


## SYSTEMATIC REVIEW AND META-ANALYSIS

# Implantable Cardioverter–Defibrillators in Trials of Drug Therapy for Heart Failure: A Systematic Review and Meta-Analysis

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**BACKGROUND:** Medical therapy for heart failure with reduced ejection fraction evolved since trials validated the use of implantable cardioverter–defibrillators (ICDs). We sought to evaluate the performance of ICDs in reducing mortality in the era of modern medical therapy by means of a systematic review and meta-analysis of contemporary randomized clinical trials of drug therapy for heart failure with reduced ejection fraction.

**METHODS AND RESULTS:** We systematically identified randomized clinical trials that evaluated drug therapy in patients with heart failure with reduced ejection fraction that reported mortality. Studies that enrolled <1000 patients, patients with left ventricular ejection fraction >40%, or patients in the acute phase of heart failure and study treatment with devices were excluded. We identified 8 randomized clinical trials, including 31 701 patients of whom 3631 (11.5%) had an ICD. ICDs were associated with a lower risk of all-cause mortality (relative risk [RR], 0.85; 95% CI, 0.78–0.94) and sudden cardiac death (RR, 0.49; 95% CI, 0.40–0.61). Results were consistent among studies published before and after 2010. In meta-regression analysis, the proportion of nonischemic etiology did not affect the associated benefit of ICD.

**CONCLUSIONS:** In our meta-analysis of contemporary randomized trials of drug therapy for heart failure with reduced ejection fraction, the rate of ICD use was low and associated with a decreased risk in both all-cause mortality and sudden cardiac death. This benefit was still present in trials with new medical therapy.

**Key Words:** all-cause mortality ■ heart failure with reduced ejection fraction ■ implantable cardioverter–defibrillators ■ sudden cardiac death

In patients with heart failure with reduced ejection fraction (HFrEF), sudden cardiac death (SCD) is a major contributor for the burden of all-cause mortality.<sup>1</sup> Medical therapy with modulators of neurohormonal systems involved in the triggering and progression of HFrEF is the mainstay of the treatment to reduce the risks of SCD and all-cause mortality.<sup>2</sup>

Implantable cardioverter–defibrillators (ICDs) further reduce these risks and are currently recommended in patients with New York Heart Association functional

class II or III and a left ventricular ejection fraction (LVEF) of 35% or less for the primary prevention of SCD and to prolong life.<sup>3–5</sup> However, the rate of ICD use in clinical practice is suboptimal, even in populations enrolled in contemporary clinical trials of drug therapy for HFrEF.<sup>2,6</sup>

We sought to evaluate the performance of ICDs in reducing SCD and all-cause mortality in populations enrolled in contemporary randomized clinical trials of drug therapy for HFrEF by means of a systematic review and meta-analysis.

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Supplementary Materials for this article are available at <https://www.ahajournals.org/doi/suppl/10.1161/JAHA.119.015177>

For Sources of Funding and Disclosures, see page 7.

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## CLINICAL PERSPECTIVE

### What Is New?

- Implantable cardioverter–defibrillator use was associated with reduced all-cause mortality and sudden cardiac death in patients enrolled in contemporary heart failure with reduced ejection fraction trials.
- Implantable cardioverter–defibrillator benefit was not influenced by nonischemic etiology.
- Implantable cardioverter–defibrillators were only used in 12% of patients.

### What Are the Clinical Implications?

- Implantable cardioverter–defibrillator use still appears to reduce mortality among patients with heart failure with reduced ejection fraction on top of contemporary optimal medical therapy.
- The findings support current implantable cardioverter–defibrillator guidelines.

## Nonstandard Abbreviations and Acronyms

|              |  |
|--------------|--|
| <b>ACEI</b>  | angiotensin-converting-enzyme inhibitors     |
| <b>ARB</b>   | angiotensin-2 receptor blockers              |
| <b>CRT</b>   | cardiac resynchronization therapy            |
| <b>HFrEF</b> | heart failure with reduced ejection fraction |
| <b>ICD</b>   | implantable cardioverter–defibrillator       |
| <b>LVEF</b>  | left ventricular ejection fraction           |
| <b>SCD</b>   | sudden cardiac death                         |

## METHODS

### Search of the Studies

All data and materials have been made publicly available at the Dataverse Project and can be accessed at <https://dataverse.harvard.edu/dataset.xhtml?persistentId=doi%3A10.7910%2FDVN%2FVU8QNE>.

A systematic review and trial-level meta-analysis of randomized clinical trials that evaluated drug therapy in patients with HFrEF were performed according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses guidelines.<sup>7</sup> Potential trials were identified from PubMed, EMBASE, and CENTRAL (Cochrane Central Register of Controlled Trials) from December 1996, the date of the publication of the first clinical trial demonstrating the efficacy of ICD in reducing mortality,<sup>8</sup> through February 8, 2019 using the following search terms ([heart failure OR cardiac

failure OR cardiomyopathy] AND [reduced ejection fraction OR ejection fraction less OR systolic] AND [randomized OR randomised OR randomly] AND [mortality OR death]). We excluded studies enrolling <1000 patients, patients with left ventricular ejection fraction >40%, patients enrolled in the acute phase of heart failure, and study treatments with devices.

### Data Extraction

Two authors (F.G., J.F.) independently assessed titles, abstracts, and full texts, when appropriate, for eligibility and data extraction. Disagreements were resolved by consensus or, if necessary, by a third author (F.C./J.C.). Details on the study design, patient characteristics, treatments, and outcome measures of all-cause death and SCD were collected from the main publication<sup>9–16</sup> and subsequent subanalysis publications.<sup>2,17,18</sup>

### Assessment of Risk of Bias

Two authors (J.C., F.C.) independently assessed the risk of bias within the trials using the Cochrane Collaboration risk-of-bias tool. The reviewers evaluated the risk of bias as “low,” “high,” or “unclear” for the following 6 domains: random sequence generation, allocation concealment, participants and personnel blinding, outcome assessment blinding, selective reporting, and other sources of bias.

### Statistical Analysis

Random effects were used to pool the relevant studies and summarize the evidence because of the variability of demographic, clinical, and pharmacologic treatment baseline characteristics among the included study populations (Table 1). The results were presented as relative risk (RR) with 95% CIs. A 2-sided  $P < 0.05$  was considered significant.

We assessed for heterogeneity using the Cochran Q test, which was quantified by the  $I^2$  statistic. A fixed-effects model was additionally used in case of heterogeneity across studies.

We conducted sensitivity analyses in studies published before and after 2008, studies including patients with LVEF 35% to 40% and only patients with LVEF <35%, and studies reporting the use of cardiac resynchronization therapy (CRT) and not reporting the use of this device. We set the median of the search period of studies (January 2008) as the landmark to differentiate older from newer studies.

We performed random-effects meta-regression with the baseline characteristics of study populations (prevalence for categorical variables and mean/median value for continuous variables) as a covariate to assess their potential effects on the impact of the ICD on sudden death.

