Efficacy of new medical therapies in patients with heart failure, reduced ejection fraction and chronic kidney disease already receiving neurohormonal inhibitors: a network meta-analysis

Efficacy of additional medical therapies in patients with heart failure, reduced ejection fraction and chronic kidney disease already receiving neurohormonal inhibitors: a network meta-analysis

Pietro Ameri[1,2] *, Vincenzo De Marzo[1,2] *, Giuseppe Biondi Zoccai[3,4], Lucia Tricarico[5,6], Michele Correale[5], Natale Daniele Brunetti[5,6], Marco Canepa[1,2], Gaetano Maria De Ferrari[7,8], Davide Castagno[7,8], Italo Porto[1,2]

1. Cardiology Unit, Cardiothoracic and Vascular Department, IRCCS Ospedale Policlinico San Martino, Genova, Italy – IRCCS Italian Cardiology Network
2. Department of Internal Medicine, University of Genova, Genova Italy
3. Department of Medical-Surgical Sciences and Biotechnologies, Sapienza University of Rome, Latina, Italy
4. Mediterranea Cardiocentro, Napoli, Italy
5. Cardiology Unit, Ospedali Riuniti di Foggia, Foggia, Italy
6. University of Foggia, Foggia, Italy
7. Division of Cardiology, Cardiovascular and Thoracic Department, Città della Salute e della Scienza Hospital, Turin, Italy
8. Department of Medical Sciences, University of Turin, Turin, Italy

* equally contributed

Word count:

Address for correspondence
Pietro Ameri, MD, PhD, FHFA
IRCCS Ospedale Policlinico San Martino and Department of Internal Medicine, University of Genova
Viale Benedetto XV, 6 - 16132 Genova, Italy
Phone: +390103538928, fax: +390105556513
Email: pietroameri@unige.it

Abstract

Aims: We assessed the efficacy of add-on drugs in patients with heart failure with reduced ejection fraction (HFrEF) and concomitant chronic kidney disease (CKD) already receiving neurohormonal inhibition (NEUi).

Methods and results: The literature was systematically searched for phase 3 randomized controlled trials (RCTs) involving ≥90% patients with left ventricular ejection fraction <45%, of whom <30% were acutely decompensated, and with published information about the subgroup of estimated glomerular filtration rate <60 mL/min/1.73m2. Six RCTs were included in a study-level network meta-analysis evaluating the effect of NEUi, ivabradine, angiotensin receptor-neprilysin inhibitor (ARNI), sodium-glucose cotransporter-2 inhibitors (SGLT2i), vericiguat, and omecamtiv mecarbil (OM) on a composite outcome of cardiovascular death or hospitalization for heart failure. In a fixed-effects model, SGLT2i (HR 0.78, 95%CrI 0.69-0.89), ARNI (HR 0.79, 95%CrI 0.69-0.90), and ivabradine (HR 0.82, 95%CrI 0.69-0.98) decreased the risk of the composite outcome vs. NEUi, whereas OM did not (HR 0.98, 95%CrI 0.89-1.10). A trend for improved outcome was also found for vericiguat (HR 0.90, 95%CrI 0.80-1.00). In indirect comparisons, both SLGT2i (HR 0.80, 95%CrI 0.68-0.94) and ARNI (HR 0.80, 95%CrI 0.68-0.95) reduced the risk vs. OM; furthermore, there was a trend for a greater benefit of SGLT2i vs. vericiguat (HR 0.88, 95%CrI 0.73-1.00) and ivabradine vs. OM (HR 0.84, 95%CrI 0.68-1.00). Results were comparable in a random-effects model and in sensitivity analyses. SUCRA scores were 81.8%, 80.8%, 68.9%, 44.2%, 16.6%, and 7.8% for SGLT2i, ARNI, ivabradine, vericiguat, OM, and NEUi, respectively.

Conclusion: Expanding pharmacotherapy beyond NEUi improves outcomes in HFrEF with CKD.

Keywords

Chronic kidney disease; SGLT2; ARNI; ivabradine; vericiguat; omecamtiv.

Introduction

The cornerstone of the medical treatment of heart failure with reduced ejection fraction (HFrEF) has traditionally consisted of neurohormonal inhibition (NEUi) with beta-blockers (BB), angiotensin-converting enzyme inhibitor (ACEi)/angiotensin receptor blockers (ARB), and mineralocorticoid receptor antagonists (MRA) (1). These drugs improve the survival of subjects with HFrEF (2, 3). Nonetheless, the prognosis of specific patient subsets, such as those who also have chronic kidney disease (CKD), is often dismal. The prevalence of moderate to severe CKD, as defined by an estimated glomerular filtration rate (eGFR) below 60 ml/min/1.73m^2, is as high as 40% in HFrEF(4) and it is an independent predictor of short- and long-term cardiovascular (CV) events and death (5-7). Moreover, the more severe is CKD in HFrEF, the worse the prognosis (8, 9).

In the last years, several randomized controlled trials (RCTs) evaluated new medications in patients with HFrEF already on NEUi. The angiotensin receptor neprilysin inhibitor (ARNI), sacubitril-valsartan (10), and the sodium-glucose cotransporter-2 inhibitors (SGLT2i), dapagliflozin (11) and empagliflozin (12), reduced CV death and hospitalization for HF (HHF) as compared with placebo. HHF, and thereby the composite outcome of death from CV causes and HHF, were also decreased by ivabradine (13) and by the soluble guanylate cyclase inhibitor vericiguat (14). Finally, the myosin activator omecamtiv mecarbil (OM) resulted in a modest, yet significant, reduction in the risk of CV death or HF event (HHF or urgent HF visit), although it was not superior to placebo for either component of this outcome (15).

The efficacy of these drugs in HFrEF patients with concomitant CKD has also been assessed individually within the relevant RCTs (15-20). We performed a network meta-analysis (NMA) to gain insights into how these therapies perform in HFrEF with CKD, both collectively and relatively one to another.

Methods

This NMA was registered in PROSPERO (ID: CRD42021224505) and conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) recommendations (**Table S1**) (21). All data are available within the article and Supplementary Material.

Search strategy

We systematically searched MEDLINE, Embase, Scopus, and Cochrane Library using the strings "heart failure", "randomized controlled trial", and the combination of them. We also manually screened the bibliographies of original research articles, guidelines, reviews, and meta-analyses to identify additional eligible studies. The search was limited to English language, peer-reviewed publications and is updated to June 25th, 2021. The search outputs are summarized in **Table S2**.

