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Efficacy of Modern Therapies for Heart Failure with Reduced Ejection Fraction in Specific Population Subgroups: A Systematic Review and Network Meta-Analysis

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Keywords
Heart failure with reduced ejection fraction · Treatment · Cardiovascular death · Hospitalization for heart failure · Meta-analysis

Abstract

Introduction: The efficacy and safety of emerging therapies for heart failure with reduced ejection fraction (HFrEF) have never been compared in specific subgroups of patients. ***Methods:*** PubMed, Cochrane Registry, Web of Science, Scopus, and EMBASE libraries were used to extract data. We used the following keywords: (heart failure with reduced ejection fraction OR HFrEF) AND (treatment OR therapy) OR (cardiovascular death) OR (hospitalization for heart failure). We compared randomized clinical trials for HFrEF emerging therapies focusing on the elderly (patients >65 years old and >75 years old), chronic kidney disease (CKD) (estimated glomerular filtration rate (eGFR) < 60 mL/min), patients with diabetes mellitus (DM), coronary heart disease (CAD), New York Heart Association (NYHA) class III/IV, women, patients on sacubitril/valsartan (S/V). The primary outcome was the efficacy composite endpoint of cardiovascular death (CVD) and HF hospitalization (HFH). ***Results:*** S/V significantly reduced the primary outcome in patients >65 years old (RR: 0.80; 95% CI: 0.68–0.94) and with CKD (RR: 0.79; 95% CI: 0.69–0.90); dapagliflozin in patients >65 (RR: 0.72; 95% CI: 0.60–0.86) and >75 years old (RR: 0.68; 95% CI: 0.53–0.87), in those with CKD (RR: 0.72; 95% CI: 0.59–0.88), DM (RR: 0.75; 95% CI: 0.63–0.89), and CAD (RR: 0.77; 95% CI: 0.65–0.92); empagliflozin in patients >65 years old (RR: 0.78; 95% CI: 0.66–0.93), those with DM (RR: 0.72; 95% CI: 0.60–0.86), CAD (RR: 0.82; 95% CI: 0.68–0.99), women (RR: 0.59; 95% CI: 0.44–0.79), and in patients on S/V (RR: 0.64; 95% CI: 0.45–0.91); vericiguat in patients with CKD (RR: 0.84; 95% CI: 0.73–0.97) and NYHA class III/IV (RR: 0.87; 95% CI: 0.77–0.98); omecamtiv mecarbil in patients with CAD (RR: 0.90; 95% CI: 0.82–0.99) and NYHA III/IV (RR: 0.88; 95% CI: 0.80–0.97). ***Conclusion:*** Emerging HFrEF therapies show a clinical benefit with the reduction

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of the primary composite endpoint of CVD and HFH, with each drug being more effective in specific patient population.

Introduction

Heart failure (HF) is a clinical syndrome responsible for a high hospitalization rate and mortality with a significant reduction in quality of life. It affects a sizable portion of the adult population, and its prevalence increases with age [1]. Across the spectrum of HF, patients affected by heart failure with reduced ejection fraction (HFrEF) have the worst prognosis [2]. When compared to the results of the first treatment trials, prognosis has markedly improved thanks to new effective evidence-based therapeutic options. Recent trials promoted new molecules as emerging therapies for HFrEF to reduce mortality and hospitalization rates [3–7] (shown in Fig. 1). However, there is often a gap between clinical features of patients enrolled in randomized clinical trials (RCTs) and real-world patients seen in clinical practice, especially those at higher clinical risk. This mismatch results in difficulty to validate the efficacy data from RCTs and to translate them in clinical practice [8, 9]. HF mainly affects the elderly, patients with chronic kidney disease (CKD), patients with diabetes mellitus (DM), patients with coronary artery disease (CAD); it is not clear how the new therapies for HFrEF perform in these subgroups and in other specific patient populations: patients in New York Heart Association (NYHA) class III–IV, women, patients on or off sacubitril/valsartan therapy. The aim of this analysis was the evaluation of the efficacy of different HF drugs in specific subgroups of HFrEF patients, for whom clinical management is particularly challenging.

Methods

Data Sources and Searches

This review was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) [10]. An online search of PubMed, Cochrane Registry, Web of Science, Scopus, and EMBASE libraries (from inception to December 1, 2023) was performed, in addition to manual screening. We used the following keywords: (heart failure with reduced ejection fraction OR HFrEF) AND (treatment OR therapy) OR (cardiovascular death) OR (hospitalization for heart failure). No language restriction was applied.

