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Cardiovascular Benefits of Finerenone Beyond Renal Protection: A Meta-Analysis of Renal and Cardiovascular Phase 3 Randomized Trials

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Index

Abstract

Background

Mineralocorticoid receptor (MR) overactivation promotes inflammation, fibrosis, and adverse cardiac remodelling, contributing to the progression of heart failure and cardiovascular disease. Finerenone is a non-steroidal MR antagonist characterized by high MR selectivity, balanced heart–kidney tissue distribution, and a favourable safety profile. Although phase 3 trials have shown cardiovascular benefit, it remains uncertain whether these effects reflect direct cardio-protection or are predominantly mediated through renal mechanisms.

Methods

We conducted a systematic review and meta-analysis of phase 3 randomized controlled trials comparing finerenone with placebo or standard therapy. PubMed, Embase, and Cochrane CENTRAL were searched through December 31, 2025. Outcomes included a composite cardiovascular endpoint, heart failure hospitalization (HFH), and cardiovascular (CV) death. Pooled odds ratios (ORs) with 95% confidence intervals (CIs) were estimated using random-effects models. Treatment effects were compared between renal-focused trials and a dedicated cardiovascular trial, with exploratory meta-regression analyses.

Results

Four phase 3 trials including 19,827 patients were analysed. Finerenone significantly reduced the composite cardiovascular endpoint (OR 0.81, 95% CI 0.74–0.89) and HFH (OR 0.76, 95% CI 0.69–0.83), with low heterogeneity and consistent effects across trial populations. A non-significant trend toward reduced CV death was observed (OR 0.89, 95% CI 0.79–1.00). No effect modification by trial type or baseline characteristics was detected.

Conclusions

The consistency of heart failure risk reduction across renal and cardiovascular trial settings supports a direct cardioprotective effect of finerenone, likely mediated through attenuation of MR-driven inflammation and fibrosis, rather than a purely renal-dependent mechanism.

Introduction

Cardiovascular disease represents the foremost cause of morbidity and mortality worldwide [1]. Heart failure (HF) is a growing healthcare burden associated with adverse outcome, such as recurrent hospitalizations, poor quality of life and high rate of mortality [1].

Among the cornerstone of the medical treatments of HF, the mineralocorticoid receptor antagonists (MRAs) play a central role due to positive effects on cardiac fibrosis, inflammation, and remodelling [2-4].

Steroidal mineralocorticoid receptor antagonists (MRAs), such as spironolactone and eplerenone, have demonstrated clinical benefits, but their use is constrained by a significant risk of hyperkalaemia, particularly in the high-risk cardiorenal population [2]. Finerenone, a novel non-steroidal mineralocorticoid receptor antagonist (MRA), was designed to provide potent cardiorenal protection with an improved safety profile related with a balanced heart-kidney distribution, a selective MR binding, and a short half-life [2, 3].

Several studies already demonstrated a significant reduction in composite cardiovascular and renal endpoints, but it is also unclear whether this beneficial effect represent a direct cardioprotective effect or are principally mediated through renal protection [5-7].

While previous meta-analyses have provided an early synthesis of finerenone efficacy, they also included Phase II data or aggregated heterogeneous populations [5, 6]. A direct comparative analysis specifically assessing whether finerenone cardiovascular efficacy profile differs substantially between patients enrolled in trials with a primary renal focus and those enrolled in a dedicated cardiovascular trial is lacking.

This meta-analysis aims to fill that gap by comparing the treatment effects on key endpoints—cardiovascular death, heart failure hospitalization, and their composite—between the cohort of renal studies and the cardiovascular trial, aiming at clarifying the nature and generalizability of finerenone cardiovascular benefit and contributing to a more precise definition of its role in clinical practice.

Methods

This systematic review and meta-analysis was carried out following the recommendations outlined in the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) framework [8]. The protocol of review was registered with PROSPERO.

Literature search

A systematic literature search was conducted in electronic databases, including PubMed, Embase, and Cochrane CENTRAL, to identify randomized controlled trials (RCTs) comparing finerenone versus placebo, from database inception through December 31, 2025. The search strategy included combinations of keywords and Medical Subject Headings (MeSH) related to "finerenone," "cardiovascular," "heart failure," and "cardiovascular outcomes." Titles and abstracts were screened to assess relevance, and studies not meeting the predefined inclusion criteria were excluded, resulting in articles selected for full-text review.