**Table 1. Study Design, Baseline Characteristics, Duration of Follow-Up, and Major Outcomes of Included Studies**

| Randomized Clinical Trial                 | BEST <sup>9</sup>        | CHARM-Added <sup>10</sup> | CHARM-Alternative <sup>11</sup> | CORONA <sup>12</sup>                   | EMPHASIS-HF <sup>13</sup>             | WARCEF <sup>14</sup>                  | PARADIGM-HF <sup>15</sup>         | ATMOSPHERE <sup>16</sup>                      |
|---|--------------------------|---------------------------|---------------------------------|--|---------------------------------------|---------------------------------------|-----------------------------------|---|
| Year of publication                       | 2001                     | 2003                      | 2003                            | 2007                                   | 2011                                  | 2012                                  | 2014                              | 2016  |
| Design                                    |                          |                           |                                 |  |                                       |                                       |                                   |   |
| Target population                         | ACEI treated HF patients | ACEI treated HF patients  | ACEI intolerant HF patients     | Older, ischemic and stable HF patients | Optimized medical therapy HF patients | Optimized medical therapy HF patients | Enalapril treated HF patients     | Optimized medical therapy HF patients         |
| Target LVEF (%)                           | ≤35                      | ≤40                       | ≤40                             | ≤40                                    | ≤30 (≤35 if QRS >130 ms)              | ≤35                                   | ≤40                               | ≤35   |
| Study treatments                          | Bucindolol vs placebo    | Candesartan vs placebo    | Candesartan vs placebo          | Rosuvastatin vs placebo                | Eplerenone vs placebo                 | Warfarin vs aspirin                   | Sacubitril-valsartan vs enalapril | Aliskiren+enalapril vs aliskiren vs enalapril |
| Population                                |                          |                           |                                 |  |                                       |                                       |                                   |   |
| Total (N)                                 | 2708                     | 2548                      | 2028                            | 5011                                   | 2737                                  | 2293                                  | 8442                              | 7016  |
| Age, y                                    | 60                       | 64.1                      | 66.6                            | 73                                     | 68.7                                  | 61                                    | 63.8                              | 63.3  |
| Female, %                                 | 22                       | 21.3                      | 31.9                            | 24                                     | 22.3                                  | 20                                    | 21.8                              | 21.7  |
| Hypertension, %                           | 41                       | 51.8                      | 55.1                            | 63                                     | 66.5                                  | 59.6                                  | 70.7                              | 61.7  |
| Diabetes mellitus, %                      | 35.5                     | 29.8                      | 27                              | 29.5                                   | 31.4                                  | 31.5                                  | 34.7                              | 27.7  |
| Nonischemic, %                            | 41.5                     | 37.6                      | 30.2                            | 0                                      | 31                                    | 57                                    | 40                                | 44  |
| Atrial fibrillation, %                    | 11.5                     | 46.1                      | 74.6                            | 23.5                                   | 30.9                                  | 3.7                                   | 36.8                              | 40.6  |
| Mean eGFR, mL/min per 1.73 m <sup>2</sup> | 65.5±23.2                | 71.5±28                   | 71.5±28                         | 58±15                                  | 70.8±21.8                             | 68.4±20.5                             | 67.6±18.5                         | 74±24   |
| NYHA III/IV, %                            | 100                      | 75.9                      | 52.4                            | 62.9                                   | 0                                     | 30.9                                  | 24.6                              | 36.7  |
| LVEF, %                                   | 23                       | 28                        | 29.9                            | 31                                     | 26.2                                  | 25.0                                  | 29.5                              | 28.4  |
| Beta-blockers, %                          | 50                       | 55.5                      | 54.5                            | 75.2                                   | 86.7                                  | 89.9                                  | 92.5                              | 91.7  |
| ACEI/ARB, %                               | 97.6                     | 99.9                      | 50                              | 91.8                                   | 93.4                                  | 98.4                                  | 100                               | 66.6  |
| Mineralocorticoid antagonist, %           | 3.5                      | 17.2                      | 23.8                            | 39.2                                   | 49.8                                  | 60.4                                  | 55.3                              | 37.1  |
| ICD, %                                    | 3.4                      | 3.9                       | 3.4                             | 2.7                                    | 15.4                                  | 18.2                                  | 14.7                              | 14.9  |
| CRT, %                                    | NR                       | NR                        | NR                              | NR                                     | 8.5                                   | NR                                    | 6.8                               | 5.6   |
| Follow-up, mo                             | 24                       | 41                        | 33.7                            | 32.8                                   | 21                                    | 22.8                                  | 27                                | 36.6  |
| All-cause death (100 patient/years)       | 15.88                    | 9.06                      | 9.85                            | 10.86                                  | 8.02                                  | 11.71                                 | 8.18                              | 8.86  |
| Sudden death (100 patient/years)          | ...                      | 3.65                      | 3.35                            | 4.69                                   | 2.84                                  | 4.07                                  | 2.97                              | ...   |

ACEI indicates angiotensin-converting-enzyme inhibitors; ARB, antitensin-2 receptor blockers; ATMOSPHERE, Aliskiren Trial to Minimize Outcomes in Patients with Heart Failure; BEST, Beta-Blocker Evaluation of Survival Trial; CHARM - Added, Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity - Added Trial; CHARM - Alternative, Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity - Alternative Trial; CORONA, Controlled Rosuvastatin Multinational Trial in Heart Failure; CRT, cardiac resynchronization therapy; eGFR, estimated glomerular filtration rate; EMPHASIS-HF, Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure; HF, heart failure; ICD, implantable cardioverter-defibrillator; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association functional class; NR, not reported; and WARCEF, Warfarin versus Aspirin in Reduced Cardiac Ejection Fraction.

We looked for potential publication bias using funnel plots and Egger's test.

The primary analyses were performed using RevMan version 5.3 (The Nordic Cochrane Center, The Cochrane Collaboration, Copenhagen, Denmark).

## RESULTS

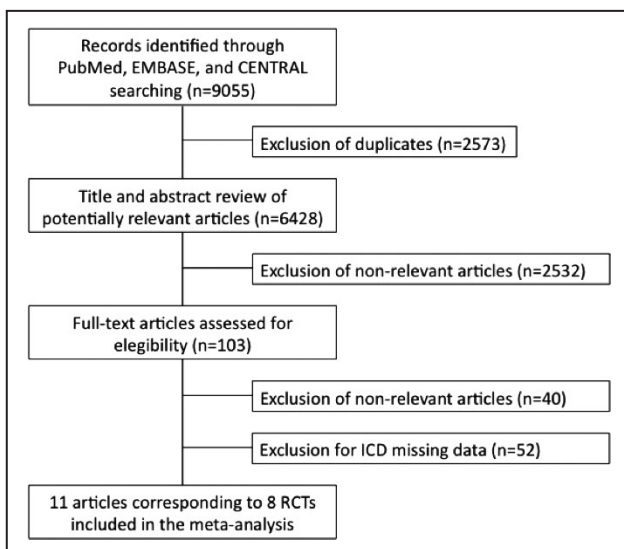
### Studies Included

After manual screenings of the titles, abstracts, and full texts, we identified 8 studies that fulfilled the inclusion and exclusion criteria with outcome measures of interest for patients with and without ICD (Figure 1). In the ATMOSPHERE (Aliskiren Trial to Minimize Outcomes in Patients with Heart Failure)<sup>16</sup> study, the results were reported together for 1048 patients with ICDs and 107 patients with isolated CRT pacemakers. The WARCEF (Warfarin versus Aspirin in Reduced Cardiac Ejection Fraction) study data refer to a propensity-matched analysis with the entire cohort of ICD patients and 44.6% of the cohort without an ICD.<sup>18</sup>

The SHIFT (Ivabradine and outcomes in chronic heart failure)

study, although reporting univariable association of ICDs with all-cause mortality using a hazard ratio (HR) (0.85; 95% CI, 0.58–1.58) could not be included because of missing absolute data.<sup>19</sup>

We included a total of 31 701 patients in this analysis, of whom 3631 (11.5%) had an ICD. Table 1 provides a comprehensive description of each included study.



**Figure 1.** Flowchart diagram illustrating studies selection methodology.

ICD indicates implantable cardioverter–defibrillator; and RCT, randomized clinical trial.