Study Selection, Outcomes, and Definition

Studies on HF patients with the following characteristics were considered eligible for the meta-analysis: landmark RCTs comparing standard-of-care HF therapy with sacubitril/valsartan, dapagliflozin, empagliflozin, vericiguat, or omecamtiv mecarbil (OM) where results on efficacy of different HF therapies on the overall study population and in the different study subgroups were clearly reported. Reviews, editorials, letters, meta-analyses, case reports, and abstracts were excluded. The main outcome of interest was the efficacy composite endpoint of cardiovascular death (CVD) and HF hospitalization (HFH).

Data Extraction and Quality Assessment

Two independent reviewers (M.V.M. and C.L.) screened all abstracts and titles to identify potentially eligible studies, of which full text was subsequently interrogated. Agreement of the two reviewers was required for eligibility of studies for analysis. Disagreements regarding the inclusion or the classification of a study were solved by a third reviewer (P.S.). For each study, extracted data were as follows: trial general information (first author, publication year), population enrolled, patient demographics (gender, age, mean left ventricular ejection fraction [EF], mean N-terminal pro-B-type natriuretic peptide [NT-pro-BNP]), outcomes of interest in the overall population and in the following subgroups: patients >65 years, patients >75 years, women, patients with CKD (estimated glomerular filtration rate [eGFR] cutoff: 60 mL/min), patients with DM, patients in NYHA class III–IV, patients with CAD, and patients on or off sacubitril/valsartan therapy. The quality of RCT studies was assessed independently by the two investigators using the risk bias assessment tool recommended by the Cochrane Collaboration [11] (Table 1). Each study was classified as low, high, or unclear risk of bias evaluating the following parameters: selection, performance, attrition, detection, and reporting.

Evidence Synthesis

Descriptive analysis was based on counts (percentages) for categorical variables and mean ± standard deviation for continuous variables, whereas the evidence network was visually summarized using network plots. Exploratory frequentist pairwise meta-analyses were based primarily on a random-effect method, relying on relative risks (RRs) for dichotomous endpoints. Results were reported as point summary of effect, 95% confidence intervals (CIs), and p values for effect and graphically represented as forest plots. In addition, we performed a