Eligibility criteria and data extraction

First, we selected phase 3 RCTs in which ≥90% subjects had left ventricular ejection fraction (LVEF) <45% and were representative of the general HFrEF population (i.e., not limited to specific patient categories). Moreover, the proportion of individuals admitted for acutely decompensated HF had to be <30%. Next, we selected the RCTs comparing new drugs vs. placebo in populations already treated with NEUi as per guidelines (BB, ACEi/ARB, and MRA, unless contraindicated and at the maximally tolerated doses). Comparisons within the same drug group were excluded. Finally, we retrieved the articles reporting sufficient information about the outcome of interest in patients with eGFR <60 mL/min/1.73m^2 of body-surface area according to the Chronic Kidney Disease Epidemiology Collaboration Group or Modification of Diet in Renal Disease equations (hereafter, referred to as CKD). We excluded the publications assessing renal function according to an increase in serum creatinine or a reduction in creatinine clearance as estimated by the Cockroft-Gault formula.

Information was collected from the eligible articles regarding patient characteristics, follow-up duration, total numbers of patients and outcome events in the RCT arms, and hazard ratios (HRs). The gathered data were organized into a database with double entry with reconciliation.

When medications other than the investigational one were taken by ≥50% of the RCT participants, the investigational treatment was considered as administered on top of these other drugs (22).

Analysis outcome

The outcome evaluated was a composite CV death or first HHF (**Table S3** reports the definitions for each included RCT).

Quality of evidence

We examined the quality of evidence (high, moderate, low, or very low) according to the GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) tool (21), taking the following parameters into consideration: study design, risk of bias, inconsistency, indirect evidence, imprecision, and publication bias.

Assessment of risk of bias

According to the Cochrane Collaboration's tool (21), the risk of bias was assessed in 6 pre-specified domains: selection bias, performance bias, detection bias, attrition bias, reporting bias, and other bias. Studies were deemed with low risk of bias if all 6 domains were classified as low risk, with medium risk of bias if there was some concern in ≥1 domain, and with high risk of bias if the risk was estimated as high in ≥1 domain or there was concern in several domains.

Network meta-analysis

The NMA was graphically represented by means of a network, in which each treatment was connected to every other treatment, regardless of the existence of head-to-head comparisons.

The methodology adopted was similar to that of previous NMAs in HF (2, 3), with a modelling framework proposed by Dias et al (23). This comprises both a fixed-effects model (primarily presented) and a more conservative random-effects model within a Bayesian framework using R software and JAGS software. The Markov chain Monte Carlo method was used running 4 chains with 200000 iterations after a burn-in of 100000. Non-informative priors were used.

The dataset for the models was built based on the total number of patients with CKD randomized per RCT arm, and the number of patients with CKD in each arm having an event during the exposure time, corresponding to the reported mean or median follow-up.

Thereafter, the log mean/median follow-up time was used to transform the probability of an event into a constant rate for each RCT arm by assuming an underlying Poisson process, and a log link was used to model the event rates (23).

For 2 RCTs (SHIFT (13) and GALACTIC-HF (15)), we used contrast-based data, i.e. we included in the model the effect estimates and their standard errors, since only HRs with 95% confidence interval (CI), instead of the numbers of patients with and without events, were available for the CKD subgroup.

The outputs from the models are presented as HRs with 95% credible intervals (CrI) for the Bayesian probability that the treatment is better than NEUi. Results for pairwise comparisons are also given.

The number needed to treat (NNT) was calculated as 1/(control-group event rate - investigational-group event rate).

Heterogeneity was measured through the I^2 statistic, with <25%, 25-50% and >50% I^2 indicating low, moderate, or high heterogeneity, respectively, and through τ^2 heterogeneity. Convergence was evaluated according to Gelman-Rubin-Brooks.

The analyzed therapies were also ranked by computing the Surface Under the Cumulative Ranking Area (SUCRA) values for the composite endpoint, with higher SUCRA indicating better-performing treatments. The following sensitivity analyses were also conducted: a) repeating the analysis with a frequentist approach, using both a fixed-effects model and a random-effects model with the DerSimonian-Laird estimator (24); b) excluding the selected studies sequentially (leave-one-out analysis); c) excluding SHIFT and GALACTIC-HF, because the rate of events in patients with CKD were not published for these RCTs; d) considering empagliflozin and dapagliflozin as different treatments.

The NMA was conducted in R environment (RStudio Desktop, version 1.2.5033) with *gemtc*, *ggplot2*, *igraph*, and *netmeta* packages. Statistical significance was set at $p < 0.05$ for the frequentist NMA.

Results

The PRISMA diagram showing the search and selection of references is provided in **Figure S1**, while the references included in the qualitative synthesis and subsequently excluded based on inclusion and exclusion criteria are listed in **Table S4**.

Six RCTs were included, investigating ivabradine (SHIFT (13)), sacubitril-valsartan (PARADIGM-HF (10)), dapagliflozin (DAPA-HF (11)), empagliflozin (EMPEROR-REDUCED (12)), vericiguat (VICTORIA (14)), and OM (GALACTIC-HF (15)) in addition to NEUi (**Figure 1**). The network had a pentagonal shape with 6 nodes, since dapagliflozin and empagliflozin were grouped together as SGLT2i.

Study and patient characteristics

The selected RCTs were multicenter, double-blind, and placebo-controlled, with a median follow-up duration of 20.0 (16.6-26.6) months (**Tables S5-S7).** All were categorized as of high-quality based on the GRADE system, and risk of bias was always low, both globally and in individual domains (**Table S8**).

The proportion of patients with CKD ranged from 25.6% in SHIFT to 53.2% in VICTORIA. Their baseline characteristics, as published for 5 of the 6 RCTs, are summarized in **Table 1**. Mean age was 70.2 years, 76.7% of participants were males, and NYHA class was mostly II or III. The etiology of HF was mainly ischemic and around 40% of patients had a history of atrial fibrillation (AF), with the exception of SHIFT consistently with ivabradine indication. The mean prevalence of hypertension was 79.9% and that of diabetes 47.8%, although this latter was lower in SHIFT and PARADIGM-HF than in the other RCTs (**Table 1**). While the frequency of BB, MRA, and diuretic use was similar across the selected RCTs, ACEi/ARB were taken by 100% subjects in PARADIGM-HF (as per study

design), 94% in SHIFT, and progressively lower percentages in the most recent RCTs, in which however the use of ARNI gradually increased up to 20.1% in EMPEROR-REDUCED (**Table 2**).