Study Selection

Studies were included in the quantitative synthesis (meta-analysis) if they met the following criteria:

- Phase-3 randomized controlled trial design
- Comparison of finerenone versus placebo (e.g. optimal medical therapy for HF)
- Reporting of at least one of the outcomes of interest (heart failure hospitalization (HFH), cardiovascular death (CV death), or a pre-specified composite cardiovascular endpoint)
- Sufficient data available to extract events and sample sizes for both intervention and control arms

Studies were excluded if they were observational studies and focused on outcomes unrelated to CV events. Editorials, reviews and commentaries were also excluded.

Data Extraction

For each included study, the following data were extracted: number of events and total sample size in treatment and control groups, endpoint definitions (composite cardiovascular endpoint, HFH and CV death), mean age, proportion of male participants, and concomitant use of SGLT2 inhibitors. Data were compiled into a structured dataset for statistical analysis.

Assessment of Risk of Bias

The quality of each included RCT was assessed using the latest Cochrane Risk of Bias tool version 2.0 (RoB 2.0) [9], which evaluates the methodological soundness across five core domains: (i) the process used to generate the randomization sequence, (ii) any deviations from the intended intervention, (iii) handling of missing data, (iv) accuracy and validity of outcome measurement, and (v) potential selective reporting of results. Each domain was rated as either "low risk," "some concerns," or "high risk" of bias. Furthermore, an overall risk of bias judgment was assigned for each study based on the collective assessment of all domains. This assessment process was performed by two independent reviewers and verified by a third reviewer.

Quality of evidence

The quality of evidence (high, low, or unclear) was examined according to the Grading of Recommendations, Assessment, Development, and Evaluation tool [10].

Statistical Analysis

The meta-analysis was conducted in R environment (RStudio Desktop, version 1.2.5033) setting statistical significance at $p < 0.05$. For each binary outcome, odds ratios (ORs) with 95% confidence intervals (CIs) were calculated. Log(OR) and corresponding variances were computed using the escalc() function from the metafor package, which allows appropriate effect size estimation for dichotomous outcomes in clinical trials. Studies were combined using a random-effects model with Mantel–Haenszel method using a random-effects model, which was selected to account for anticipated variability between studies [11]. The Paule–Mandel method was used to estimate the between-study variance (τ^2) [12]. The extent of heterogeneity between studies was assessed using the I^2 statistic, with thresholds for interpretation as follows: 0%–40% suggesting low heterogeneity, 30%–60% indicating moderate heterogeneity, 50%–90% reflecting substantial heterogeneity, and 75%–100% signifying considerable heterogeneity [11].

Forest plots were generated for each outcome to visually summarize study-specific and pooled effect estimates. The forest() function from metafor was used to display the ORs with CIs, including study labels and endpoint titles.

Considering the 1:1:1 randomization of CONFIDENCE [13], we considered patients of "Finerenone+Empagliflozin" and "Finerenone" arms as only one group.

Exploratory meta-regression analyses were performed using random-effects models, including one covariate at a time, due to the limited number of included studies.

Results

Literature Search Results

A total of 914 records were initially identified and after duplicates removal 89 articles were screened by two independent investigators using their titles and abstracts; 68 records were removed and full-texts of 21 studies were retrieved (Table S1). The review of full texts identified 4 eligible phase-3 RCTs [13-16] as reported in Figure 1.

Study Characteristics and Quality Assessment

This meta-analysis included 19827 patients across four studies, with 10055 patients receiving finerenone and 9772 receiving control. The baseline characteristics of the included studies are summarized in Table 1, whereas definition of the composite cardiovascular endpoint in the included RCTs are reported in Table 2.

RCTs were all double-blind, placebo-controlled, and multicenter. The publication year was between 2021 and 2025.

Median follow-up was 2.7 (IQR: 2.1-2.9), mean age was 67.0±3.4 years, 12959 (65.4%) patients were males.

One of the included studies (CONFIDENCE) [13] used empagliflozin and empagliflozin+finerenone as control groups while the others used placebo (namely optimal medical therapy).

The risk of bias assessment revealed that four included studies were all of high methodological quality, exhibiting a low risk of bias in all key domains. The risk of bias summary is presented in Figure 2.

