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Original article

Safety and efficacy of ultrafiltration versus diuretics in patients with decompensated heart failure: A systematic review and meta-analysis

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A B S T R A C T

Background: Ultrafiltration (UF) is used for fluid removal patients with acute decompensated heart failure with reduced ejection fraction (HFrEF) refractory to diuretics. However, data on the relative merits of UF and diuretics are limited.

Methods: Online databases were queried to identify clinical trials on the comparison of UF and diuretics. The major adverse cardiovascular (MACE) and its components (mortality and re-hospitalizations) were compared using the random-effects model to calculate the unadjusted odds ratio (OR) with its 95% confidence interval (CI).

Results: A total of 10 clinical trials comprising 838 patients (413 UF, 425 diuretics) were included in the analysis. At a median follow-up of 90 days, there was no significant difference in the odds of MACE (OR 0.71, 95% CI 0.47–1.07) and all-cause mortality (OR 1.08, 95% CI 0.77–1.52) between patients undergoing UF compared with those receiving diuretics therapy. The need for emergency department visits (OR 1.05, 95% CI 0.38–2.90), all-cause admissions (OR 0.97, 95% CI 0.72–1.30) and heart failure-related re-hospitalization (OR 0.47, 95% CI 0.21–1.02) was also similar between the two groups. The in-hospital risk for hypotension (OR 0.49, 0.23–1.04) and post-therapy creatinine rise>0.3 mg/dL (OR 1.18, 95% CI 0.74–1.89) was also not significantly different between the UF and diuretics arms. A sensitivity analysis of MACE and mortality did not show any deviation from the pooled outcomes.

Conclusions: In patients with HFrEF, UF appears to be safe but might not provide significant benefits in terms of reducing the risk of mortality or readmission rates compared with those treated with diuretics.

1. Introduction

Acute decompensated heart failure, a constellation of dyspnea, edema, and fatigue due to volume overload, accounts for the high healthcare costs, projected to increase from $21 billion in 2012 to $70 billion in 2030 [1–4]. Therapies such as diuretics and ultrafiltration (UF) have been explored to target volume overload in patients with HF with reduced ejection fraction (HFrEF). Decongestion with diuretics has proven benefits in terms of decreasing symptoms and HF-related hospitalizations [5]. However, continuous or repeated diuretic use has been linked with decremental responses and increased resistance. Studies have also indicated a less prominent decongestive effect of diuretics in patients with worsening HF, citing the need for higher doses of diuretics to achieve the same effect (right shift dose-response curve). As such, extracorporeal ultrafiltration (UF) has been proposed as an alternative therapeutic option for decongestion in these patients [6]. UF can potentially provide a greater decline in the mean pulmonary capillary wedge and right atrial pressure, increasing the stroke volume and cardiac output in diuretics-resistant patients with HFrEF [7]. Some small-scale studies suggest that UF in patients with decompensated HF is associated with lesser HF rehospitalization rates in comparison to diuretic groups [8]. However, there has been no large-scale study on the comparison of diuretics and UF use in these patients.

2. Methods

Digital databases including PubMed, Embase, and Cochrane were queried until December 2021 to identify all relevant clinical trials. Studies comparing the safety and efficacy of UF and diuretics in patients with HF were included in the quantitative analysis. Case reports,

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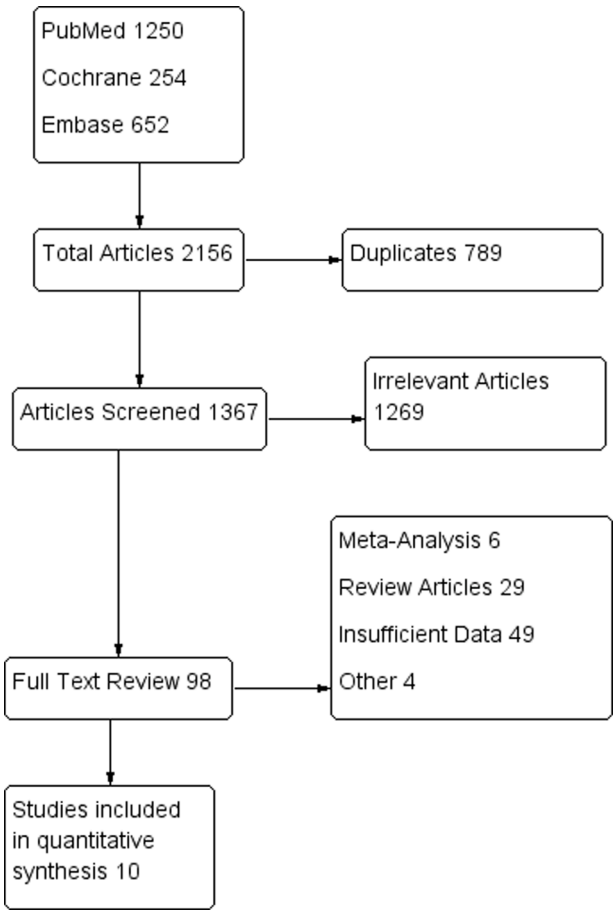