### All-Cause Death

In 8 studies there were 715 deaths in 3631 patients (19.7%) with ICDs and 7086 deaths in 28 070 patients (25.2%) without ICDs (random-effects risk ratio, 0.85; 95% CI, 0.78–0.94;  $I^2=24%$ ) (Figure 2). Mortality per 100 patient/year was 8.00 and 9.84, respectively. Fixed-effects risk ratio was 0.86 (95% CI, 0.80–0.92) (Figure S1).

### Sudden Cardiac Death

In 6 studies there were 91 SCDs in 2386 patients (3.8%) with ICDs and 1855 SCDs in 19 591 patients (9.5%) without ICDs (random-effects risk ratio, 0.49; 95% CI, 0.40–0.61;  $I^2=0%$ ) (Figure 3). SCDs per 100 patient/year was 1.74 and 3.79, respectively. Fixed-effects risk ratio was 0.48 (95% CI, 0.39–0.60) (Figure S2).

### Sensitivity Analysis

The results were consistent among studies published before and after 2008, those that did or did not include patients with LVEF between 35% and 40%, and studies that did or did not report the use of CRT devices (Table 2).

The sensitivity analysis for all-cause death after exclusion of the ATMOSPHERE study showed similar results (RR, 0.83; 95% CI, 0.75–0.91;  $I^2=11%$ ).

### Meta-Regression Analysis

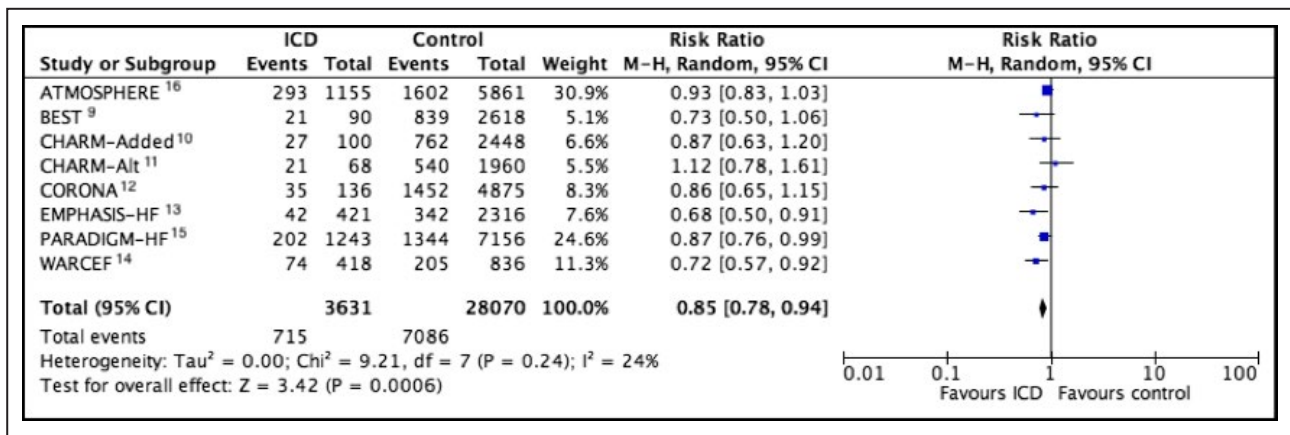
Meta-regression analyses investigating the potential effects of demographic and clinical characteristics on the all-cause death associated with ICD compared to no ICD revealed significant effects of atrial fibrillation ( $P=0.013$ ), left ventricular ejection fraction ( $P=0.040$ ), and use of angiotensin-converting-enzyme inhibitors (ACEI) or antiotensin-2 receptor blockers (ARB) ( $P=0.035$ ) (Figure S3). There was no significant impact of age, sex, hypertension, diabetes mellitus, nonischemic etiology, New York Heart Association III to IV functional classes, use of beta-blockers, or mineralocorticoid antagonists on the effect of ICDs on all cause-death.

### Risk of Bias

All of the included studies did not randomize ICD implantation. No publication bias was found using visual inspection of a funnel plot and an Egger test ( $P=0.302$ ) (Figure S4).

## DISCUSSION

In this systematic review and meta-analysis of contemporary clinical trials for drug therapy of HFrEF, the use of ICDs was scarce but associated with a significant



**Figure 2. Forest plots comparing patients with ICD vs without ICD for the outcome all-cause death.**

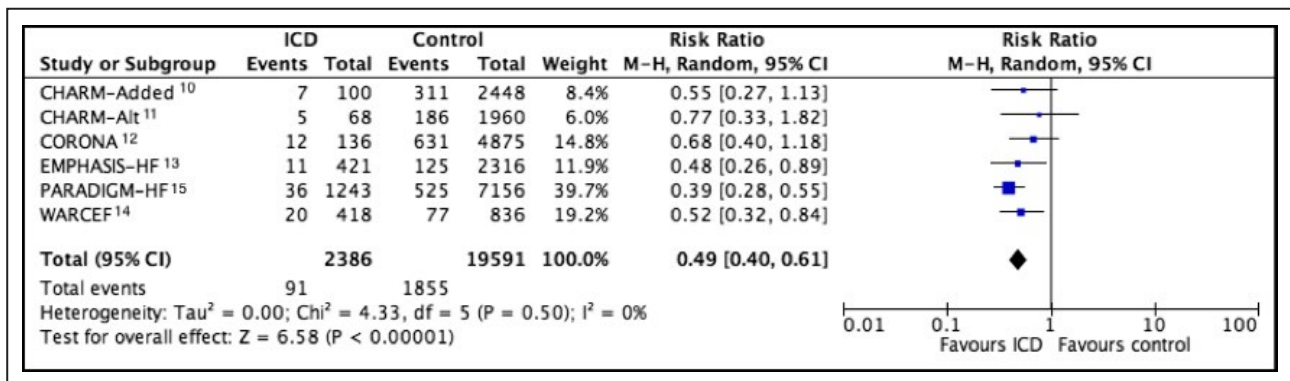
Pooled estimates were calculated by random effects. ATMOSPHERE indicates Aliskiren Trial to Minimize Outcomes in Patients with Heart Failure; BEST, Beta-Blocker Evaluation of Survival Trial; CHARM-Added, Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity - Added Trial; CHARM-Alt, Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity - Alternative Trial; CORONA, Controlled Rosuvastatin Multinational Trial in Heart Failure; EMPHASIS-HF, Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure; ICD, implantable cardioverter-defibrillator; M-H, Mantel-Haenszel methods; PARADIGM-HF, Prospective Comparison of ARNI (Angiotensin Receptor-Nepriylsin Inhibitor) with ACEI (Angiotensin-Converting Enzyme Inhibitor) to Determine Impact on Global Mortality and Morbidity in Heart Failure Trial; and WARCEF, Warfarin versus Aspirin in Reduced Cardiac Ejection Fraction.

reduction in all-cause death and SCD when compared to no use.

Current guidelines supporting ICD implantation for primary prevention are backed up on long-standing trials, namely, the MADIT II (Multicenter Automatic Defibrillator Implantation Trial II)<sup>20</sup> and the SCD-HeFT (Sudden Cardiac Death in Heart Failure Trial)<sup>3</sup> that showed up to a 31% reduction in all-cause mortality. However, HFrEF patients faced dramatic changes over time regarding epidemiology, etiology, and optimal medical therapy concept, including beta-blockers, ACEI/ARB, mineralocorticoid antagonists,

sacubitril-valsartan, and even mechanical support concerning end-stage heart failure. These medical advances culminated in the progressive reduction of all-cause death and SCD,<sup>2</sup> challenging the present additional benefit of ICDs.