Global I^2 for composite endpoint was 16% (τ^2=0.0027), whereas I^2 for heart failure hospitalization and CV death were both 0% (τ^2=0).

Table 3 reports endpoint occurrence in all the included RCTs.

Composite cardiovascular endpoint

Three out of four included studies reported composite cardiovascular endpoint data. The meta-analysis (Figure 3) yielded a OR of 0.81 (95% CI 0.74–0.89), indicating a significant 19% risk reduction with finerenone. Effect estimates were consistent: FIGARO-DKD [14] OR 0.86 (0.75–0.98), FIDELIO-DKD [16] OR 0.86 (0.74–1.00), FINEARTS-HF [15] OR 0.75 (0.68–0.84).

Heart failure hospitalization

All the included studies reported HFH data. For HFH (Figure 4), the pooled analysis showed a OR of 0.76 (95% CI 0.69–0.83) with a significant 24% risk reduction with finerenone. Effect estimates

were all consistent FIGARO-DKD [14] OR 0.71 (0.55–0.90), FIDELIO-DKD [16] OR 0.86 (0.74–1.00), FINEARTS-HF [15] OR 0.75 (0.68–0.84), except for CONFIDENCE [13] OR 1.51 (0.06–37.12).

Cardiovascular death

All the included studies reported CV death data. The pooled analysis (Figure 5) demonstrated a significant reduction in CV death with finerenone therapy compared to the control group (OR 0.89, 95% CI: 0.79–1.00).

Effect estimates were non-significant for all the included studies.

Meta-regression analysis

Meta-regression analysis (Figure 6) revealed no significant effect modification by baseline age, sex, background SGLT2 inhibitor use, or trial type (renal vs. cardiovascular) for composite cardiovascular endpoint, HFH or CV death outcomes.

Discussion

This meta-analysis of about 20,000 patients provides a comprehensive synthesis of phase 3 RCT data on the use of finerenone in the cohort of renal vs. cardiovascular studies, aiming at clarifying the nature and generalizability of finerenone cardiovascular benefit.

The following findings of our study deserve consideration: 1) the occurrence of cardiovascular composite endpoint is significantly reduced of 19% with finerenone vs. placebo irrespective of RCT type (renal vs. cardiovascular); 2) there was a 24% risk reduction of HFH with finerenone irrespective of the type of cohort; 3) there was no significant reduction in CV death with finerenone despite a trend towards a beneficial effect.

The relative risk reduction for the composite cardiovascular endpoint was significant and overlapping and even more relevant is the consistency of the effect on HFH. This represents the most significant finding from the analysis since it reflects a significant impact on quality of life and overall disease management. These benefits, together with a favourable safety profile, make finerenone a valuable plus to HF management.

From a pathophysiological point of view, our meta-analysis results refute the hypothesis that finerenone cardiovascular benefit was merely an epiphenomenon linked exclusively to improved renal function in a selected nephropathic population.

On the contrary, it strongly suggests that the drug exerts a direct and intrinsic cardioprotective effect, whose clinical expression, particularly in terms of preventing worsening heart failure, is reproducible regardless of the patient's primary reason for enrolment.

The potent antifibrotic and anti-remodelling action of finerenone, well-documented in preclinical studies [2, 3], thus finds transversal clinical confirmation, positioning the drug as an effective agent in preventing heart failure events across a broad spectrum of cardiorenal risk patients [2, 3, 5-7].

Interestingly, the treatment effects on cardiovascular endpoint and HFH appear remarkably consistent across populations with differing baseline characteristics.

On the contrast, a more nuanced result emerges from the analysis of cardiovascular mortality. Although all point estimates favour finerenone, the confidence interval of the pooled random-effect model touches the null value.

This pattern, also observed in the individual trials [13-16], indicates that while the drug shows a trend toward reducing cardiac death, the magnitude of this effect is more modest and probably requires longer follow-up to reach the significance. These results are consistent with earlier studies [11, 13-17], where finerenone did not demonstrate a reduction in CV death. The discrepancy between a robust reduction in HHF and a less certain effect on mortality is not unique to finerenone but reflects a common challenge with many heart failure therapies [4]. It may reflect the complexity of cardiac

death, influenced by mechanisms (e.g., arrhythmic) on which MR antagonism has a different impact than on the progression of heart failure. This aspect remains an area for future investigation.