Fig. 1. PRISMA flow diagram of the studies included in this meta-analysis.

conference papers, studies with duplicate populations, and those with insufficient data were excluded. All articles were screened at the title and abstract level, and potentially relevant articles were reviewed in the full-text form. Duplicate studies and articles not qualifying our selection criteria were excluded. Due to the retrospective nature of data, this study did not require institutional review board (IRB) approval.

The primary endpoint was MACE, a composite of all-cause mortality and all-cause re-hospitalizations. Secondary outcomes included components of MACE, need for HF-related re-hospitalization, change in the mean creatinine level, change in blood pressure, total fluid loss, mean change in weight, and mean change in sodium level. The study-level definitions of all outcomes are given in Supplementary (S.) Tables S1–S5.

The statistical analysis was performed using the DerSimonian and Laird test on a random-effects model to calculate unadjusted odds ratios (OR) for dichotomous variables. Hedge's equation was used to determine the standardized mean difference for continuous variables. Sensitivity analysis based on the "leave-one-out" strategy was also performed to assess the influence of individual studies on MACE and all-cause mortality pooled estimates. Higgins I-squared (I^2) statistical model was used to assess variations in outcomes of the included studies and determine the significance of heterogeneity. Publication bias was illustrated graphically using a funnel plot and calculated quantitatively using Egger's Regression Equation (ERE). The methodological quality assessment of the included RCTs was performed using the Oxford scoring scale. The probability value of $p < 0.05$ was considered statistically significant. The "test for overall effect" was reported as the z value with its 95% confidence interval (CI). All statistical analysis was performed using STATA version 16 and R 3.0.

3. Results

On initial search, 2156 items were identified. After the exclusion of duplicates (789), 1269 studies were excluded by screening at the level of title and abstract. Of the 98 shortlisted articles for full-text review, 10 clinical trials qualified for quantitative analysis [8–17]. Fig. 1 outlines the detailed flow diagram.

A total of 838 patients (425 UF, 413 diuretics) were included in the analysis. Most studies were reported from developed countries. The mean age was 66 years, comprising 77% male patients in both groups. The Caucasians constituted the most common race in both UF and diuretics groups. The mean weight at the start of the index procedure in the UF group was 99.1 kg, while it was 92.9 kg in the diuretics group ($p = 0.8$). Prior history of heart failure and hypertension were the most common comorbidities in both groups. (Fig. 2) The mean follow-up duration was 90 days for both groups. The detailed patient demographics, baseline comorbidities, laboratories characteristics, and clinical presentations are given in Tables S6–S9. The detailed inclusion criteria of all studies are given in Tables S10 and S11.

On pooled analysis there was no significant difference in the odds of MACE (OR 0.71, 95% CI 0.47–1.07), all-cause mortality (OR 1.08, 95% CI 0.77–1.52), need for all-cause rehospitalization (OR 0.97, 95% CI 0.72–1.30), HF-related re-hospitalization (OR 0.47, 95% CI 0.21–1.02) need for emergency room visits (OR 1.05, 95% CI 0.38–2.90) and hypotensive episodes (0.49, 95% CI 0.23–1.04) between patients undergoing UF and those receiving diuretics therapy. The pooled dichotomous outcomes estimates are given in Fig. 3. The mean difference in the fluid loss with UF (−0.34, 95% CI −0.83–0.14) was similar to diuretics. However, the mean rise in serum creatinine level (0.23, 95% CI 0.07–0.40) and mean decrease in serum sodium level (−0.53, 95% CI −0.81–0.25) from baseline was significantly higher with UF. Nonetheless, there was no difference in the odds of new-onset acute kidney injury (OR 0.87, 95% CI 0.56–1.34), weight changes (mean −1.00, 95% CI −2.27–0.26), and length of hospital stay (mean 0.47, 95% CI −0.65–1.60) between the two groups. The detailed pooled and study-level effect sizes are given in Fig. 4 and Figs. S1–S10).