Our study analyzed contemporary randomized clinical trials that were performed within a highly selected population where those with significant comorbidities, such as significant renal or hepatic diseases and any other condition that substantially reduces life expectancy, are often excluded and where compliance toward optimal medical therapy is assured in greater



**Figure 3. Forest plots comparing patients with ICD vs without ICD for the outcome sudden cardiac death.**

Pooled estimates were calculated by random effects. CHARM-Added indicates Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity - Added Trial; CHARM-Alt, Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity - Alternative Trial; CORONA, Controlled Rosuvastatin Multinational Trial in Heart Failure; EMPHASIS-HF, Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure; ICD, implantable cardioverter-defibrillator; M-H, Mantel-Haenszel methods; PARADIGM-HF, Prospective Comparison of ARNI (Angiotensin Receptor-Nepriylsin Inhibitor) with ACEI (Angiotensin-Converting Enzyme Inhibitor) to Determine Impact on Global Mortality and Morbidity in Heart Failure Trial; and WARCEF, Warfarin versus Aspirin in Reduced Cardiac Ejection Fraction.



**Table 2. Sensitivity Analysis for Studies Published Before and After 2010 and Studies That Did or Did Not Include Patients With LVEF Between 35% and 40%**

|  | Risk Ratio and 95% CI | P Value for Interaction |
|--|-----------------------|-------------------------|
| All-cause death                          |                       |                         |
| Studies published before 2008            | 0.88 (0.75–1.04)      | 0.57                    |
| Studies published after 2008             | 0.83 (0.73–0.94)      | ...                     |
| Studies with EF 35% to 40% patients      | 0.89 (0.79–0.99)      | 0.27                    |
| Studies with only EF <35% patients       | 0.79 (0.65–0.94)      | ...                     |
| Studies reporting the use of CRT         | 0.86 (0.76–0.98)      | 0.70                    |
| Studies not reporting the use of CRT     | 0.83 (0.72–0.96)      | ...                     |
| Sudden cardiac death                     |                       |                         |
| Studies published before 2008            | 0.66 (0.45–0.97)      | 0.09                    |
| Studies published after 2008             | 0.44 (0.34–0.56)      | ...                     |
| Studies with LVEF 35% to 40% patients    | 0.52 (0.38–0.73)      | 0.89                    |
| Studies without LVEF 35% to 40% patients | 0.51 (0.35–0.74)      | ...                     |
| Studies reporting the use of CRT         | 0.41 (0.31–0.55)      | 0.08                    |
| Studies not reporting the use of CRT     | 0.60 (0.44–0.81)      | ...                     |

CRT indicates cardiac resynchronization therapy; EF, Ejection Fraction; and LVEF, left ventricular ejection fraction.

proportion than in a real-world setting. This investigation showed a relative reduction both in all-cause death and SCD by 15% and 50%, respectively, on top of the optimal conditions associated with the use of ICDs. These results are consistent with previous studies,<sup>3,4,20</sup> even though a theoretic different HFREF population sample.

The absence of significant heterogeneity among the studies analyzed emphasizes the association between ICD use and lower risk of all-cause death. The RR of all-cause death was not favorable to the use of ICD only in the CHARM (Candesartan in Heart Failure: Assessment of Reduction in Mortality and morbidity) Alternative study, which may be related to the small number of ICD patients, only 68, that may have generated a random distribution effect on events. In the SHIFT study, ICD use was also associated with 15% RR reduction in all-cause death,<sup>19</sup> which is superimposable to that observed in our meta-analysis. The association with reduced risk of SCD revealed no heterogeneity among the 6 studies included in the analysis. The lower risk of SCD observed in ICD patients should be framed in a possible context of perceived higher risk of death in these patients. Despite the fact that PARADIGM HF (Prospective Comparison of ARNI [Angiotensin Receptor-Nepriylsin Inhibitor] with ACEI [Angiotensin-Converting Enzyme Inhibitor] to

Determine Impact on Global Mortality and Morbidity in Heart Failure Trial) and ATMOSPHERE have excluded patients with ventricular arrhythmias occurring 3 months prior to screening that were untreated, it is possible that ICD implantation has been performed for the secondary prevention of sudden death, and no study has excluded these patients.<sup>9–16</sup> The rates of recurrent ventricular arrhythmias and mortality remain high in patients who received an ICD for secondary prevention.<sup>21</sup>

The growing adherence of evidence-based heart failure medication throughout the years should be highlighted. When comparing the older (BEST [Beta-Blocker Evaluation of Survival Trial], CHARM-Added, and CHARM-Alternative)<sup>9–11</sup> against the newer trials (PARADIGM-HF and ATMOSPHERE),<sup>15,16</sup> both beta-blockers and mineralocorticoid antagonists almost doubled their compliance rates. It is a different case scenario regarding ACEI/ARB adherence because it remained persistently high from early trials, with the exception of CHARM-Alternative,<sup>11</sup> where half of the population with intolerance to ACEI received an ARB, and ATMOSPHERE,<sup>16</sup> where 2 of 3 patients were on ACEI, although all received a renin-angiotensin-aldosterone system inhibitor blockage (enalapril and/or aliskiren). Since 2008, the utilization rate of ACEI/ARB was >93%, beta-blockers >86%, and mineralocorticoid antagonists >50%. However, sensitivity analysis did not reveal significant differences in all-cause death or SCD in studies published either before<sup>9–12</sup> or after 2008.<sup>13–16</sup> These results reinforce the impact of ICD on preventing sudden death, even in patients with contemporary guideline optimal medical therapy. The results were also consistent in studies that included patients with LVEF between 35% and 40%. As the indication for ICD is based on the presence of LVEF <35%, the inclusion of patients with LVEF between 35% and 40% in the group without ICD and therefore with a lower risk of SCD could reduce its benefit in these studies.

The reproducibility of our results is shown in the recently published real-world SwedeHF (Swedish Heart Failure) Registry that enrolled 1305 patients fulfilling European Society of Cardiology criteria for ICD implantation for primary prevention.<sup>22</sup> After 1:1 propensity score matching to non-ICD recipients, all-cause mortality risk within 1 and 5 years reduced 27% and 12%, respectively. The results were consistent with all subgroup analysis, but data on SCD were not reported.

The ICD rate of use was 11.5%, which is low for a class I recommended treatment in patients with HFREF.<sup>5</sup> However, the use of this device therapy consistently increased >4-fold between studies published before and after 2008. One study reported improvement in LVEF, limited life expectancy, New York Heart Association functional class IV, and patient refusal as the main causes for nonimplantation of ICDs.<sup>23</sup> Patients with HFREF followed

in primary health care are less often referred for ICD implantation because of the poor perception of benefits against contraindications.<sup>22</sup> The implementation of quality control and performance measure programs has been shown to increase adherence to the primary prevention of SCD with ICD.<sup>6</sup> Only 3 studies, all published after 2008, reported the use of CRT, whose prevalence ranged from 5.6% to 8.5%.<sup>13,15,16</sup> Although CRT amplifies the benefit of ICD in reducing mortality in patients with HFrEF,<sup>24</sup> our sensitivity analysis with studies reporting the use of CRT showed no significant differences in all-cause death or SCD compared to studies not reporting the use of CRT.