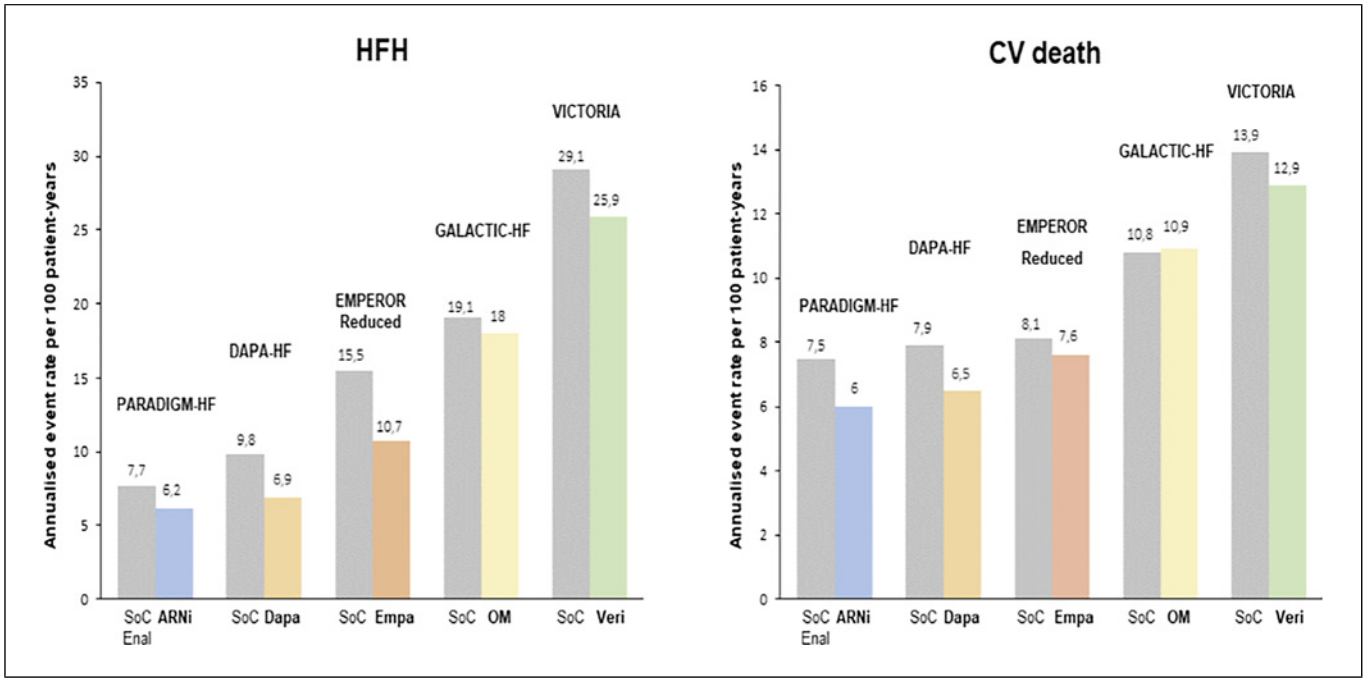

Fig. 1. Contemporary heart failure with reduced ejection fraction (HFrEF) trials [3–7]. Secondary endpoint outcomes. ARNI, angiotensin receptor/neprilysin inhibitor; CV, cardiovascular; Dapa, dapagliflozin; Empa, empagliflozin; HFH, heart failure hospitalization; OM, omecamtiv mecarbil; SoC, source of compare; Veri, vericiguat.

Table 1. Risk of bias of individual studies by revised Cochrane risk assessment tool

	Bias arising from the randomization process	Bias due to deviations from intended interventions	Bias due to missing outcome data	Bias in measurement of the outcome	Bias in selection of the reported result
PARADIGM-HF [3]	+	+	+	+	+
DAPA-HF [4]	+	+	+	+	+
EMPEROR-Reduced [5]	+	+	+	+	+
VICTORIA [6]	+	+	+	+	+
GALACTIC-HF [7]	+	+	+	+	+

Each field should be graded as low+/high−/some concerns±.

sensitivity analysis using a fixed-effect method. Statistical significance was set at the two-tailed 0.05 level for effect estimation and 0.10 level for heterogeneity testing. Computations were performed using the netmeta package in R 3.5.3 or above (R Foundation for Statistical Computing, Vienna, Austria).

Results

This literature search strategy retrieved a total of 4,382 records (shown in online suppl. Fig. S.1; for all online suppl. material, see https://doi.org/10.1159/000541393). After duplicate removal (n = 2,031), 1,992 articles were

Table 2. Baseline characteristics of the included RCTs

Study	Year	Treatment	Follow-up, months	NNT	AAR	Patients, *n*	Age, years	Men, %	EF, %	Median NT-pro-BNP, pg/mL	DM, %	ACEI/ ARB, %	ARNI, %	BB, %	MRA, %
PARADIGM-HF [3]	2014	S/V versus enalapril	27	37	2.7	8,442	64	78	30	1,615	35	50	50	93	56
VICTORIA [6]	2020	Vericiguat versus placebo	10.8	24	4.2	5,050	67	76	29	2,812	47	73	15	93	70
GALACTIC-HF [7]	2021	OM versus placebo	21.8	48	2.1	8,232	65	79	27	2,134	40	87	19	94	78
DAPA-HF [4]	2019	Dapa versus placebo	18.2	25	4.0	4,744	66	76	31	1,437	42	84	11	96	71
EMPEROR-Reduced [5]	2020	Empa versus placebo	16	19	5.2	3,730	67	76	27	1,907	50	70	19	95	71

This graph shows available comparisons between study treatments (with respect to the primary endpoint). ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; ARNI, angiotensin receptor-neprilysin inhibitor; ARR, absolute risk reduction; BB, beta-blocker; Dapa, dapagliflozin; Empa, empagliflozin; DM, diabetes mellitus; EF, ejection fraction; HF, heart failure; MRA, mineralocorticoid receptor antagonist; NNT, number needed to treat; NT-pro-BNP, N-terminal pro-B-type natriuretic peptide; OM, omecamtiv mecarbil; S/V, sacubitril/valsartan.