Bayesian network meta-analysis

The number of events for the outcome of interest, or the HRs with 95%CI, are reported in **Table 3**. The NNT within the individual RCTs ranged from 14-16 (SHIFT, PARADIGM-HF, and DAPA-HF) to 27-28 (VICTORIA and EMPEROR-REDUCED).

In the fixed-effects NMA, SGLT2i (HR 0.78, 95%CrI 0.69-0.89), ARNI (HR 0.79, 95%CrI 0.69-0.90), and ivabradine (HR 0.82, 95%CrI 0.69-0.98) decreased the risk of CV death or HHF as compared with NEUi (**Figure 2** and **Table 4**). Vericiguat was also associated with a trend for lower rates of CV death or HHF (HR 0.90, 95%CrI 0.80-1.00), whereas OM had a neutral effect (HR 0.98, 95%CrI 0.89-1.10). In indirect comparisons, both SLGT2i (HR 0.80, 95%CrI 0.68-0.94) and ARNI (HR 0.80, 95%CrI 0.68-0.95) reduced the composite endpoint as compared with OM; furthermore, a trend was found for superiority of SGLT2i over vericiguat (HR 0.88, 95%CrI 0.73-1.00) and of ivabradine over OM (HR 0.84, 95%CrI 0.68-1.00) (**Table 4**). Pairwise and network comparisons, as well as ranking probabilities, were similar in the random-effects model (**Table S9**).

Heterogeneity and convergence

The global I^2 for the composite endpoint was 22%, indicating low heterogeneity. τ^2 was also very low (0.0005). The Gelman-Rubin-Brooks plot showed high convergence (**Figure S2**).

Treatment ranking

SGLT2i (81.8%) and ARNI (80.8%) had the highest SUCRA scores for the composite endpoint, followed by ivabradine (68.9%) and vericiguat (44.2%) (**Figure 3**).

Sensitivity analyses

Pairwise and network comparisons as well as ranking probabilities were also similar when frequentist fixed-effects (**Table 5** and **Figure S3**) and random-effects (**Table S10**) models were used.

The results of the leave-one-out analysis were also overall comparable to the main ones (**Table S11**). However, when DAPA-HF was removed, the SUCRA value for empagliflozin was 64.4%, while after removing EMPEROR-REDUCED the SUCRA value for dapagliflozin was 90.8%.

After excluding SHIFT and GALACTIC-HF, SGLT2i (HR 0.78, 95%CrI 0.69-0.89) and ARNI (HR 0.79, 95%CrI 0.69-0.90) were still associated with a significant reduction in the composite endpoint vs. NEUi, and SGLT2i also tended to be better than vericiguat (HR 0.88, 95%CrI 0.73-1.00) (**Table S12**).

Finally, when DAPA-HF and EMPEROR-REDUCED were considered separately, dapagliflozin (HR 0.73, 95%CrI 0.60-0.88) and ARNI (HR 0.79, 95%CrI 0.68-0.90) were superior to NEUi with respect to CV death or HHF. Conversely, the HR for empagliflozin was 0.85 with a 95%CrI between 0.70 and 1.00. In addition, dapagliflozin (HR 0.81, 95%CrI 0.65-1.00), but not empagliflozin (HR 0.95, 95%CrI 0.76-1.20) showed a trend for a decrease in the composite endpoint vs. vericiguat (**Table S13**).

Discussion

NEUi has been the backbone of medical therapy for HFrEF. Over the last decade, however, the addition of several other drugs to NEUi has proved to be superior to NEUi alone in diminishing CV mortality and/or HHF in patients with HFrEF(25). Although NEUi improves outcomes in subjects whose eGFR is between 30 and 60 mL/min/1.73m^2 (26), concomitant CKD still portends a 2-fold higher risk of mortality in HFrEF (8). Thus, there is still need for better treatment options in this setting.

This NMA confirms that, in the pivotal RCTs, most new medications retained efficacy in patients with HFrEF, CKD, and symptoms and clinical and/or biochemical signs of inadequately controlled HF despite maximized NEUi: SGLT2i, ARNI, and ivabradine decreased the risk of CV death or HHF by around 20%, and vericiguat by around 10%.

The knowledge that some of these therapies exert favorable actions in the kidney strengthens our results. Unlike ACEi/ARB, ARNI induces preferential vasorelaxation of the afferent arteriole and relative vasoconstriction of the efferent arteriole, eventually preserving glomerular filtration; furthermore, it positively modulates podocytes and mesangial cells and inhibits renal inflammation and fibrosis (27). By enhancing sodium delivery to the macula densa, SGLT2i stimulate the release of molecules that cause afferent artery vasoconstriction, decreasing intraglomerular hypertension and hyperfiltration and, thereby, eGFR decline and albuminuria progression. SGLT2i may also be nephroprotective in other ways, such as reduction of glucose burden to the nephrons as well as of oxidative stress, inflammation, and fibrosis (28). Cyclic guanosine monophosphate signaling, which is activated by vericiguat, underlies pro-homeostatic intracellular pathways (29).

It may be argued that there is a disconnection between our results and real life, since the RCTs we examined evaluated cohorts optimally treated with NEUi, whereas implementation of NEUi is often insufficient in clinical practice, with up-titration being low and discontinuation rates substantial (30). RCTs and analyses based on the information gathered from RCTs remain fundamental to establish therapeutic indications and gain insights into subgroups, but should ideally be integrated with real-world data. The available evidence does not allow concluding that ivabradine and ARNI confer advantage over NEUi in real-life HFrEF patients with CKD (31, 32), and post-marketing data are still lacking for SGTL2i, vericiguat, and OM. Therefore, the findings of this NMA should be verified in datasets deriving from registries.

Nonetheless, we show that, in principle, expanding the spectrum of HFrEF pharmacotherapy beyond NEUi is associated with a lower risk of CV death or HHF in individuals with comorbid CKD. It is also noteworthy that 11%, 14%, and 20% of participants with CKD, respectively, were also taking ARNI in the RCTs evaluating dapagliflozin, vericiguat, and empagliflozin, indicating that the combination of NEUi, ARNI, and the most recent medications is feasible even in the challenging subset of patients with HFrEF and CKD.