From a methodological point of view, the inclusion of the CONFIDENCE RCT [13], with its small size and short follow-up, introduces wide variability in estimates for rare events like CV death, without, however, altering the main conclusions on morbidity endpoints. The strength of this analysis lies precisely in the choice to transparently compare two homogeneous blocks of trials, allowing for a direct observation of the transferability of the efficacy signal.

In conclusion, this analysis supports the idea that finerenone has a solid and generalizable cardiovascular benefit, particularly for the prevention of worsening heart failure. The consistency of results across different populations reinforces the drug's pathophysiological rationale and broadens its potential field of clinical application beyond the strictly nephro-diabetological scenario.

The positive trend on cardiovascular mortality, together with its manageable safety profile, helps defining finerenone as an important therapeutic option in the arsenal for cardiorenal syndrome. Future studies, possibly with individual patient-level data, may identify subgroups that derive the greatest prognostic benefit, optimizing its use in clinical practice.

Several unavoidable limitations should be acknowledged in our meta-analysis. First, we included only four studies with relatively short follow-up that offers valuable short-term insights, but longer follow-up durations are needed to assess the sustained effects and safety of finerenone over time. In addition, individual patient data meta-analyses will provide further insights. Second, the definition of composite cardiovascular endpoint varies across different studies, hampering clinical heterogeneity. Finally, this meta-analysis mainly involved patients with HF and/or kidney disease, limiting the applicability of these findings to broader populations.

Conclusion

This meta-analysis demonstrates that finerenone confers a consistent cardiovascular benefit across both renal and cardiovascular phase 3 trials, particularly by significantly reducing heart failure hospitalizations. The homogeneity of effects across trial settings supports a direct cardioprotective mechanism beyond renal mediation. These findings reinforce finerenone role as a valuable therapeutic option in patients with cardiorenal risk.

Tables

Table 1. Baseline characteristics of included studies.

RCT	Year	CV RCT	Median FUP	Interventional treatment	Control treatment	Total sample size	N° Interventional treatment	N° Control treatment	Age	Male sex	SGLT2i Interventional treatment	SGLT2i Control treatment
FIGARO-DKD	2021	No	3.4	Finererone	Placebo	7352	3686	3666	64.1	5105	314	304
FIDELIO-DKD	2021	No	2.6	Finererone	Placebo	5674	2833	2841	65.6	3983	124	135
CONFIDENCE	2025	No	0.6	Finererone	Placebo	800	533	267	66.5	602	269	267
FINEARTS-HF	2024	Yes	2.7	Finererone	Placebo	6001	3003	2998	71.9	3269	393	424

Table 2. Definition of the composite cardiovascular endpoint in the included RCTs.

RCT	Definition of the composite cardiovascular endpoint
FIGARO-DKD	A composite of death from cardiovascular causes, non-fatal myocardial infarction, non-fatal stroke, or hospitalization for heart failure
FIDELIO-DKD	Time to first onset of cardiovascular death, nonfatal MI, non-fatal stroke, or hospitalization for heart failure
CONFIDENCE	-
FINEARTS-HF	Composite of total (first and recurrent) HF events (i.e. HF hospitalization or urgent HF visit) and CV death

Table 3. Endpoint occurrence in the included studies.

RCT	Composite endpoint (Finererone arm)	Composite endpoint (Placebo arm)	CV death (Finerenone arm)	CV death (Placebo arm)	HFH (Finerenone arm)	HFH (Placebo arm)
FIGARO-DKD	458	519	194	214	117	163
FIDELIO-DKD	367	420	128	150	139	162
CONFIDENCE	-	-	2	2	1	0
FINEARTS-HF	1083	1283	242	260	842	1024

Table S1. List of retrieved full-text after first literature screening.

