of 14 randomized controlled trials were included in this meta-analysis. Ten studies involved drug therapies developed since the introduction of ACE inhibitors and BB as standard of care. These include angiotensin receptor blockers (ARBs) [13–15], mineralocorticoid receptor antagonists (MRAs) [16–18], ivabradine [19], n3-PUFA [20], ferric carboxymaltose [21], and aliskiren [22]. Four studies trialled ICDs [3–5,23]. The characteristics of the participants involved in these trials are summarized in Table 1.

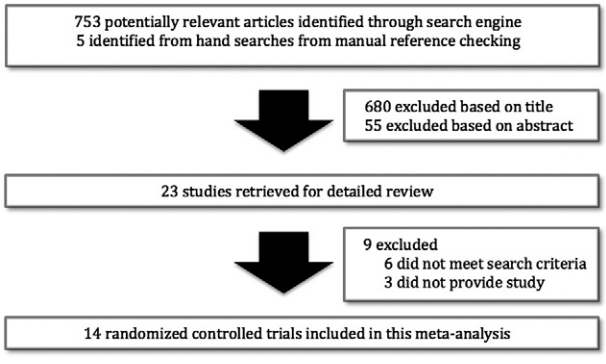

Fig. 1. Flow chart showing the search strategy and exclusion of articles.

The risk of bias was assessed as low overall. Of the 14 trials, 12 reported adequate randomization except for the RALES and Val-HeFT trial; hence, these two trials were deemed as low quality. All trials involving medications were adequately blinded, and the ICD trials were unblinded. However, this was considered not likely to have influenced outcomes. Losses to follow-up were low and generally equal across all trials.

3.2. Sudden cardiac death (SCD)

Overall, there was a statistically significant reduction in SCD with drug therapies when compared with placebo ($n = 36{,}172$, RR = 0.89 [0.82–0.98], $p = 0.02$) (Fig. 2). This result was unchanged when studies of low quality were excluded ($n = 29{,}499$, RR = 0.89 [0.80–0.98], $p = 0.02$). When post-MI studies were excluded, there was a borderline statistically significant reduction in the risk of SCD compared with placebo ($n = 29540$, RR = 0.91 [0.82–1.00], $p = 0.05$) (Fig. 3). MRAs alone compared with placebo were most effective in reducing SCD by 21% ($n = 11{,}032$, RR = 0.79 [0.68–0.91], $p = 0.001$) (Fig. 4). ICD insertion greatly reduced SCD by 61% ($n = 4{,}269$, RR = 0.39 [0.30–0.51], $p < 0.00001$) compared with placebo (Fig. 5). The test of interaction indicated that the difference in treatment effect between the ICD and the drug therapy was significant ($p < 0.002$), and between ICD and MRAs also significant ($p < 0.002$).

3.3. All-cause mortality

Drug therapies in addition to background ACE inhibitors and/or BB significantly reduced the risk of all-cause mortality compared to placebo by 10% overall ($n = 36172$, RR = 0.90 [0.85–0.95], $p = 0.0002$) (Fig. 6). This result was unchanged when studies of low quality were excluded ($n = 29499$, RR = 0.91 [0.87–0.95], $p < 0.0001$). ICD insertion reduced all-cause mortality by 26% ($n = 4{,}269$, RR = 0.74 [0.65–0.83], $p < 0.00001$) (Fig. 7).

3.4. Assessment of potential publication bias

No evidence of publication bias was suggested by visual inspection of the funnel plots (Fig. 8) and the Egger regression asymmetry test (p = 0.13248).

4. Discussion

Sudden cardiac death generally refers to an unexpected death from a cardiovascular cause in a person with or without pre-existing heart disease [24]. SCD ranges from 50 to 100 per 100,000 in the general population [24]. It has been known that ACE inhibitors and beta-blockers do offer protection against SCD [25,26]. However, it is unclear whether more recently studied pharmacological therapies when added to ACE inhibitors and/or beta-blockers may also have beneficial effects on SCD and how this may compare to SCD reduction observed with the implantation of ICDs.