Meta-regression analyses demonstrated that increasing the proportion of patients with atrial fibrillation attenuates the benefit of ICD in reducing death from any cause. In patients with HFrEF, atrial fibrillation has been described as a marker of disease severity,<sup>25</sup> so its presence may lead to a higher risk of death from pump failure, with the consequent lower benefit of ICD in reducing mortality.<sup>26</sup>

Clinical trials with lower LVEF mean values showed a greater reduction in all-cause death associated with ICD use, which is in line with the inverse relationship between LVEF and the risk of SCD described in the literature.<sup>27,28</sup>

Widespread use of ACEI/ARB was associated with a lower risk of all-cause death in patients with ICD compared to patients without ICD, highlighting the complementarity of pharmacological therapy with devices in patients with HFrEF. In a post hoc analysis of the COMPANION (Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure) trial, the authors reported that both ACEI and ARB lowered the risk of appropriate ICD therapy, thus demonstrating a synergistic effect between these therapies.<sup>29</sup>

An important issue regarding the effectiveness of ICDs is the relative uncertainty of their benefit in reducing all-cause death in patients with nonischemic HFrEF.<sup>30</sup> The WARCEF study was the only study that published results on the relative benefit of ICD use compared to nonuse on all-cause death in patients with nonischemic etiology.<sup>18</sup> The use of ICD was associated with no significant benefit on all-cause death in those patients (HR, 0.984; 95% CI, 0.641–1.509;  $P=0.941$ ), unlike that observed in patients with ischemic etiology (HR, 0.640; 95% CI, 0.448–0.915;  $P=0.015$ ). Notwithstanding these facts, meta-regression analysis showed no significant correlation between changes in the proportion of nonischemic etiology and the relative benefit on all-cause death of ICD use compared to nonuse.

## Limitations

This is a meta-analysis of aggregate data from estimates of individual studies, and therefore individual participant data were not available. Although the studies have different designs, populations, pharmacological

treatments, and follow-up, any significant heterogeneity on the reported outcomes was not found, and sensitivity analyses were consistent with the main results. In the absence of randomization, it is possible that patients without ICD could have more comorbidity than patients with ICDs, leading to higher all-cause death. However, it is well known that patients enrolled in clinical trials generally do not have many comorbidities, which is confirmed by the baseline characteristics of the population with and without ICD before propensity matching included in the WARCEF study.<sup>18</sup> The clinical trials included in this systematic review and meta-analysis did not report the type of ICD implanted or the incidence of appropriate and inappropriate shocks during the study follow-up. Recognizing that ICD shocks have a negative impact on prognosis<sup>31</sup> and the subcutaneous ICD is for selected patients,<sup>32</sup> the inclusion of these variables in sensitivity analyses could bring new insights to the results. Finally, the use of CRT in ICD patients may have amplified the benefit of this device, although concomitant use was relatively low.

## CONCLUSIONS

In our meta-analysis of contemporary randomized trials of drug therapy for HFrEF, the rate of ICD use was low. The use of ICDs was associated with significant reductions in all-cause death and SCD, and the results were consistent in all sensitivity analyses. Our results call for the need to adhere to the current guidelines for the management of HFrEF.

## ARTICLE INFORMATION

Received November 12, 2019; accepted March 10, 2020.

### Affiliations

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### Sources of Funding

None.

### Disclosures

Dr Cavaco has consulting fees under 2000 dollars/year from being an advisory board member of Boston Scientific. Dr Morgado has consulting fees under 1000 dollars/year from being proctor and speaker of Johnson & Johnson and Microport, respectively. The remaining authors have no disclosures to report.

### Supplementary Materials

Figures S1–S4

References 9–16

## REFERENCES

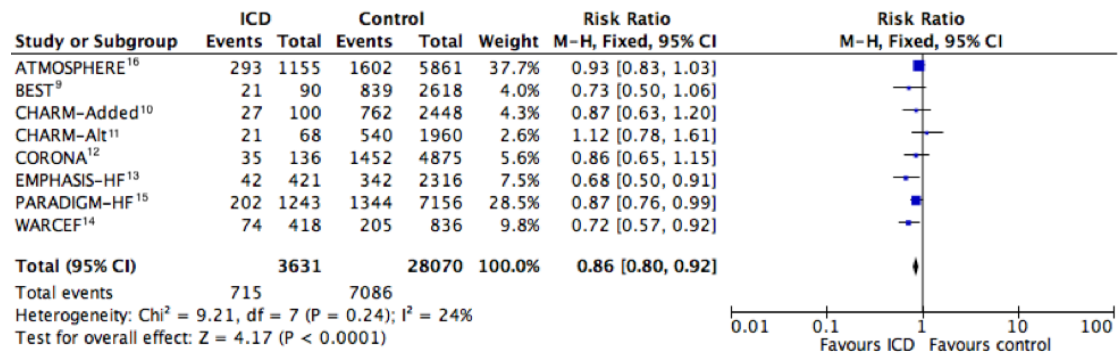
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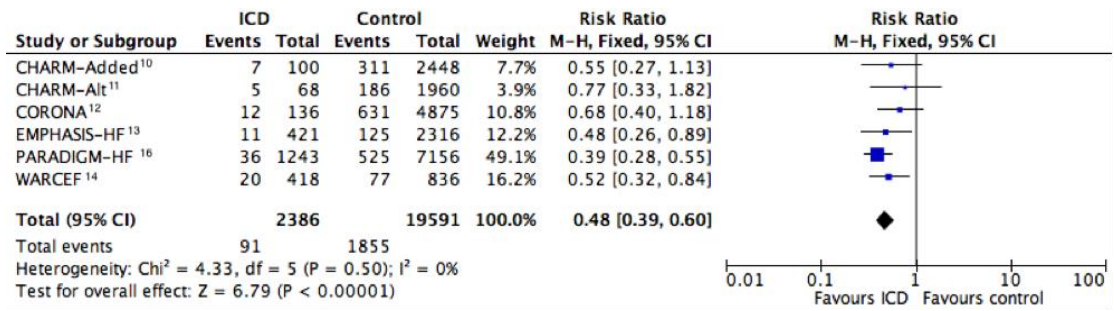


# **Supplemental Material**

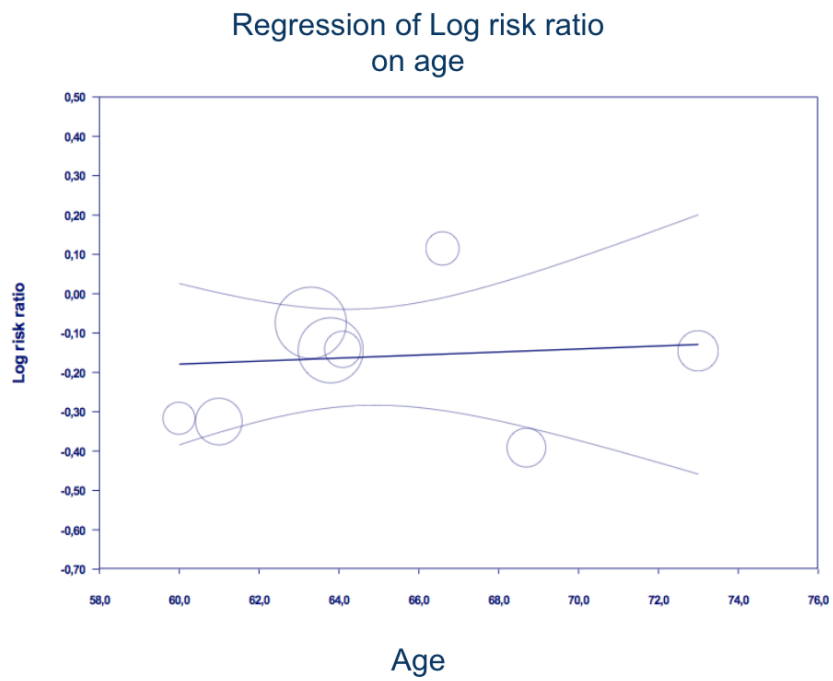
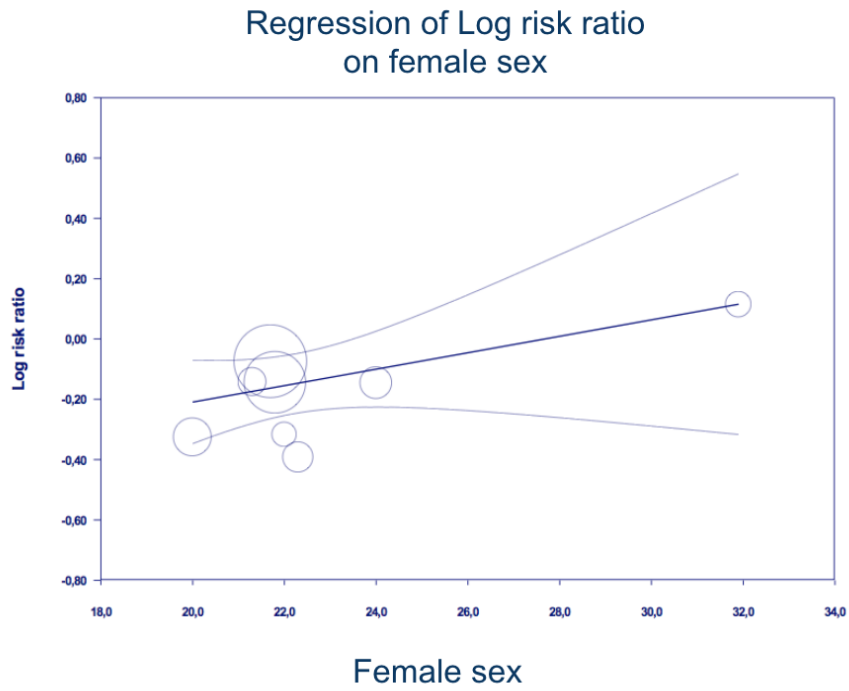
**Figure S1. Fixed-effects Risk Ratio for All-Cause Death.**