10.2337/dc25-0472
10.1056/NEJMoa2410659
10.1001/jamacardio.2025.1101
10.3389/fendo.2025.1568438
10.1002/ejhf.3669
10.1093/eurheartj/ehw132
10.1161/CIRCULATIONAHA.120.051898
10.2337/dc21-1944
10.1002/ejhf.3569
10.1001/jamacardio.2024.4539
10.1016/j.jacc.2024.09.004
10.1161/CIRCULATIONAHA.124.072055
10.1056/NEJMoa2407107.
10.1136/bmjopen-2023-076444
10.1111/dom.14883
10.2337/dc22-0294
10.1093/eurheartj/ehab777
10.1093/ndt/gfab336
10.1161/CIRCULATIONAHA.121.057983
10.1056/NEJMoa2110956
10.1111/dom.14558

Figures

Figure 1. PRISMA diagram.

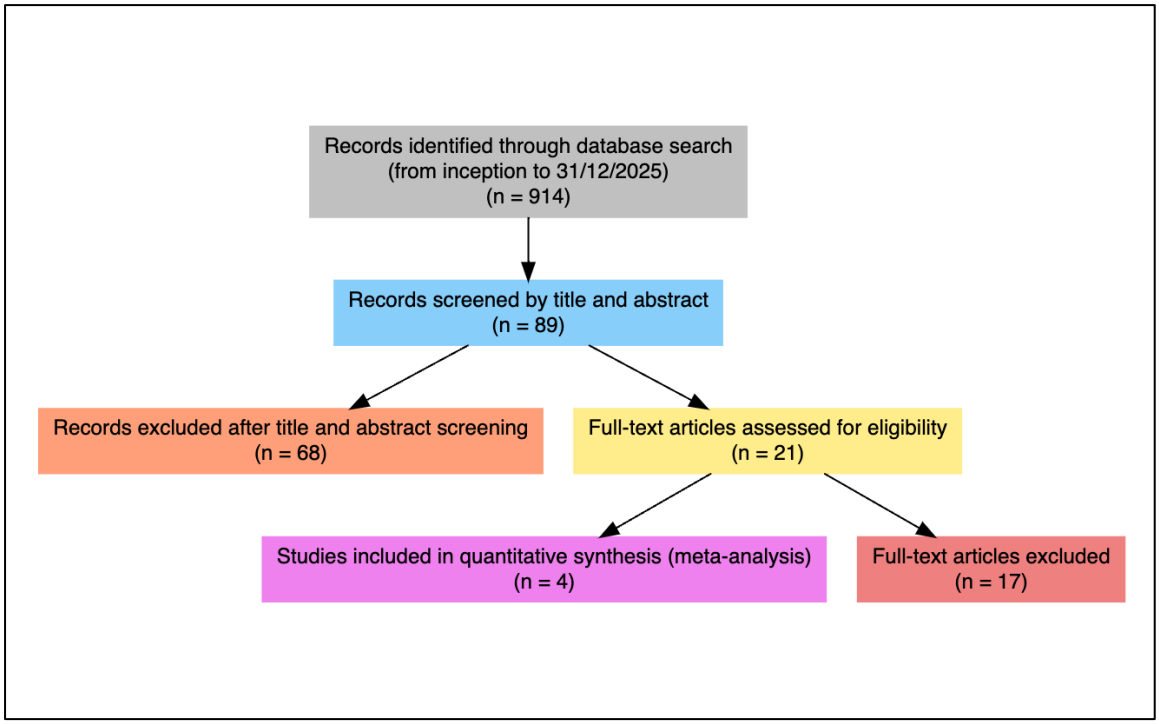

Figure 2. Risk of bias summary in the included trials.

RCT	D1	D2	D3	D4	D5	OVERALL
FIGARO-DKD	+	+	+	+	+	+
FIDELIO-DKD	+	+	+	+	+	+
CONFIDENCE	+	+	+	+	+	+
FINEARTS-HF	+	+	+	+	+	+

D1: Bias arising from the randomization process
D2: Bias due to deviations from intended intervention
D3: Bias due to missing outcome data
D4: Bias in measurement of the outcome
D5: Bias in selection of the reported result

Figure 3. Results of the random-effects meta-analysis for composite cardiovascular endpoint.