Although we used the same definition of CKD – i.e., eGFR <60 mL/min/1.73m^2 – for all RCTs, important dissimilarities among the included studies should be highlighted. The investigational drug was always compared with placebo and administered on top of BB, ACEi/ARB, and MRA, with the exception of PARADIGM-HF, in which eligible subjects received sacubitril-valsartan or enalapril besides background BB and MRA (10). Furthermore, randomization in PARADIGM-HF was preceded by a run-in phase to select those who could tolerate the target dose of both sacubitril-valsartan and enalapril. A key inclusion criterion in SHIFT was the presence of sinus rhythm at screening, which made an history of AF less common than in the other RCTs, while VICTORIA and GALACTIC-HF were enriched in patients with worsening HF. These features may have influenced the impact of the interventions in the CKD subgroups, since AF and events of decompensation have independent effects on HF prognosis (33, 34). Glomerular filtration is function of systolic blood pressure, which could be as low as 85 mmHg in GALACTIC-HF and VICTORIA, in contrast with the cut-off value at screening of 95 or 100 mmHg in the other RCTs. Finally, the eGFR threshold below which participation in the RCT was precluded ranged from 15 mL/min/1.73m^2 in VICTORIA to 20 mL/min/1.73m^2 in EMPEROR-REDUCED and GALACTIC-HF to 30 mL/min/1.73m^2 in DAPA-HF and PARADIGM-HF. In SHIFT, baseline serum creatinine had to be <220 micromol/L. Therefore, the addition of novel drugs to NEUi improved the outcomes of distinct patient phenotypes within the heterogeneous HFrEF population with CKD.

On the one hand, this consideration substantiates the conclusion that, in general, the newest medical therapies should be used in HFrEF with concomitant CKD. SGLT2i are particularly appealing, since they were evaluated in broader patient profiles as compared with those assessed in the other RCTs and were among the most effective treatments. Interestingly, the leave-one-out analysis and the sensitivity analysis in which DAPA-HF and EMPEROR-REDUCED were considered separately suggest that the benefit of SGLT2i was more pronounced in the former than in the latter RCT.

On the other hand, the differences across studies lend support to the claim that a tailored therapeutic approach may be preferable for HFrEF with CKD, with different drugs being the first choice

depending on key patient characteristics (35). In this regard, OM may find a place notwithstanding the results reported here. The benefit of OM was greater when LVEF was lower in the entire GALACTIC-HF population (36) and this might be true also in subjects with CKD, although we could not verify this hypothesis due to the lack of published information. For the same reason we could not investigate the effects of the latest medications in subsets of patients with HFrEF and CKD, such as those hospitalized for acute decompensation or diabetic.

In conclusion, the totality of available data from RCTs indicates that adding the newest drugs to NEUi provides incremental benefit in HFrEF with concomitant CKD, with SGLT2i, ARNI, and ivabradine being associated with the greatest risk reduction. Further analyses are needed to point out the phenotypes that are most suitable for each medication, including OM, within the generic category of patients with HFrEF and CKD.

Acknowledgements

None.

Funding

None.

Conflicts of interest

P.A. received speaker and/or advisor fees related to the content of this article from AstraZeneca and Novartis,and served as scientific consultant for Bayer on behalf of the Department of Internal Medicine of the University of Genova. I. P. reports consultant or speaker fees in the last 2 years from Biotronik, ABIOMED, Terumo, Philips, Sanofi, Amgen, Daiichi-Sankyo, Astra Zeneca, Bayer, not related to this work.

References

1. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, Falk V, Gonzalez-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GMC, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P, Group ESCSD. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J* 2016; 37(27):2129-2200.

2. Burnett H, Earley A, Voors AA, Senni M, McMurray JJ, Deschaseaux C, Cope S. Thirty Years of Evidence on the Efficacy of Drug Treatments for Chronic Heart Failure With Reduced Ejection Fraction: A Network Meta-Analysis. *Circ Heart Fail* 2017; 10(1).

3. Komajda M, Bohm M, Borer JS, Ford I, Tavazzi L, Pannaux M, Swedberg K. Incremental benefit of drug therapies for chronic heart failure with reduced ejection fraction: a network meta-analysis. *Eur J Heart Fail* 2018; 20(9):1315-1322.

4. McAlister FA, Ezekowitz J, Tarantini L, Squire I, Komajda M, Bayes-Genis A, Gotsman I, Whalley G, Earle N, Poppe KK, Doughty RN, Meta-analysis Global Group in Chronic Heart Failure I. Renal dysfunction in patients with heart failure with preserved versus reduced ejection fraction: impact of the new Chronic Kidney Disease-Epidemiology Collaboration Group formula. *Circ Heart Fail* 2012; 5(3):309-14.

5. Tuegel C, Bansal N. Heart failure in patients with kidney disease. *Heart* 2017; 103(23):1848-1853.

6. Schefold JC, Filippatos G, Hasenfuss G, Anker SD, von Haehling S. Heart failure and kidney dysfunction: epidemiology, mechanisms and management. *Nat Rev Nephrol* 2016; 12(10):610-23.

7. House AA, Wanner C, Sarnak MJ, Pina IL, McIntyre CW, Komenda P, Kasiske BL, Deswal A, deFilippi CR, Cleland JGF, Anker SD, Herzog CA, Cheung M, Wheeler DC, Winkelmayer WC, McCullough PA, Conference P. Heart failure in chronic kidney disease: conclusions from a Kidney

Disease: Improving Global Outcomes (KDIGO) Controversies Conference. *Kidney Int* 2019; 95(6):1304-1317.

8. Damman K, Valente MA, Voors AA, O'Connor CM, van Veldhuisen DJ, Hillege HL. Renal impairment, worsening renal function, and outcome in patients with heart failure: an updated meta-analysis. *Eur Heart J* 2014; 35(7):455-69.

9. Lofman I, Szummer K, Dahlstrom U, Jernberg T, Lund LH. Associations with and prognostic impact of chronic kidney disease in heart failure with preserved, mid-range, and reduced ejection fraction. *Eur J Heart Fail* 2017; 19(12):1606-1614.

10. McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, Rouleau JL, Shi VC, Solomon SD, Swedberg K, Zile MR, Investigators P-H, Committees. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Engl J Med* 2014; 371(11):993-1004.

11. McMurray JJV, Solomon SD, Inzucchi SE, Kober L, Kosiborod MN, Martinez FA, Ponikowski P, Sabatine MS, Anand IS, Belohlavek J, Bohm M, Chiang CE, Chopra VK, de Boer RA, Desai AS, Diez M, Drozdz J, Dukat A, Ge J, Howlett JG, Katova T, Kitakaze M, Ljungman CEA, Merkely B, Nicolau JC, O'Meara E, Petrie MC, Vinh PN, Schou M, Tereshchenko S, Verma S, Held C, DeMets DL, Docherty KF, Jhund PS, Bengtsson O, Sjostrand M, Langkilde AM, Committees D-HT, Investigators. Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. *N Engl J Med* 2019; 381(21):1995-2008.

12. Packer M, Anker SD, Butler J, Filippatos G, Pocock SJ, Carson P, Januzzi J, Verma S, Tsutsui H, Brueckmann M, Jamal W, Kimura K, Schnee J, Zeller C, Cotton D, Bocchi E, Bohm M, Choi DJ, Chopra V, Chuquiure E, Giannetti N, Janssens S, Zhang J, Gonzalez Juanatey JR, Kaul S, Brunner-La Rocca HP, Merkely B, Nicholls SJ, Perrone S, Pina I, Ponikowski P, Sattar N, Senni M, Seronde MF, Spinar J, Squire I, Taddei S, Wanner C, Zannad F, Investigators EM-RT. Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure. *N Engl J Med* 2020; 383(15):1413-1424.

13. Swedberg K, Komajda M, Bohm M, Borer JS, Ford I, Dubost-Brama A, Lerebours G, Tavazzi L, Investigators S. Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study. *Lancet* 2010; 376(9744):875-85.

14. Armstrong PW, Pieske B, Anstrom KJ, Ezekowitz J, Hernandez AF, Butler J, Lam CSP, Ponikowski P, Voors AA, Jia G, McNulty SE, Patel MJ, Roessig L, Koglin J, O'Connor CM, Group VS. Vericiguat in Patients with Heart Failure and Reduced Ejection Fraction. *N Engl J Med* 2020; 382(20):1883-1893.

15. Teerlink JR, Diaz R, Felker GM, McMurray JJV, Metra M, Solomon SD, Adams KF, Anand I, Arias-Mendoza A, Biering-Sorensen T, Bohm M, Bonderman D, Cleland JGF, Corbalan R, Crespo-Leiro MG, Dahlstrom U, Echeverria LE, Fang JC, Filippatos G, Fonseca C, Goncalvesova E, Goudev AR, Howlett JG, Lanfear DE, Li J, Lund M, Macdonald P, Mareev V, Momomura SI, O'Meara E, Parkhomenko A, Ponikowski P, Ramires FJA, Serpytis P, Sliwa K, Spinar J, Suter TM, Tomcsanyi J, Vandekerckhove H, Vinereanu D, Voors AA, Yilmaz MB, Zannad F, Sharpsten L, Legg JC, Varin C, Honarpour N, Abbasi SA, Malik FI, Kurtz CE, Investigators G-H. Cardiac Myosin Activation with Omecamtiv Mecarbil in Systolic Heart Failure. *N Engl J Med* 2020.

16. Voors AA, Mulder H, Reyes E, Cowie MR, Lassus J, Hernandez AF, Ezekowitz JA, Butler J, O'Connor CM, Koglin J, Lam CSP, Pieske B, Roessig L, Ponikowski P, Anstrom KJ, Armstrong PW, Group VS. Renal function and the effects of vericiguat in patients with worsening heart failure with reduced ejection fraction: insights from the VICTORIA (Vericiguat Global Study in Subjects with HFrEF) trial. *Eur J Heart Fail* 2021.

17. Zannad F, Ferreira JP, Pocock SJ, Zeller C, Anker SD, Butler J, Filippatos G, Hauske SJ, Brueckmann M, Pfarr E, Schnee J, Wanner C, Packer M. Cardiac and Kidney Benefits of Empagliflozin in Heart Failure Across the Spectrum of Kidney Function: Insights From EMPEROR-Reduced. *Circulation* 2021; 143(4):310-321.

18. Jhund PS, Solomon SD, Docherty KF, Heerspink HJL, Anand IS, Bohm M, Chopra V, de Boer RA, Desai AS, Ge J, Kitakaze M, Merkley B, O'Meara E, Shou M, Tereshchenko S, Verma S,

Vinh PN, Inzucchi SE, Kober L, Kosiborod MN, Martinez FA, Ponikowski P, Sabatine MS, Bengtsson O, Langkilde AM, Sjostrand M, McMurray JJV. Efficacy of Dapagliflozin on Renal Function and Outcomes in Patients With Heart Failure With Reduced Ejection Fraction: Results of DAPA-HF. *Circulation* 2021; 143(4):298-309.

19. Voors AA, van Veldhuisen DJ, Robertson M, Ford I, Borer JS, Bohm M, Komajda M, Swedberg K, Tavazzi L, investigators S. The effect of heart rate reduction with ivabradine on renal function in patients with chronic heart failure: an analysis from SHIFT. *Eur J Heart Fail* 2014; 16(4):426-34.

20. Damman K, Gori M, Claggett B, Jhund PS, Senni M, Lefkowitz MP, Prescott MF, Shi VC, Rouleau JL, Swedberg K, Zile MR, Packer M, Desai AS, Solomon SD, McMurray JJV. Renal Effects and Associated Outcomes During Angiotensin-Neprilysin Inhibition in Heart Failure. *JACC Heart Fail* 2018; 6(6):489-498.

21. Hutton B, Salanti G, Caldwell DM, Chaimani A, Schmid CH, Cameron C, Ioannidis JP, Straus S, Thorlund K, Jansen JP, Mulrow C, Catala-Lopez F, Gotzsche PC, Dickersin K, Boutron I, Altman DG, Moher D. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. *Ann Intern Med* 2015; 162(11):777-84.