**Figure S2. Fixed-effects Risk Ratio for Sudden Cardiac Death.**

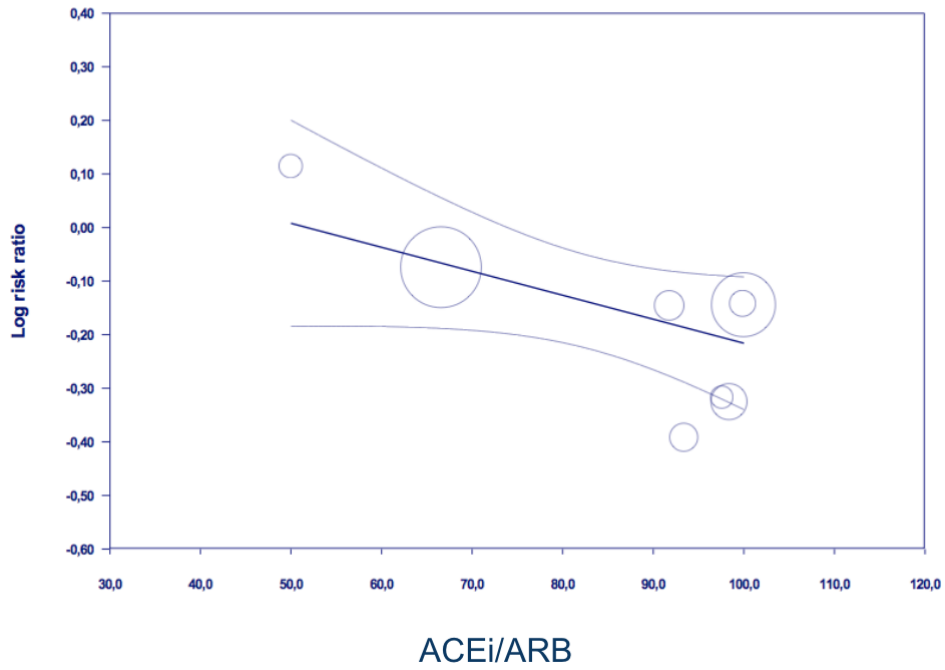


**Figure S3. Meta-regression analysis on all-cause death.**

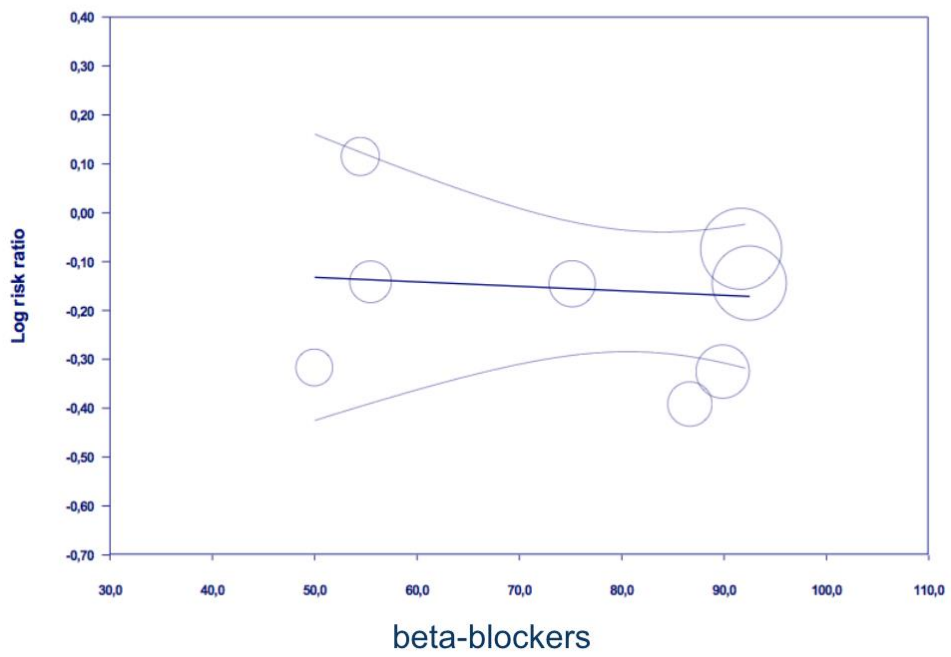




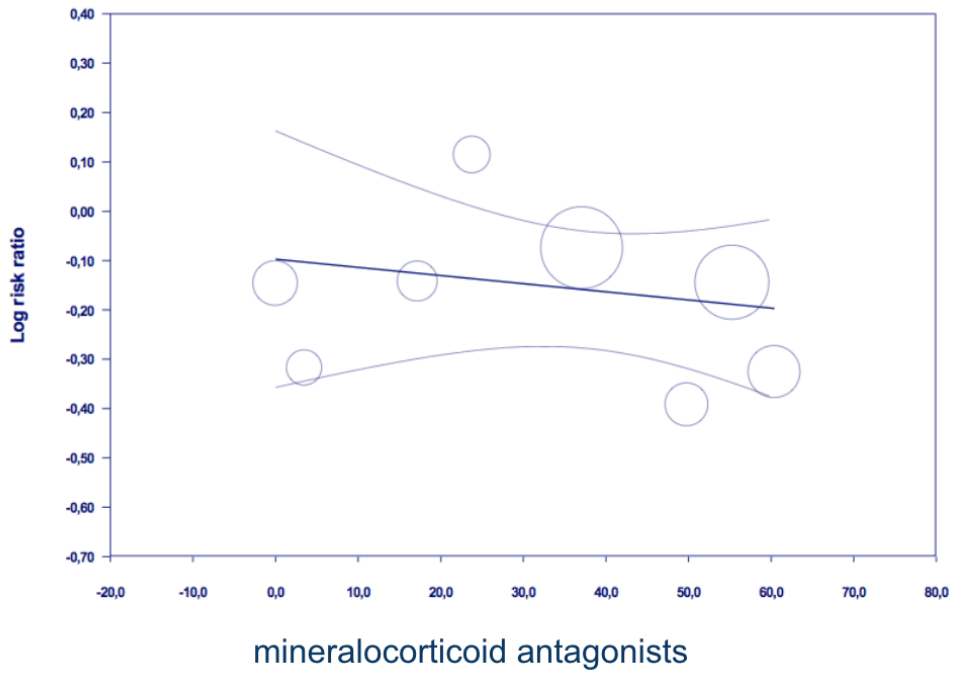
Regression of Log risk ratio  
on ACEi/ARB