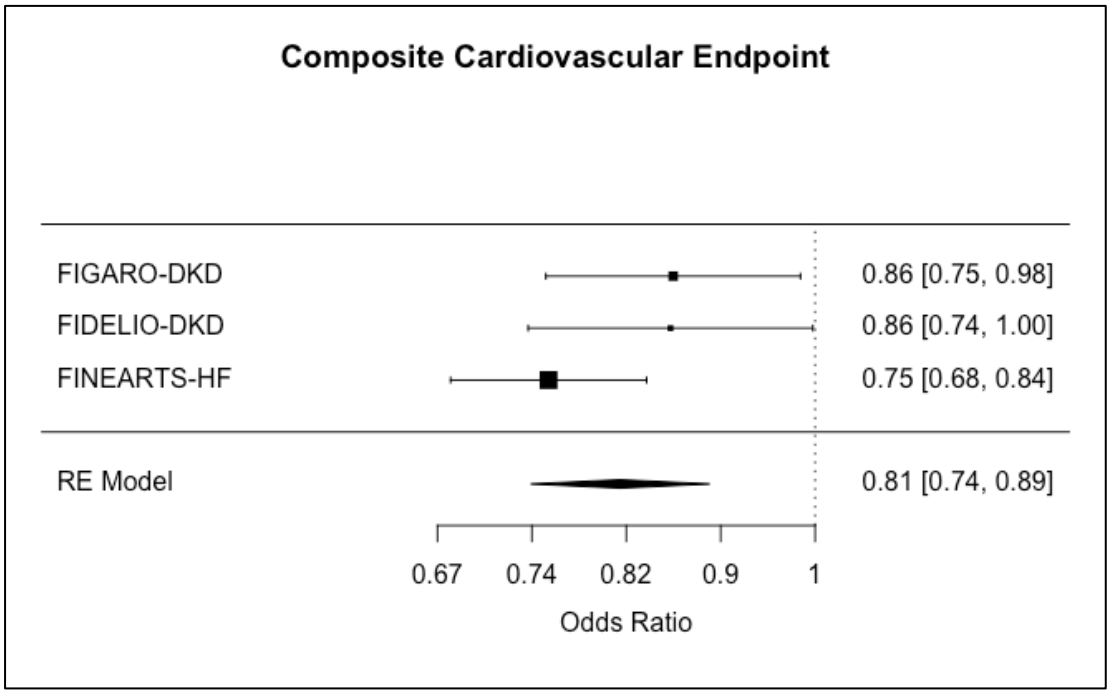

Figure 4. Results of the random-effects meta-analysis for heart failure hospitalization.

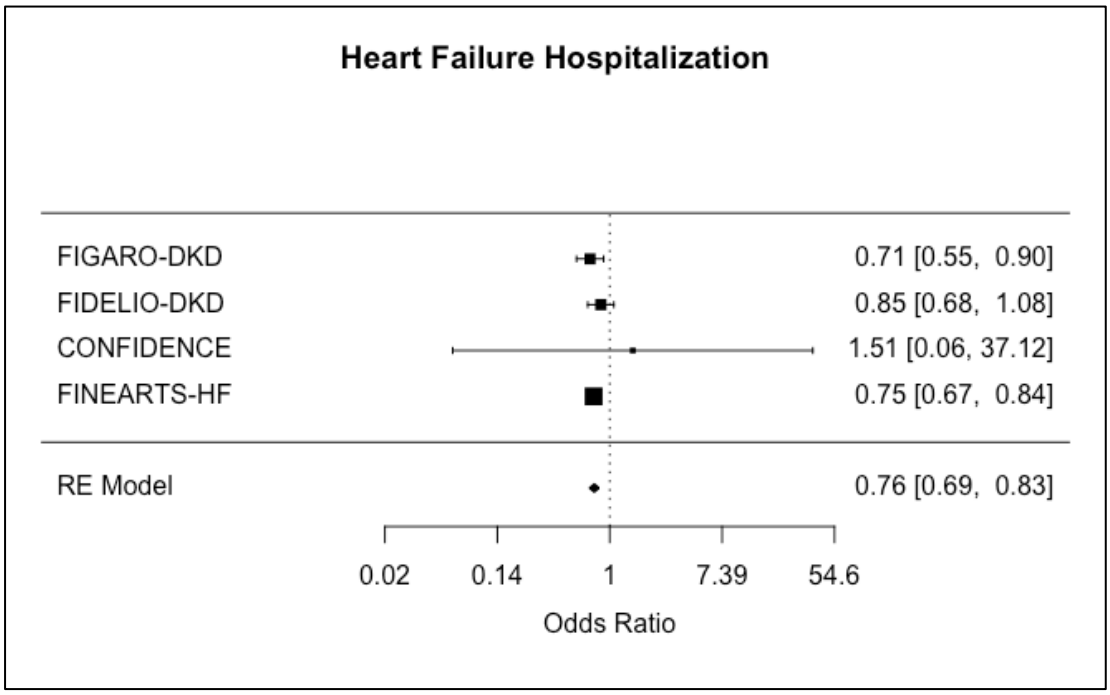

Figure 5. Results of the random-effects meta-analysis for cardiovascular death.