excluded based on title/abstract screening and 39 studies were fully reviewed; a total of 5 studies were included in the network meta-analysis: Prospective comparison of angiotensin receptor/neprilysin inhibitor (ARNI) with angiotensin-converting enzyme inhibitors (ACEI) to Determine Impact on Global Mortality and morbidity in Heart Failure (PARADIGM-HF) [3], Dapagliflozin and Prevention of Adverse-Outcomes in Heart Failure (DAPA-HF) [4], EMPagliflozin outcomE tRial in Patients With chrOnic heaRt Failure With Reduced Ejection Fraction (EMPEROR-Reduced) [5], Vericiguat Global Study in Subjects with Heart Failure with Reduced Ejection Fraction (VICTORIA) trial [6], and Global Approach to Lowering Adverse Cardiac Outcomes through Improving Contractility in Heart Failure (GALACTIC-HF) [7] (shown in online suppl. Fig. S.1). We compared results of these RCTs for modern HFrEF therapies in the following specific subgroups of patients: the elderly (patients >65 years old and >75 years old), patients with CKD (eGFR <60 mL/min), patients with DM, CAD-related HF, patients in NYHA class III/IV, women, patients on ARNI. The main outcome of interest was the efficacy composite endpoint of CVD and HFH. No statistical inconsistency and/or heterogeneity were found. When using the fixed-effects model for the analysis, no differences were found as compared to the main analysis using the random-effects model (online suppl. material: Tables S.1–S.18, shown in Fig. S.2–S.10). Baseline characteristics such as average age, gender, mean left ventricular EF, median NT-pro-BNP values, and medications taken at randomization are summarized in Table 2.

The Elderly

Results regarding elderly patients are shown in Figure 2. In the PARADIGM-HF trial, the average age of the 8,442 enrolled patients was 63.8 and 48.8% of them was ≥65 years old. In this subgroup, sacubitril/valsartan resulted in significant reduction in the primary endpoint (RR: 0.80; 95% CI: 0.68–0.94); statistical significance was not achieved in the 1,563 patients who were ≥75 years old (RR: 0.86; 95% CI: 0.72–1.03). In DAPA-HF trial, patients with a mean age of 66.2 ± 11.0 years were analyzed; dapagliflozin showed to significantly reduce the composite endpoint of HFH and CVD in both the ≥65-year-old (RR: 0.72; 95% CI: 0.60–0.86) and ≥75-year-old (RR: 0.68; 95% CI: 0.53–0.87) groups. In the EMPEROR-Reduced trial, 2,315 patients were ≥65 years old (62%); empagliflozin resulted in a significant reduction of the

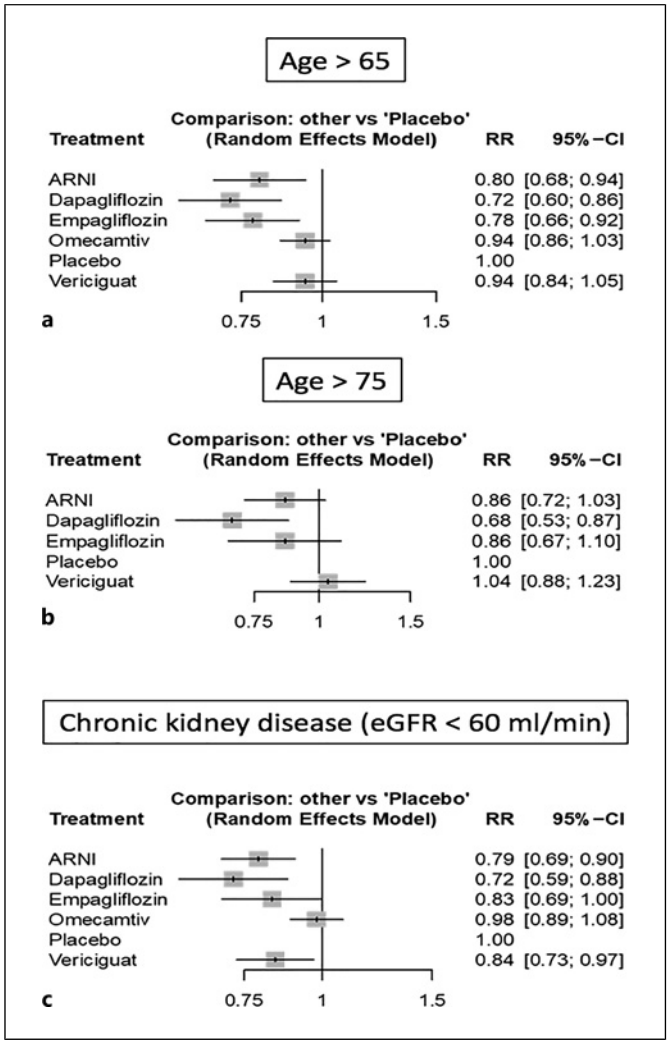

Fig. 2. Forest plot for reduction in composite outcome of cardiovascular death (CVD) and heart failure hospitalization (HFH) in elderly: age > 65 (**a**), age > 75 (**b**), patients with chronic kidney disease (CKD) and estimated glomerular filtration rate (eGFR) < 60 ml/min (**c**). ARNI, angiotensin receptor/neprilysin inhibitor; CI, confidence interval; RR, relative risk.