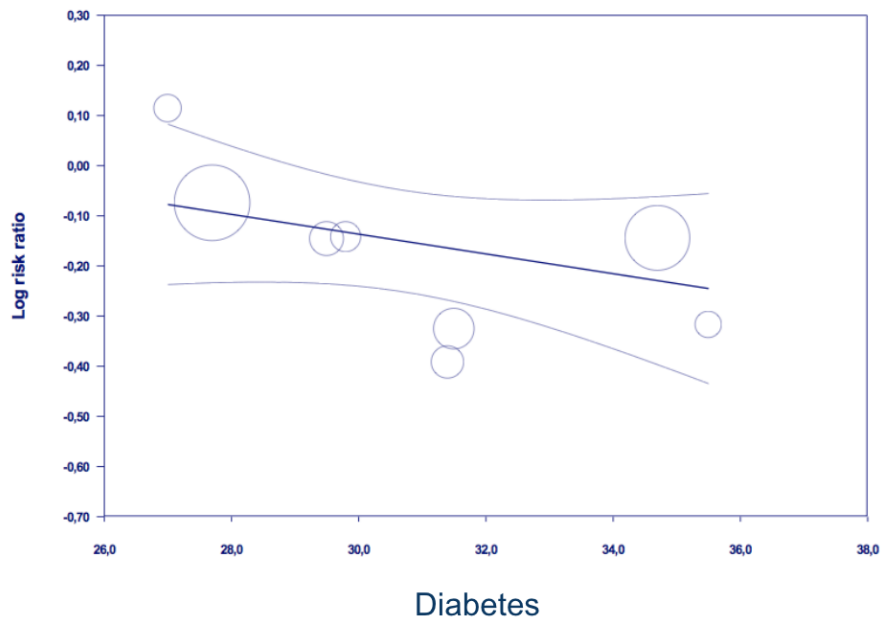
Regression of Log risk ratio  
on beta-blockers



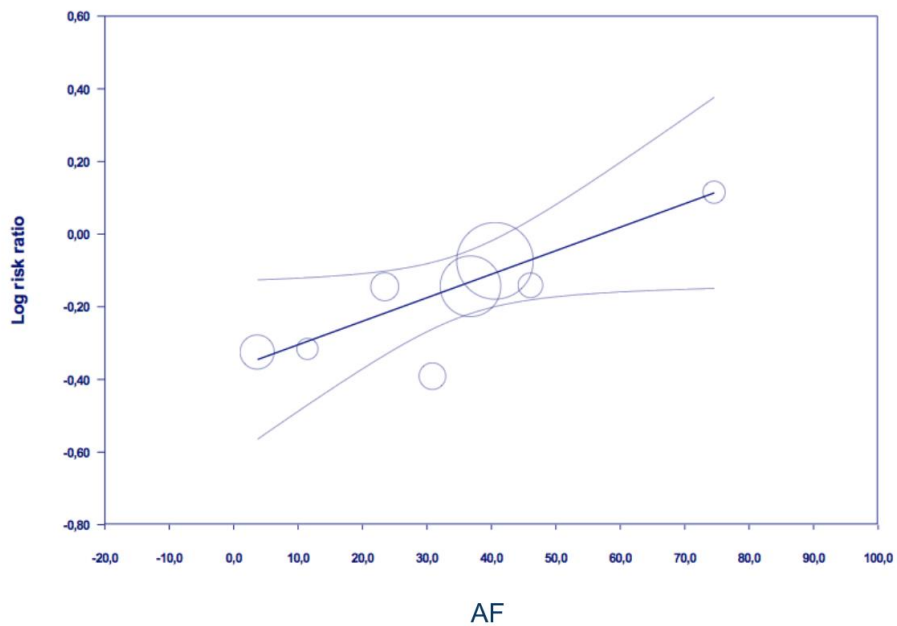
Regression of Log risk ratio on mineralocorticoid antagonists



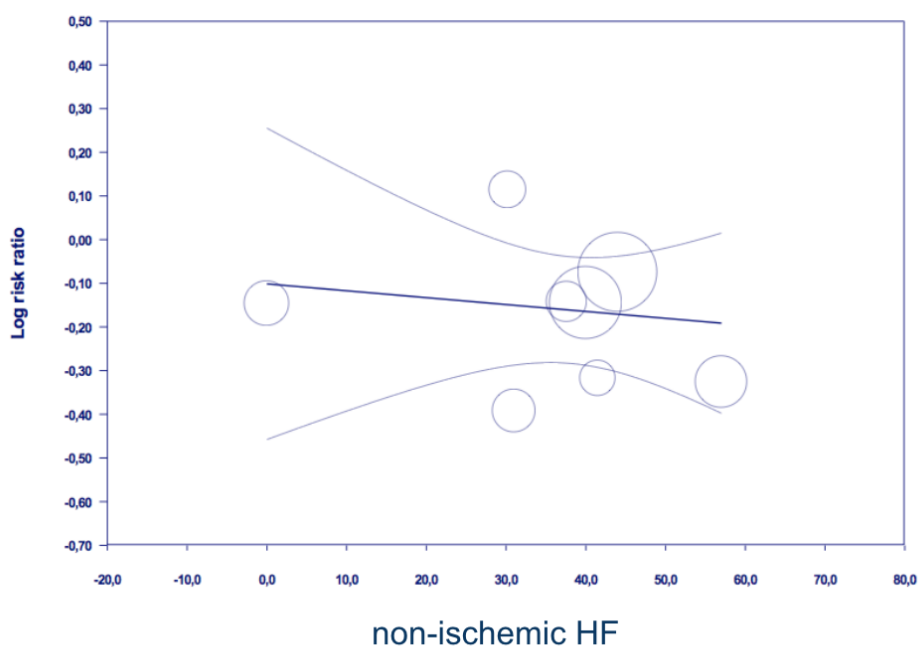
Regression of Log risk ratio on Diabetes