22. Burnett H, Cope S, Vieira MC, Sagkriotis A, Senni M, Deschaseaux C. The Importance of Treatment Classifications that Account for Concomitant Treatments in the Context of a Network Meta-Analysis Comparing Pharmacological Treatments for Chronic Heart Failure. *Value Health* 2014; 17(7):A327.

23. Dias S, Sutton AJ, Ades AE, Welton NJ. Evidence synthesis for decision making 2: a generalized linear modeling framework for pairwise and network meta-analysis of randomized controlled trials. *Med Decis Making* 2013; 33(5):607-17.

24. Jackson D, White IR, Riley RD. A matrix-based method of moments for fitting the multivariate random effects model for meta-analysis and meta-regression. *Biom J* 2013; 55(2):231-45.

25. Ameri P, Bertero E, Maack C, Teerlink JR, Rosano G, Metra M. Medical treatment of heart failure with reduced ejection fraction: the dawn of a new era of personalized treatment? *Eur Heart J Cardiovasc Pharmacother* 2021.

26. Damman K, Tang WH, Felker GM, Lassus J, Zannad F, Krum H, McMurray JJ. Current evidence on treatment of patients with chronic systolic heart failure and renal insufficiency: practical considerations from published data. *J Am Coll Cardiol* 2014; 63(9):853-71.

27. Pontremoli R, Borghi C, Filardi PP. Renal protection in chronic heart failure: focus on sacubitril/valsartan. *Eur Heart J Cardiovasc Pharmacother* 2021.

28. Cowie MR, Fisher M. SGLT2 inhibitors: mechanisms of cardiovascular benefit beyond glycaemic control. *Nat Rev Cardiol* 2020; 17(12):761-772.

29. Stasch JP, Pacher P, Evgenov OV. Soluble guanylate cyclase as an emerging therapeutic target in cardiopulmonary disease. *Circulation* 2011; 123(20):2263-73.

30. Savarese G, Bodegard J, Norhammar A, Sartipy P, Thuresson M, Cowie MR, Fonarow GC, Vaduganathan M, Coats AJS. Heart failure drug titration, discontinuation, mortality and heart failure hospitalization risk: a multinational observational study (US, UK and Sweden). *Eur J Heart Fail* 2021.

31. Cowie MR, Schope J, Wagenpfeil S, Tavazzi L, Bohm M, Ponikowski P, Anker SD, Filippatos GS, Komajda M, Investigators Q. Patient factors associated with titration of medical therapy in patients with heart failure with reduced ejection fraction: data from the QUALIFY international registry. *ESC Heart Fail* 2021; 8(2):861-871.

32. Giovinazzo S, Carmisciano L, Toma M, Benenati S, Tomasoni D, Sormani MP, Porto I, Canepa M, Senni M, Metra M, Ameri P. Sacubitril/valsartan in real-life European patients with heart failure and reduced ejection fraction: a systematic review and meta-analysis. *ESC Heart Fail* 2021.

33. Mogensen UM, Jhund PS, Abraham WT, Desai AS, Dickstein K, Packer M, Rouleau JL, Solomon SD, Swedberg K, Zile MR, Kober L, McMurray JJV, Paradigm HF, Investigators A, Committees. Type of Atrial Fibrillation and Outcomes in Patients With Heart Failure and Reduced Ejection Fraction. *J Am Coll Cardiol* 2017; 70(20):2490-2500.

34. Butler J, Yang M, Manzi MA, Hess GP, Patel MJ, Rhodes T, Givertz MM. Clinical Course of Patients With Worsening Heart Failure With Reduced Ejection Fraction. *J Am Coll Cardiol* 2019; 73(8):935-944.

35. Rosano GMC, Moura B, Metra M, Bohm M, Bauersachs J, Ben Gal T, Adamopoulos S, Abdelhamid M, Bistola V, Celutkiene J, Chioncel O, Farmakis D, Ferrari R, Filippatos G, Hill L, Jankowska EA, Jaarsma T, Jhund P, Lainscak M, Lopatin Y, Lund LH, Milicic D, Mullens W, Pinto F, Ponikowski P, Savarese G, Thum T, Volterrani M, Anker SD, Seferovic PM, Coats AJS. Patient profiling in heart failure for tailoring medical therapy. A consensus document of the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail* 2021; 23(6):872-881.

36. Teerlink JR, Diaz R, Felker GM, McMurray JJV, Metra M, Solomon SD, Biering-Sorensen T, Bohm M, Bonderman D, Fang JC, Lanfear DE, Lund M, Momomura SI, O'Meara E, Ponikowski P, Spinar J, Flores-Arredondo JH, Claggett BL, Heitner SB, Kupfer S, Abbasi SA, Malik FI, Investigators G-H. Effect of Ejection Fraction on Clinical Outcomes in Patients Treated With Omecamtiv Mecarbil in GALACTIC-HF. *J Am Coll Cardiol* 2021; 78(2):97-108.

Tables

Table 1. Main characteristics of the patients with CKD in the selected RCTs with available information.

RCT (year)	Patients (n.)	Arm	Age (yrs)	Male (%)	NYHA I-II	NYHA III-IV	LVEF (%)	Ischemic HF (%)	AF	Hyper-tension	Diabetes	Previous HHF
EMPEROR-REDUCED (2020)	893 906	Empagliflozin Placebo	70.3	74.5%	0.0% / 72.9%	26.5% / 0.7%	27.8%	54.5%	43.7%	78.0%	53.8%	31.3%
VICTORIA (2020)	1321 1316	Vericiguat Placebo	73.5	72.4%	54.2%	46.0%	30.0%	NA	NA	86.4%	57.4%	68.5%
DAPA-HF (2019)	962 964	Dapagliflozin Placebo	70.9	72.3%	0.0% / 65.8%	33.5% / 0.7%	31.3%	61.0%	45.7%	81.0%	51.0%	49.4%
PARADIGM-HF (2014)	1333 1412	Sacubitril-valsartan Enalapril	70	75.7%	4.1% / 67.7%	27.5% / 0.7%	30.0%	66.0%	44.0%	78.0%	39.0%	63.0%
SHIFT (2010)	780 799	Ivabradine Placebo	66.7	63.0%	NA / 43.0%	NA / NA	29.1%	73.0%	11.0%	76.0%	38.0%	NA

AF: atrial fibrillation; HF: heart failure; HHF: hospitalization for HF; LVEF: left ventricular ejection fraction; NA: not available; NYHA: New York Heart Association; RCT: randomized controlled trial.