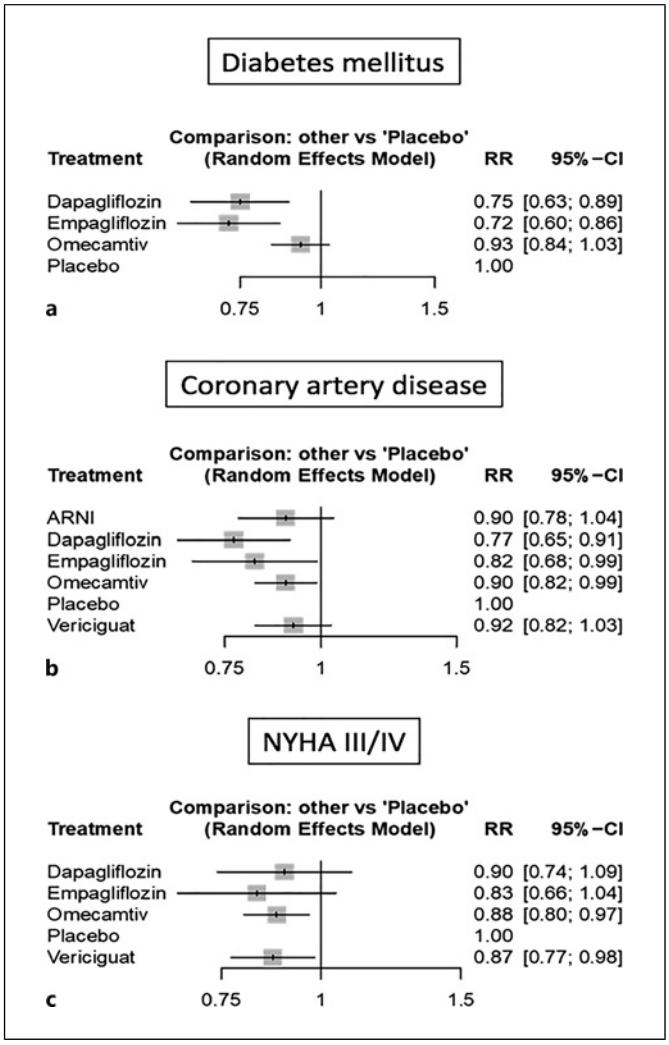

Fig. 3. Forest plot for reduction in composite outcome of cardiovascular death (CVD) and heart failure hospitalization (HFH) in patients with diabetes mellitus (DM) (**a**), patients with coronary artery disease (CAD) (**b**), patients with New York Heart Association (NYHA) III/IV (**c**). ARNI, angiotensin receptor/neprilysin inhibitor; CI, confidence interval; RR, relative risk.

primary endpoint in this population (RR: 0.78; 95% CI: 0.66–0.93) but not in the ≥75-year-old group (RR: 0.86; 95% CI: 0.67–1.10). Regarding the GALACTIC-HF trial, the mean age of the patients was 64.5 ± 11.3 years, but RR results for patients over 75 are not available. In the ≥65-year-old subgroup, OM was equivalent in terms of efficacy compared to the placebo group (RR: 0.94; 95% CI: 0.86–1.03). In the VICTORIA trial, older patients (mean age 67.5 years) were enrolled; 1,395 patients (27.6%) were ≥75 years old. In the 10.8-month follow-up, no significant reduction in the primary endpoint was found in the ≥65-year-old (RR: 0.94; 95% CI: 0.84–1.04) and ≥75-year-old (RR: 1.04; 95% CI: 0.88–1.23) groups, as compared to the placebo group.

Chronic Kidney Disease

In our analysis, three molecules were shown to significantly reduce the primary endpoint among patients with eGFR <60 mL/min compared to placebo: sacubitril/valsartan (RR: 0.79; 95% CI: 0.69–0.90), dapagliflozin (RR: 0.72; 95% CI: 0.59–0.88), and vericiguat (RR: 0.84; 95% CI: 0.73–0.97). In the case of empagliflozin (RR: 0.83; 95% CI: 0.69–1.00) and OM

(RR: 0.98; 95% CI: 0.89–1.08), significant results were not achieved in terms of reduction of the primary endpoint (shown in Fig. 2c).

Diabetes Mellitus

Regarding the subgroup of patients with DM, only three molecules (dapagliflozin, empagliflozin, and OM) were analyzed because their data were the only ones reported in literature (shown in Fig. 3a). Specifically, sodium-glucose co-transporter-2 inhibitors (SGLT2is) dapaglifozin (RR: 0.75; 95% CI: 0.63–0.89) and empaglifozin (RR: 0.72; 95% CI: 0.60–0.86) all resulted in a statistically significant reduction of the primary endpoint, while OM reduced events in a nonsignificant manner (RR: 0.93; 95% CI: 0.84–1.03).