A sensitivity analysis based on the sequential exclusion of individual trials showed no influence of any individual study on pooled estimates of MACE and all-cause mortality. (Fig. 5) The L'Abbe plot showed a non-significant spread of the log of odds ratios from the equality line indicating identical mortality benefits with both strategies. (Fig. 6)

The overall methodological quality of the studies was high. The risk of selection bias in RCTs was reduced by adequate randomization, however, all clinical trials were open-label, violating the "allocation concealment". About 40% of studies reported a significant loss to follow-up, dropouts, or withdrawal from the study protocol. The intention-to-treat analysis was used to account for attrition bias. (Table S12) The funnel plot showed no significant deviation of studies from the midline, indicating no publication bias for all-cause mortality (ERE$\approx p = 0.77$). (Fig. 7) On visual assessment, the funnel plot was symmetrical, indicating that the limited scatter on the horizontal axis was due to variable effect size, and the vertical spread was due to sampling variation.

4. Discussion

The current meta-analysis represents the most contemporary and largest analysis of trials on the clinical outcomes of UF in comparison to the mainstay diuretic approach in acute decompensated HFrEF. Our major findings indicate that there is no significant difference in the odds of major adverse cardiovascular events and all-cause re-hospitalization between patients undergoing UF compared with those receiving diuretic therapy. The risk of HF-related hospitalization at a median interval of 90-days after index hospitalization was numerically lower by 53% in the UF group, however, it did not reach the threshold of statistical significance. Similarly, the odds of unplanned emergency room visits, new-onset renal failure, rise in creatinine above 0.3 mg/dl above the