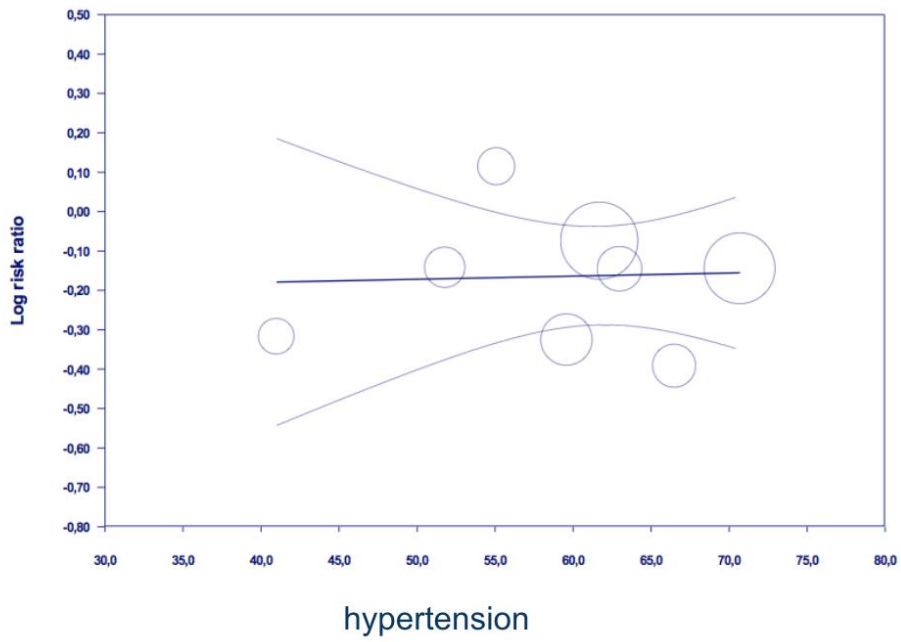
Regression of Log risk ratio on AF



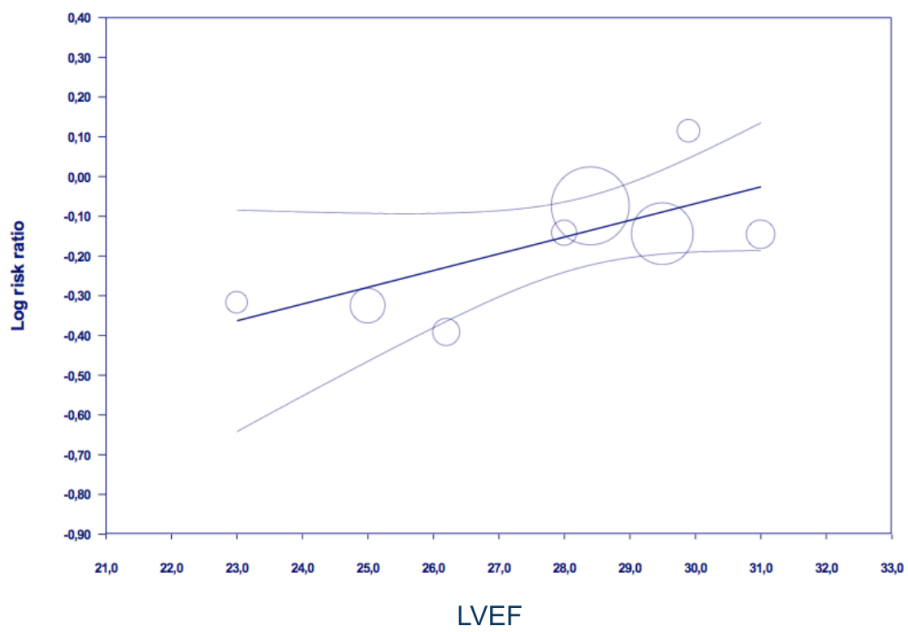
Regression of Log risk ratio on non-ischemic HF



Regression of Log risk ratio on hypertension

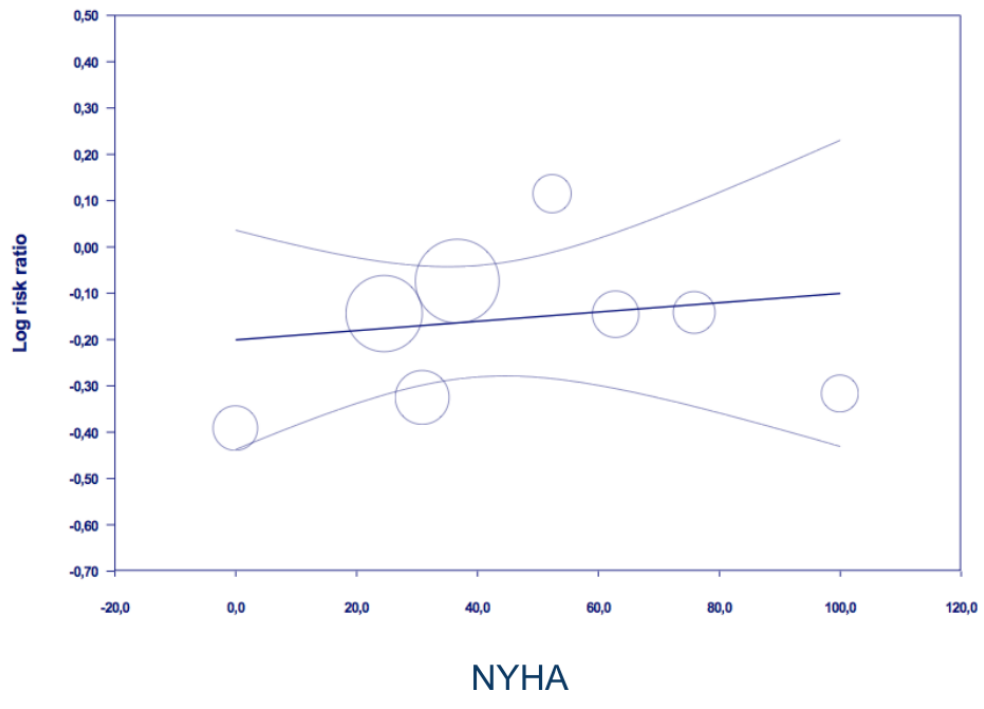


Regression of Log risk ratio on LVEF

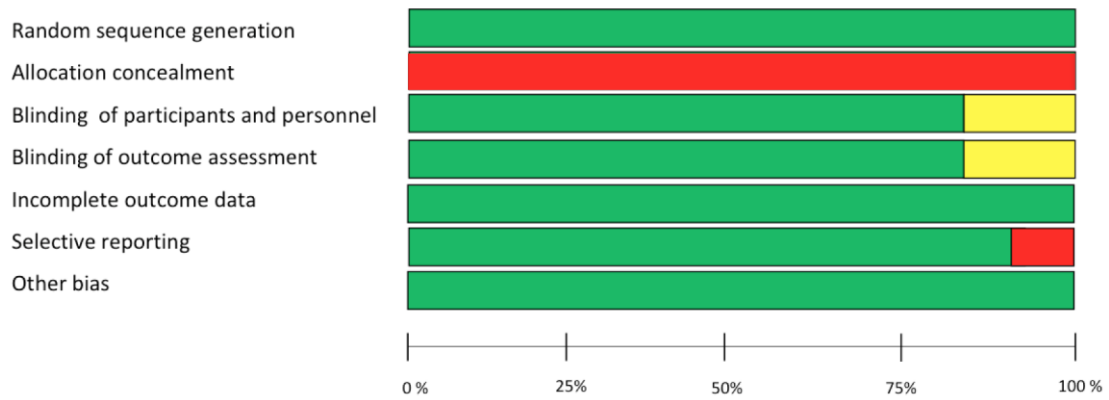




### Regression of Log risk ratio on NYHA



**Figure S4. Risk of Bias analysis.**



|                   | Random sequence generation | Allocation concealment | Blinding of participants and personnel | Blinding of outcome assessment | Incomplete outcome data | Selective reporting | Other bias |
|-------------------|----------------------------|------------------------|--|--------------------------------|-------------------------|---------------------|------------|
| BEST              | +                          | -                      | +                                      | +                              | +                       | +                   | +          |
| CHARM-Added       | +                          | -                      | +                                      | +                              | +                       | +                   | +          |
| CHARM-Alternative | +                          | -                      | +                                      | +                              | +                       | +                   | +          |
| CORONA            | +                          | -                      | ?                                      | ?                              | +                       | +                   | +          |
| EMPHASIS-HF       | +                          | -                      | +                                      | +                              | +                       | +                   | +          |
| PARADIGM-HF       | +                          | -                      | +                                      | +                              | +                       | +                   | +          |
| ATMOSPHERE        | +                          | -                      | ?                                      | ?                              | +                       | -                   | +          |
| WARCEF            | +                          | -                      | +                                      | +                              | +                       | +                   | +          |

+ Low risk of bias  
- High risk of bias  
? Unclear risk of bias

Funnel Plot of Standard Error by Log risk ratio