Coronary Artery Disease

Results of patients with CAD are shown in Figure 3b. In the PARADIGM-HF trial, 5,036 patients (60.0%) had HF with an ischemic etiology; they were older and mainly Caucasian men. However, it was impossible to retrieve data from the PARADIGM-HF trial to analyze patients with CAD as they were not reported in the paper. In the DAPA-HF, EMPEROR-Reduced, and GALACTIC-HF trials, patients with ischemic cardiomyopathy exceeded half of the enrolled population (56%, 52%, and 53%, respectively). Composite primary endpoint reduction was achieved by dapagliflozin (RR: 0.77; 95% CI: 0.65–0.92), empagliflozin (RR: 0.82; 95% CI: 0.68–0.99), and OM (RR: 0.90; 95% CI: 0.82–0.99) in these subgroups. In the VICTORIA trial, 2,704 patients (53%) had CAD history; they were mostly older, men, with DM, and with lower eGFR than no-CAD patients. In this subgroup, vericiguat was associated with a nonsignificant reduction in the primary endpoint (RR: 0.92; 95% CI: 0.82–1.03).

NYHA Class III/IV

Patients with NYHA class III/IV represented 41.4% of the population in the VICTORIA trial, 46.7% in the GALACTIC-HF trial, 38.5% in the EMPEROR-Reduced trial, 29.5% in the DAPA-HF trial, and 23.9% in the PARADIGM-HF trial. In our analysis (shown in Fig. 3c), vericiguat (RR: 0.87; 95% CI: 0.77–0.98) and OM (RR: 0.88; 95% CI: 0.80–0.97) resulted in significant reduction in the composite endpoint. Dapagliflozin (RR: 0.90; 95% CI: 0.74–1.09) and empagliflozin (RR: 0.83; 95% CI: 0.66–1.04) caused nonsignificant reduction in the primary endpoint. No data on ARNIs were found in literature for the purpose of our analysis.

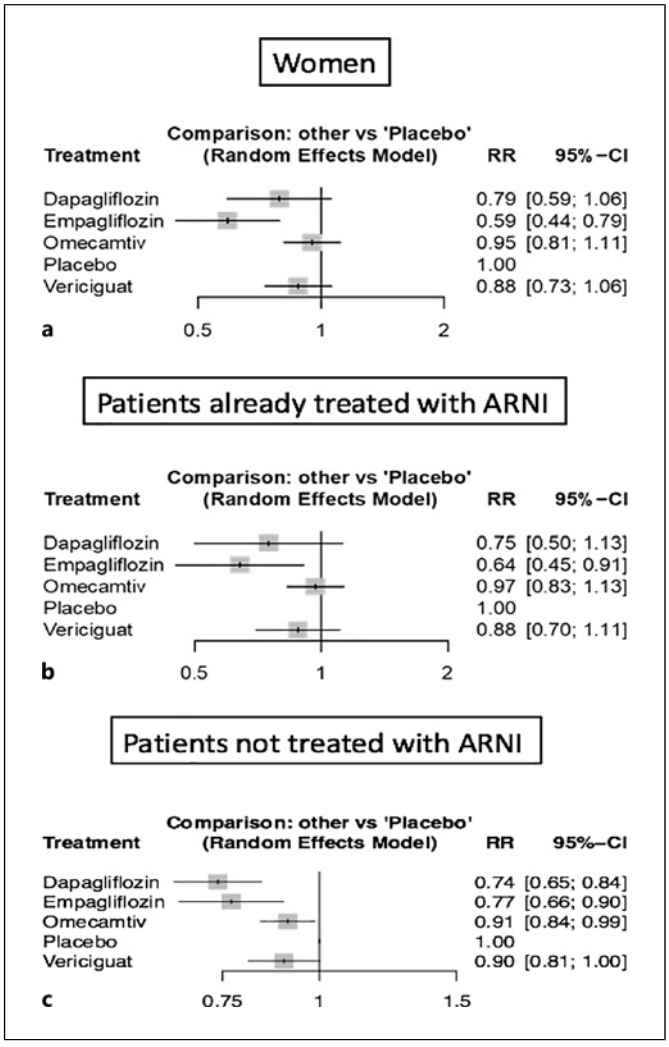

Fig. 4. Forest plot for reduction in composite outcome of cardiovascular death (CVD) and heart failure hospitalization (HFH) in women (**a**), patients already treated with angiotensin receptor/neprilysin inhibitor (ARNI) (**b**), patients not treated with ARNI (**c**). CI, confidence interval; RR, relative risk.