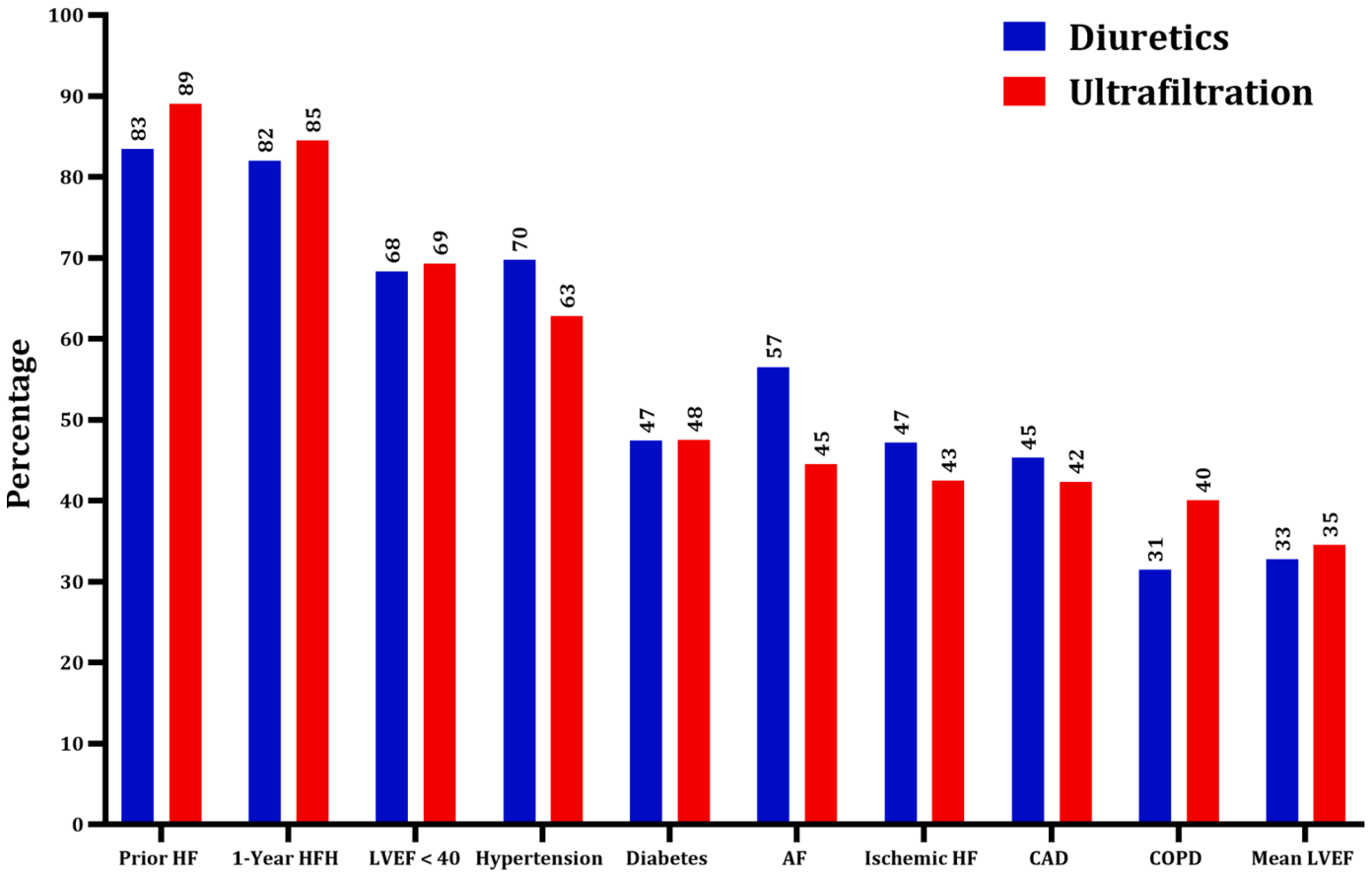

Fig. 2. Bar diagram of the baseline mean comorbidities in the included clinical trials.

baseline, and incidence of hypotension (systolic blood pressure <90 mmHg) were also similar between the two groups. UF had a significantly higher mean increase in creatinine levels and a higher incidence of hyponatremia. Nonetheless, there was no difference in the net estimates of weight loss and length of stay between UF and diuretics groups.

HF-related hospitalization is one of the most common consumers of healthcare resources, posing a high financial burden on patients and the healthcare system. This, in conjunction with impaired quality of life of HF patients, results in poor in-hospital outcomes [18]. Both UF and diuretics have established benefits in reducing HF-related re-hospitalizations, by virtue of effective decongestion of acutely decompensated HF patients. However, mechanistically, one would expect a higher efficacy of UF in terms of volume decongestion, based on well-regulated mechanical removal of fluid irrespective of baseline kidney functions and independent of renin-angiotensin neurohormonal pathway activation. UF is also thought to offer better control over the rate and volume of fluid removal. By contrast, the diuretic response is variable and can be influenced by baseline kidney function, and tolerance threshold to diuretics. However, studies have shown that the potential mechanistic benefits of UF are offset by its higher costs, the higher degree of expertise and advanced equipment requirements that are associated with UF. More importantly, these theoretical differences do not appear to translate into clinical benefits as evidenced by similar in-hospital and short-term outcomes of UF and diuretics [19–26].

Prior trials on the relative merits of UF and diuretic use had conflicting findings. While statistically non-significant, the CARRESS-HF had 28% higher, while AVOID-HF had a 10% lower incidence of re-hospitalization rate with UF [9,11]. In agreement with these trials, our large-scale study showed no difference in all-cause and HF-related re-hospitalization rates, and in the mean length of stay of the index hospitalization. The resultant weight loss as a surrogate for fluid loss during index admission was also similar between the two groups, indicating a similar efficacy of both therapies. A hospital cost analysis based on Healthcare Cost and Utilization Project (HCUP) database determined that the average cost at 90-day follow up incurred by each patient with UF and Diuretics was $23,633 and $27,608, respectively, after adjusting for reduced readmissions and hospital stay with UF [27]. This, in the context of equal efficacy of two strategies, underscores the importance of the randomized cost-benefit analysis of UF vs. diuretics strategies.