Table 2. Concomitant therapies in patients with CKD in the selected RCTs with available information.

RCT (year)	ACEi/ARB	BB	ARNI	MRA	Diuretic	ICD	CRT
EMPEROR-REDUCED (2020)	66.3%	94.8%	20.1%	67.9%	90.5%	35.6%	16.1%
VICTORIA (2020)	64.0%	93.1%	14.2%	55.5%	98.0%	31.8%	17.9%
DAPA-HF (2019)	80.1%	95.4%	11.5%	67.3%	95.3%	9.7%	
PARADIGM-HF (2014)	100.0% *	93.0%	-	58.0%	78.0%	13.0%	5.0%
SHIFT (2010)	94.0%	87.0.%	-	59.0%	89.0%	4.0%	2.0%

* before run-in

ACEi: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker; ARNI: angiotensin receptor-neprilysin inhibitor; BB: beta-blocker; CRT: cardiac resynchronization therapy; ICD: implantable cardioverter defibrillator; MRA: mineralocorticoid receptor antagonist; NA: not available; RCT: randomized controlled trial.

Table 3. Number of patients with CKD and the composite outcome events, or HRs for the composite outcome, in the selected RCTs.

RCT (year)	Intervention	Patients (n°)	Events (n°)	HR	95%CI	NNT
Arm-based data						
EMPEROR-REDUCED (2020)	Empagliflozin Placebo	893 906	202 237			28
VICTORIA (2020)	Vericiguat Placebo	1313 1311	535 583			27
DAPA-HF (2019)	Dapagliflozin Placebo	962 964	191 254			15
PARADIGM-HF (2014)	Sacubitril-valsartan Enalapril	1333 1412	358 465			16
Contrast-based data						
GALACTIC-HF (2020)	OM Placebo			0.98	0.89-1.07	-
SHIFT (2010)	Ivabradine Placebo			0.82	0.68-0.97	14

CI: confidence interval; HR: hazard ratio; NNT: number needed to treat; OM: omecamtiv mecarbil.

Table 4. Results of the fixed-effects NMA for the composite outcome of CV death or HHF.

Intervention	Comparator					
	NEUi	ARNI	SGLT2i	VERICIGUAT	IVABRADINE	OM
NEUi						
HR (95%CrI)	-	1.30 (1.10-1.50)	1.30 (1.10-1.50)	1.10 (0.99-1.30)	1.20 (1.00-1.50)	1.00 (0.93-1.10)
ARNI						
HR (95%CrI)	0.79 (0.69-0.90)	-	1.00 (0.83-1.20)	0.88 (0.73-1.10)	0.96 (0.77-1.20)	0.80 (0.68-0.95)
SGLT2i						
HR (95%CrI)	0.78 (0.69-0.89)	1.00 (0.82-1.20)	-	0.88 (0.73-1.00)	0.96 (0.77-1.20)	0.80 (0.68-0.94)
VERICIGUAT						
HR (95%CrI)	0.90 (0.80-1.00)	1.10 (0.95-1.40)	1.10 (0.96-1.40)	-	1.10 (0.88-1.40)	0.91 (0.78-1.10)
IVABRADINE						
HR (95%CrI)	0.82 (0.69-0.98)	1.00 (0.83-1.30)	1.00 (0.84-1.30)	0.92 (0.74-1.10)	-	0.84 (0.68-1.00)
OM						
HR (95%CrI)	0.98 (0.89-1.10)	1.20 (1.10-1.50)	1.20 (1.10-1.50)	1.10 (0.94-1.30)	1.20 (0.98-1.50)	-

ARNI: angiotensin receptor-neprilysin inhibitor; CrI, credible interval; HR: hazard ratio; NEUi: neurohormonal inhibition; OM: omecamtiv mecarbil; SGLT2i: sodium-glucose cotransporter 2 inhibitor.

Table 5. Results of the frequentist fixed-effects NMA for the composite outcome of CV death or HHF.

Intervention	Comparator					
	NEUi	ARNI	SGLT2i	VERICIGUAT	IVABRADINE	OM
NEUi						
HR (95%CI)	-	1.27 (1.10-1.46)	1.27 (1.12-1.46)	1.12 (0.99-1.26)	1.22 (1.02-1.45)	1.02 (0.93-1.13)
ARNI						
HR (95%CI)	0.79 (0.69-0.90)	-	1.00 (0.82-1.21)	0.88 (0.73-1.05)	0.96 (0.77-1.20)	0.80 (0.68-0.95)
SGLT2i						
HR (95%CI)	0.78 (0.69-0.89)	1.00 (0.82-1.20)	-	0.88 (0.73-1.05)	0.96 (0.77-1.19)	0.80 (0.68-0.94)
VERICIGUAT						
HR (95%CI)	0.89 (0.80-1.01)	1.14 (0.95-1.36)	1.14 (0.96-1.36)	-	1.09 (0.88-1.35)	0.91 (0.78-1.06)
IVABRADINE						
HR (95%CI)	0.82 (0.69-0.98)	1.04 (0.83-1.30)	1.05 (0.84-1.30)	0.92 (0.74-1.13)	-	0.84 (0.68-1.02)
OM						
HR (95%CI)	0.98 (0.89-1.08)	1.25 (1.05-1.47)	1.25 (1.06-1.47)	1.10 (0.94-1.28)	1.20 (0.98-1.46)	-

ARNI: angiotensin receptor-neprilysin inhibitor; CI, confidence interval; HR: hazard ratio; NEUi: neurohormonal inhibition; OM: omecamtiv mecarbil; SGLT2i: sodium-glucose cotransporter 2 inhibitor.

Figure legends

Figure 1. Network of the meta-analysis.

The size of the nodes of the network is proportional to the number of patients, the thickness of the connecting lines corresponds to the number of RCTs with direct comparisons, and the dashed lines indicate indirect comparisons.

ARNI: angiotensin receptor-neprilysin inhibitor; NEUi: neurohormonal inhibition; OM: omecamtiv mecarbil; SGLT2i: sodium-glucose cotransporter 2 inhibitor.