Women

In the PARADIGM-HF trial, we observed a similar clinical benefit of sacubitril/valsartan on the composite primary endpoint for both sexes, although women only represented 21% of the entire population and data regarding this subgroup were not available. Women represented 23.8%, 23.5%, 21.2%, and 24%, in the experimental arms of DAPA-HF, EMPEROR-Reduced, GALACTIC-HF, and VICTORIA trials, respectively. In our analysis, empagliflozin resulted in a statistically significant reduction of the primary endpoint (RR: 0.59; 95% CI: 0.44–0.79), while dapagliflozin (RR: 0.79; 95%

CI: 0.59–1.06), OM (RR: 0.95; 95% CI: 0.81–1.11), and vericiguat (RR: 0.88; 95% CI: 0.73–1.06) only reduced events nonsignificantly (shown in Fig. 4a).

Patients on/off ARNI Therapy

In our analysis, patients receiving ARNIs were 10.7%, 19.7%, 19.9%, and 14.5% in the DAPA-HF, EMPEROR-Reduced, GALACTIC-HF, and VICTORIA trials, respectively. In the ARNI subgroup, empagliflozin was the only molecule that significantly reduced the primary endpoint (RR: 0.64; 95% CI: 0.45–0.91) (shown in Fig. 4); in patients not treated with ARNI, dapagliflozin (RR: 0.74, 95% CI: 0.65–0.84), empagliflozin (RR: 0.77, 95% CI: 0.66–0.90), and OM (RR: 0.91, 95% CI: 0.84–0.99) all showed a significant reduction in event risk; in this context, vericiguat did not reach statistical significance (RR: 0.90, 95% CI: 0.81–1.00).

Discussion

Several meta-analyses have been performed in the last few years to compare efficacy and safety of emerging therapies for HFrEF [12, 13]. To our knowledge, the present network meta-analysis is the first one analyzing and comparing results of the main RCTs, namely, PARADIGM-HF [3], DAPA-HF [4], EMPEROR-Reduced [5], VICTORIA [6], and GALACTIC-HF [7] for HFrEF modern therapies, in specific subgroups of patients. We focused on the following subgroups: the elderly, patients with CKD, DM, CAD, NYHA class III/IV, women, patients on treatment with ARNI. The main results of our analysis are as follows:

- Dapagliflozin, empagliflozin, and sacubitril/valsartan reduced the main outcome of CVD and HFH as compared to OM and vericiguat in patients >65 years old, with best results obtained by dapagliflozin therapy; in addition, dapagliflozin showed a consistent reduction in the main outcome as compared to the other therapies in patients >75 years old.
- Dapagliflozin, sacubitril/valsartan, and vericiguat resulted in a statistically significant reduction in the primary endpoint in patients with CKD and eGFR<60 mL/min, while dapagliflozin showed the greatest reduction in the primary endpoint.
- Both SGLT2is (empagliflozin and dapagliflozin) resulted in a significant reduction in the main outcome in patients with DM: in this context, empagliflozin showed a lower RR (RR: 0.72; 95% CI: 0.60–0.86).
- Both SGLT2is (empagliflozin and dapagliflozin) and OM reduced the main outcome in patients with ischemic HFrEF; dapagliflozin showed the greatest reduction in the primary endpoint.
- Vericiguat and OM resulted in a statistically significant reduction in the primary endpoint in patients in NYHA class III/IV, with greatest results obtained by vericiguat therapy.
- Empagliflozin showed a consistent reduction in the main outcome as compared to the other therapies in women and in patients already treated with ARNI.
- As for patients off ARNI therapy, dapagliflozin, empagliflozin, and OM reduced the main outcome of CVD and HFH; dapagliflozin showed the greatest results; vericiguat showed a downward trend without reaching statistical significance.