In terms of safety, both UF and diuretics can cause electrolyte imbalances, renal complications, and hypotension. Prevention of acute kidney injury (defined as >0.3 mg/dL in creatinine) has important clinical implications in the short and long-term prognosis of HF patients [28,29]. Our analysis showed that the mean rise in creatinine from baseline was significantly higher with UF than diuretics; however, the incidence of acute kidney injury (AKI) remained the same in both groups. This discrepancy could be attributed partially to frequent fluctuations in creatinine albeit less than 0.3 mg/dL (below the threshold of the definition of AKI, and in absence of anuria, and uremia). The change in sodium from baseline was significantly higher with UF, however, this was largely driven by the CARRESS-HF trial [11,30]. UF was associated with lower sodium levels but was not associated with adverse clinical outcomes [31]. In our study, the pooled estimates obtained from the two trials that reported hypotensive events revealed a similar risk of hypotension, largely driven by the UNLOAD trial likely due to mild disease severity and less aggressive mean diuretic dose (124 mg/day furosemide-equivalent dose). Studies on long-term use of UF are needed to determine the impact of UF-related hyponatremia and longstanding hypotension on clinical outcomes.

It is important to note that the included trials in this meta-analysis compared UF mediated by extracorporeal methodologies with diuretics, and patients undergoing peritoneal dialysis (PD) were not