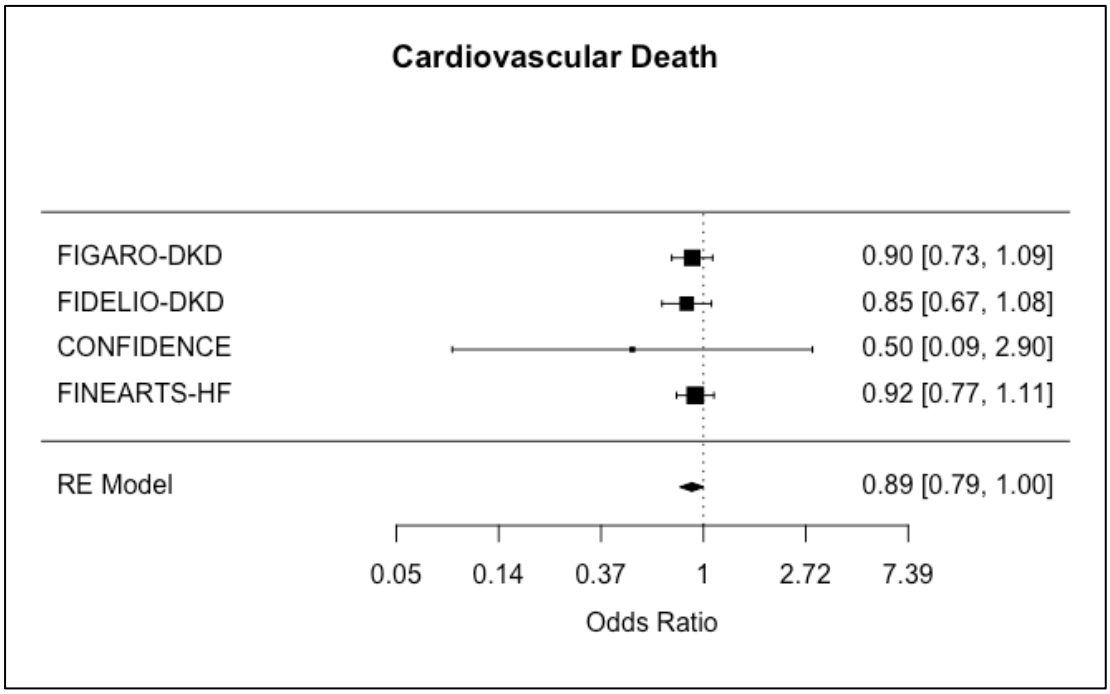

Figure 6. Meta-regressions for composite cardiovascular endpoint, heart failure hospitalization and cardiovascular death.

Covariata	Outcome	β (SE)	Z	P value
Cardiovascular RCT	Heart Failure Hospitalization	−0.0377 (0.1245)	−0.30	0.762
	Cardiovascular Death	0.0556 (0.1217)	0.46	0.648
	Composite Endpoint	−0.1307 (0.0737)	−1.77	0.076
Age (years)	Heart Failure Hospitalization	−0.0026 (0.0185)	−0.14	0.890
	Cardiovascular Death	0.0063 (0.0167)	0.38	0.706
	Composite Endpoint	−0.0180 (0.0102)	−1.76	0.079
Male sex (%)	Heart Failure Hospitalization	−0.0000 (0.0001)	−0.33	0.741
	Cardiovascular Death	0.0000 (0.0001)	0.01	0.994
	Composite Endpoint	0.0001 (0.0000)	1.54	0.125
SGLT2i use (%)	Heart Failure Hospitalization	−0.0004 (0.0005)	−0.86	0.389
	Cardiovascular Death	0.0003 (0.0006)	0.56	0.579
	Composite Endpoint	−0.0004 (0.0004)	−1.33	0.182

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