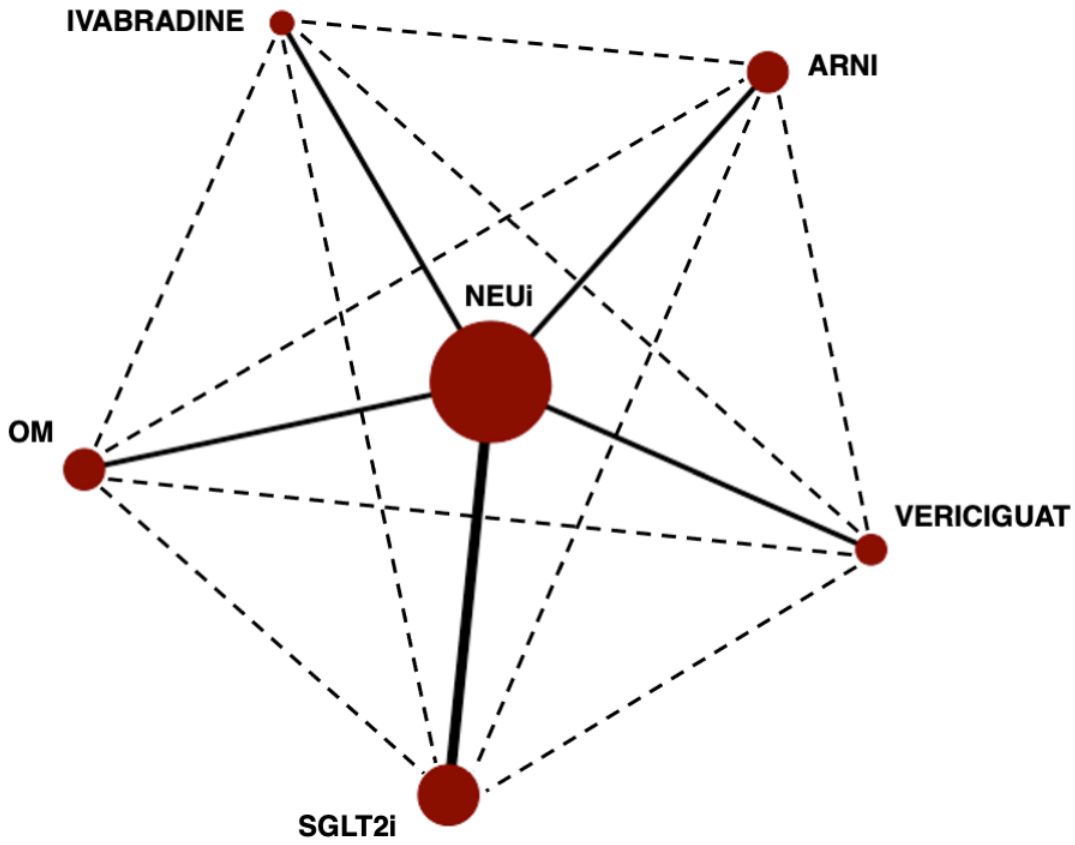

Figure 2. Risk of CV death or HHF with additional medical therapies vs. background NEUi.

ARNI: angiotensin receptor-neprilysin inhibitor; CrI, credible interval; HR: hazard ratio; NEUi: neurohormonal inhibition; OM: omecamtiv mecarbil; SGLT2i: sodium-glucose cotransporter 2 inhibitor.

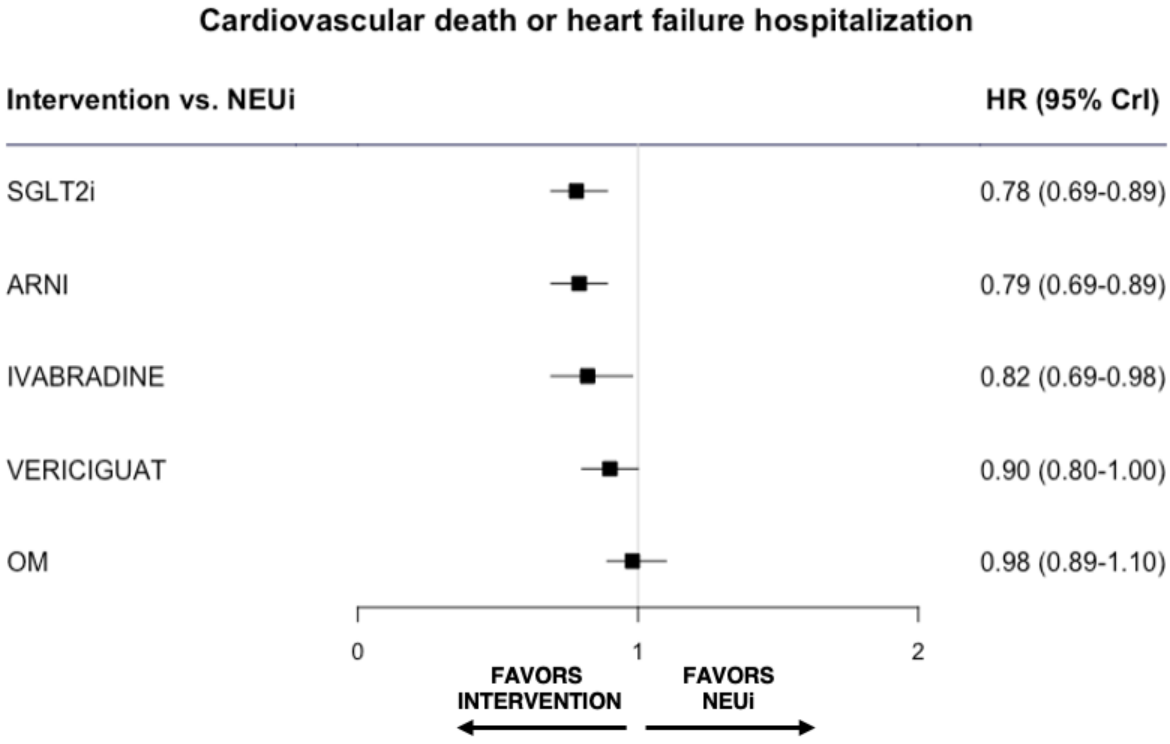

Figure 3. SUCRA scores for the composite outcome of CV death or HHF.

ARNI: angiotensin receptor-neprilysin inhibitor; NEUi: neurohormonal inhibition; OM: omecamtiv mecarbil; SGLT2i: sodium-glucose cotransporter 2 inhibitor.