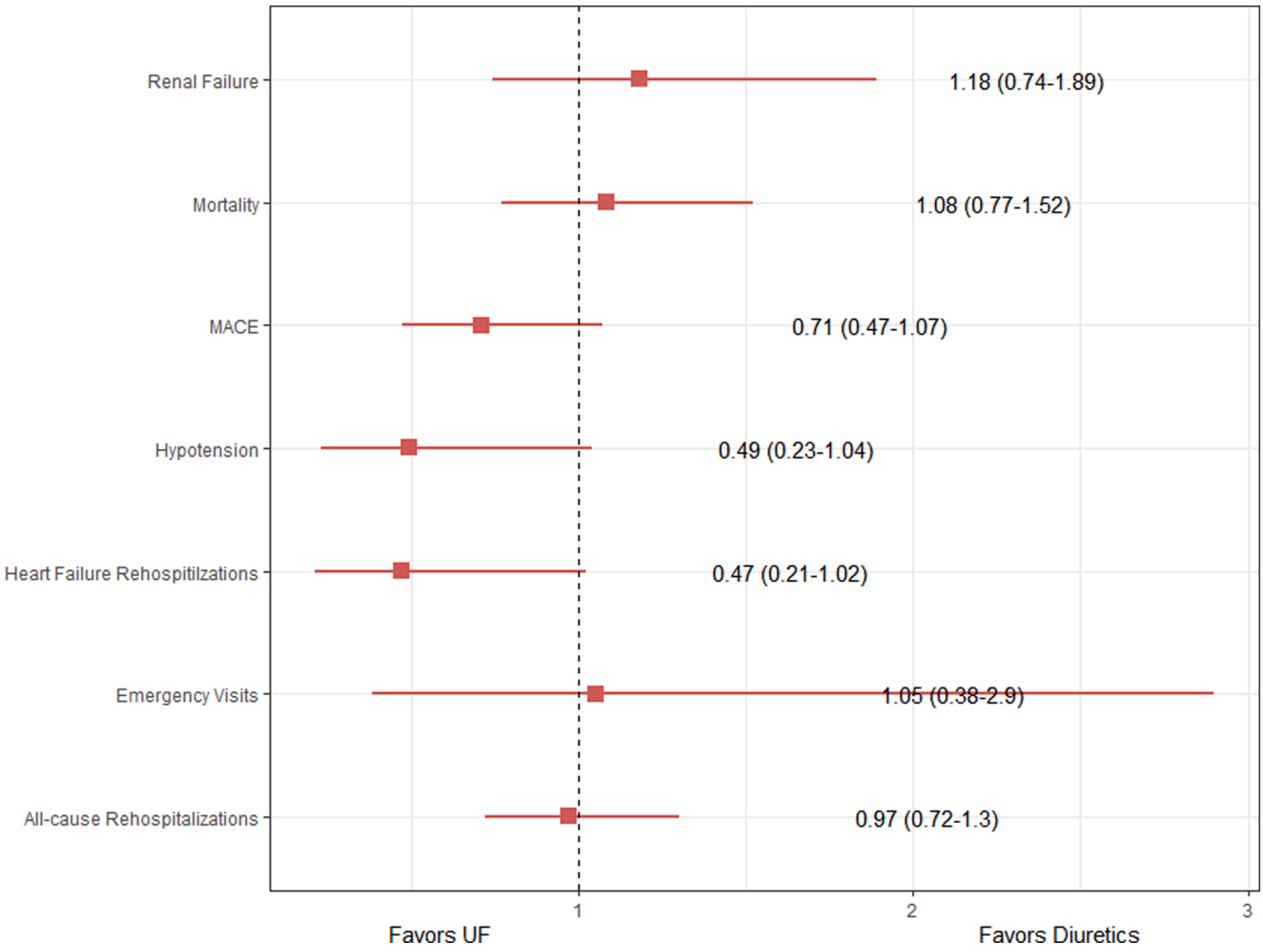

Fig. 3. Pooled Forest plot of all major dichotomous outcomes in the analysis with it's 95% confidence interval (line) and point estimates (squares).

included. PD can potentially reduce HF-related hospitalization, decrease procedural costs, and improve quality of life [32]. The reported survival benefit with PD as compared with hemodialysis in an observational study was 48% [33]. However, the lack of randomized clinical trials comparing PD head-to-head with hemodialysis precluded its inclusion in our quantitative analysis.

On review, we found 8 meta-analyses on the topic that included 6–9 trials with disputed results [19–26]. Most of these studies were released before the publication of contemporary trials. Some studies used a fixed-effect model over-estimating the efficacy of UF, while others missed describing the methodological quality of studies. The detailed descriptions of these meta-analyses are given in Table S13. In this context, our large-scale study aimed to bring consensus on this rapidly evolving topic. Briefly, our results indicate a similar safety and efficacy of the two treatment modalities.

The findings of our study should be interpreted in light of its limitations. Due to a lack of granular data, we could not comment on the type and dosages of diuretics. Similarly, details on the changes made to the mechanics of UF during hospitalization were not available. There remained some heterogeneity in the selection criteria, cutoff values, and definition of outcomes across the included trials. Therefore, our findings may not be generalizable to all patients with acute decompensated heart failure. Similarly, the included trials relied on a change in the creatinine level to define kidney failure, this approach could be misleading as baseline creatinine level of the included population is variable. Due to the lack of long-term data, medication compliance reports, and patient-level data, the findings of this meta-analysis should be interpreted with caution. Despite this, this meta-analysis can provide directions for future large-scale trials.

5. Conclusion

UF appears to have similar safety and efficacy compared with diuretics use in patients with HFrEF. The odds of major adverse cardiovascular events, mortality, renal failure, and need for rehospitalization were not significantly different between the two groups.

Disclosures

None.

Declaration of Competing Interest

None.

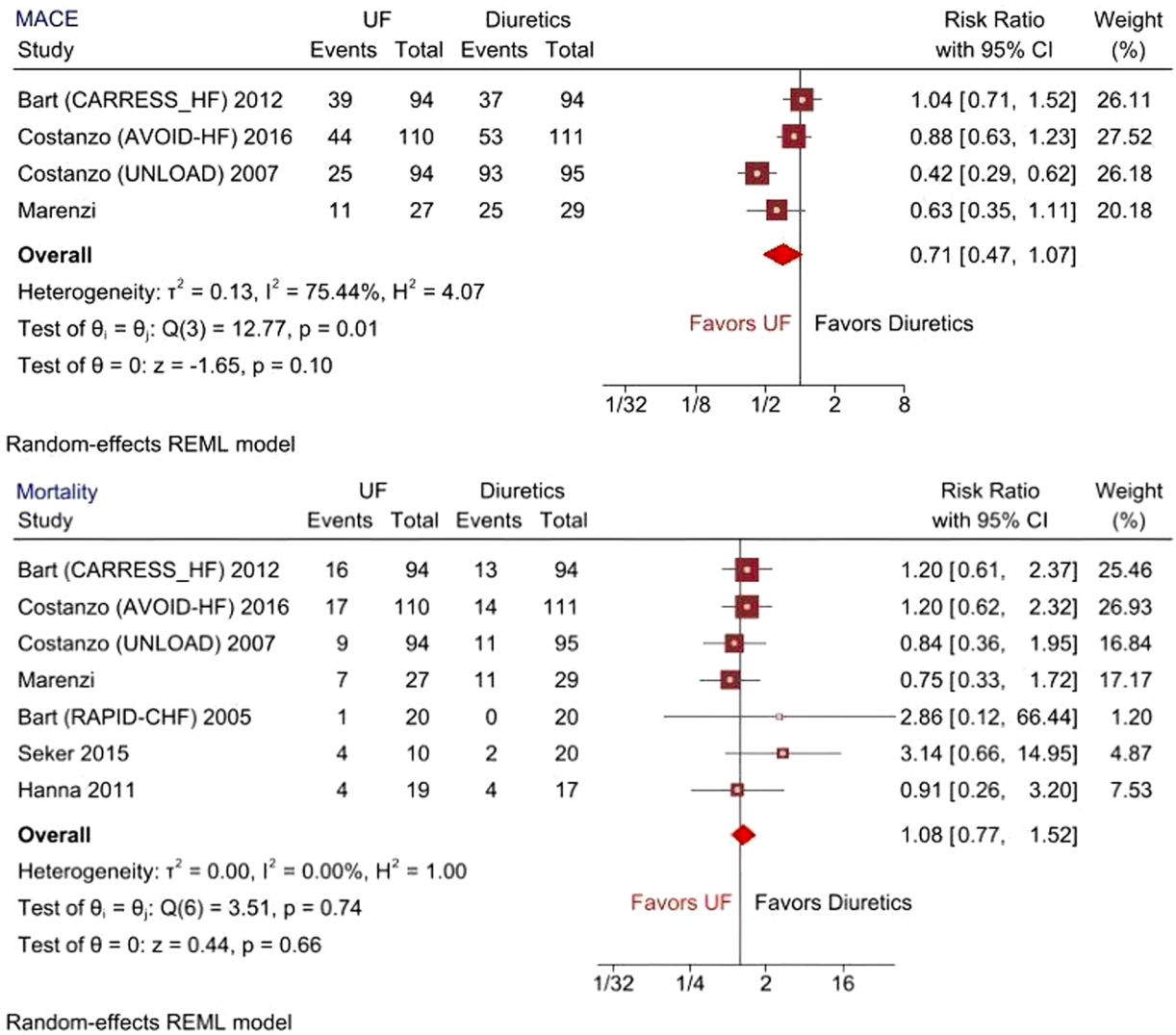

Fig. 4. Forest plot showing pooled estimate of composite of major adverse cardiovascular events and all-cause mortality between UF and diuretics.

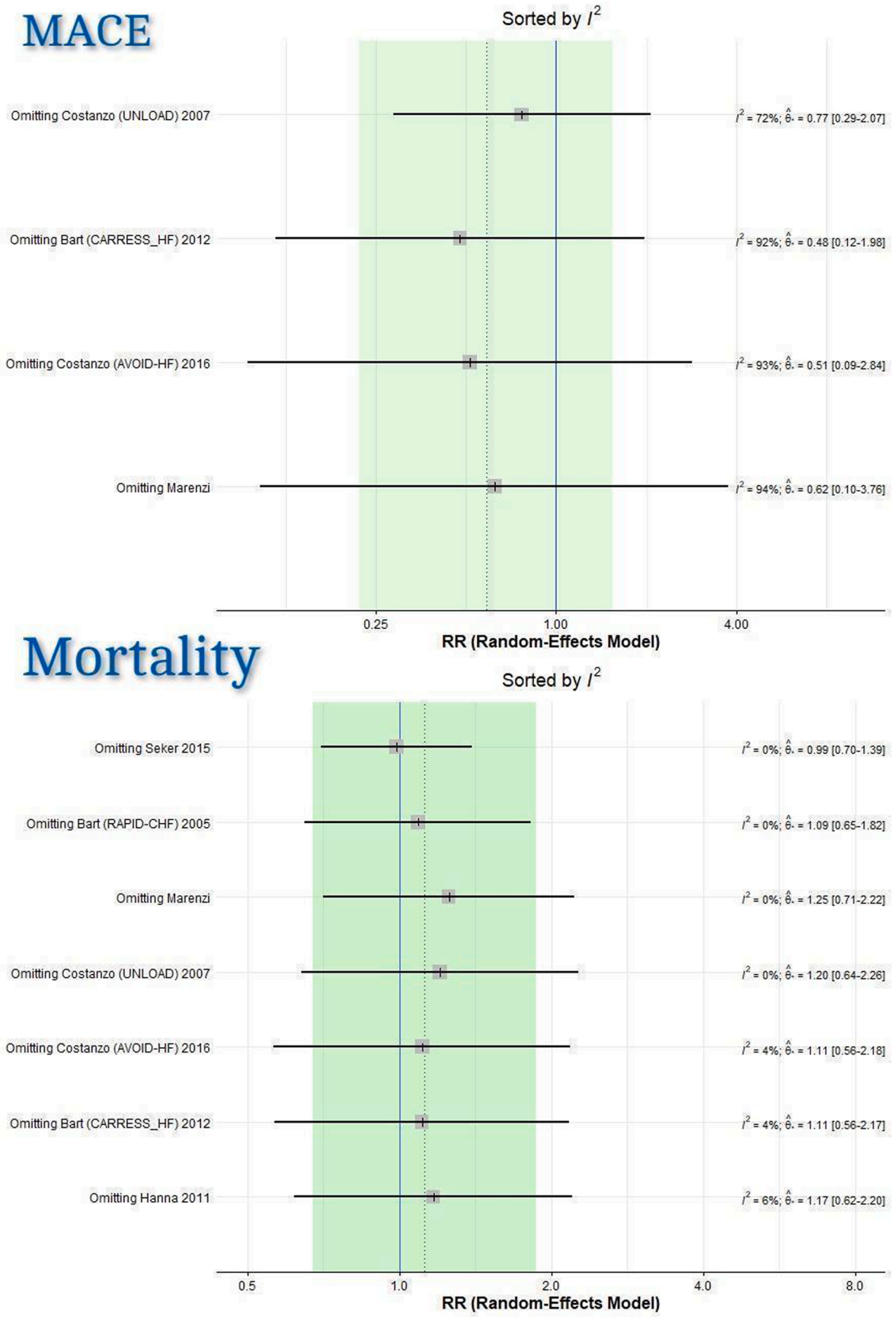

Fig. 5. Sensitivity analysis based on "leave-one-out" showing no deviation in MACE and mortality net-estimates from pooled analysis.

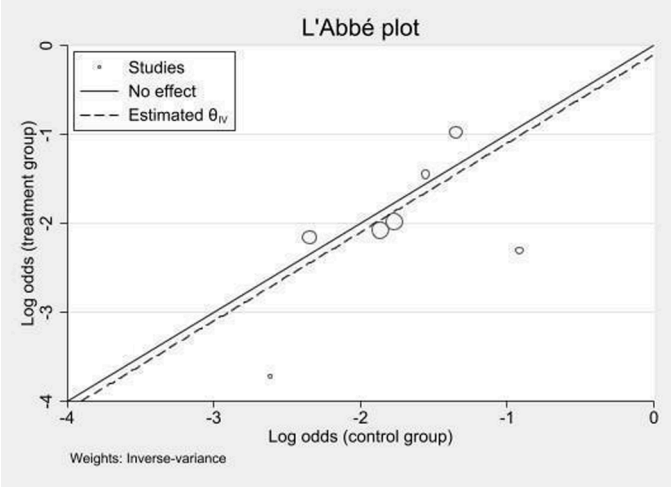

Fig. 6. L'Abbe plot illustrating log odds for diuretics on x-axis and ultrafiltration on y-axis.

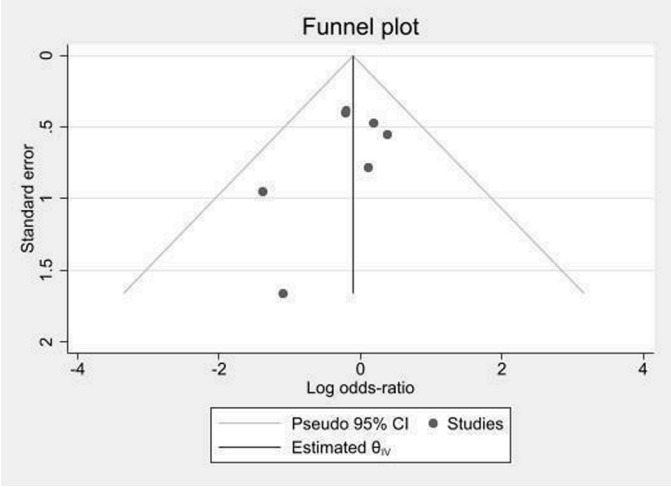

Fig. 7. Funnel plot illustrating no publication bias.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ejim.2022.05.022.

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