HF is a syndrome with complex pathophysiology and with several comorbidities, which may influence the disease course and drug efficacy [9, 14]. The incidence of HF increases with age; despite the progress made in terms of pharmacological treatment, rehospitalization and mortality rates remain high in the elderly. Our analysis showed that patients enrolled in RCTs are younger than real-life patients [15]; those are indeed treated with caution due to concerns regarding drug tolerability, polypharmacy, and side effects. Our analysis demonstrated that dapagliflozin, empagliflozin, and sacubitril/valsartan reduced the main outcome of CVD and HFH in patients >65 years old as compared to OM and vericiguat; in this context, dapagliflozin showed the highest efficacy, both in patients >65 and >75 years old. Our results are in line with those of Martinez et al. [16], who analyzed the efficacy and safety of dapagliflozin in HFrEF according to age. Furthermore, Cahn et al. [17] analyzed data from the Dapagliflozin Effect on Cardiovascular Events (DECLARE)-TIMI 58 study: in elderly patients with type-2-DM and atherosclerotic CV disease or CV risk factors, dapagliflozin showed favorable CV and renal effects, with a good efficacy and safety profile regardless of age.

HF and CKD are closely interconnected [18]. Long-standing HF may promote or worsen CKD when already present; studies on outpatients with chronic HF have shown that 30–50% of them has CKD [19]. In our analysis, dapagliflozin showed the greatest reduction in the primary outcome of CVD and HFH, followed by sacubitril/valsartan and vericiguat, in patients with HFrEF and CKD (eGFR <60 mL/min) as compared to the other therapies. According to literature, both SGLT2is and ARNI give excellent results in patients with CKD [20–24], although in our analysis empagliflozin did not reach statistical significance (RR: 0.83; 95% CI:

0.69–1.00). The relationship between HF and CKD is of particular interest because all drugs used in patients with HF may potentially have detrimental effects on renal function and CKD may represent a frequent contraindication for HF disease-modifying drug assumption. Dapagliflozin and sacubitril/valsartan can be prescribed for patients with an eGFR ≥30 mL/min/1.73 m^2, empagliflozin in patients with an eGFR ≥20 mL/min/1.73 m^2. A worsening of renal function, which is frequently seen in HF patients, can easily lead to discontinuation of these therapies, which is very common in clinical practice. In this context, vericiguat is an emerging therapy that can be safely used in patients with severe kidney disease (eGFR ≥15 mL/min). This drug acts through a novel mechanism of action: it antagonizes cyclic guanosine monophosphate deficiency by the direct stimulation of soluble guanylate cyclase, vasodilating glomerular arterioles, and reducing renal endothelial dysfunction [25, 26]. In addition, vericiguat does not affect serum potassium levels, so it can be prescribed in patients with hyperkalemia who cannot take renin-angiotensin-aldosterone system inhibitors. In accordance with our findings, Voos et al. [27] recently reported that vericiguat was safe and effective in patients with HFrEF across a wide range of eGFR (15–60 mL/min). Regarding OM and CKD, this drug did not show a significant reduction in the primary outcome; however, Trivedi et al. [28] demonstrated that OM pharmacokinetics are not influenced by renal function and its administration is safe even in patients with CKD.

DM is often present in patients with established HF. According to a European registry, about 36% of outpatients affected by chronic HF have DM, while about 50% of patients hospitalized for acute HF have DM [29]. We analyzed the role of dapagliflozin, empagliflozin, and OM in terms of primary endpoint occurrence in patients with established HF and DM; indeed, data on sacubitril/valsartan and vericiguat in the subgroup of patients with DM are not reported in literature. In this population, as expected, both dapagliflozin and empagliflozin resulted in a statistically significant reduction in the primary endpoint, while OM did not significantly impact the primary endpoint. The higher efficacy of SGLT2is is explained by their anti-diabetic role; in addition, the osmotic diuresis, the anti-remodeling, and nephroprotective functions may represent the pathophysiological basis of these compelling results [23]. In a meta-analysis, Zannad et al. [24] demonstrated the efficacy of both dapagliflozin and empagliflozin in reducing CVD and HFH regardless of DM presence; they did not find significant heterogeneity between the DAPA-HF and EMPEROR-Reduced trials. Also, our results confirmed that SGLT2is have an optimal effect in patients with and without DM.

The etiology of HF has a geographical distribution: CAD is the most common cause of HFrEF and heart failure with mid-range EF in developed countries [2]. Our analysis demonstrates that a reduction in the composite primary endpoint of CVD and HFH in patients with ischemic HFrEF was predominantly achieved by dapagliflozin, followed by empagliflozin and OM. Regarding vericiguat, a nonsignificant reduction in the primary endpoint was observed. In the present meta-analysis, we did not use data from PARADIGM-HF trial to study patients with CAD as they were not reported in the paper.

Patients with advanced HF often show persistent and progressive signs and symptoms of severe HF, which correlate with NYHA classes III and IV, optimal medical therapy, surgical therapies, or use of devices [2]. Patients with advanced HF are very frequently underrepresented in RCTs. In our analysis, vericiguat showed the greatest reduction of the primary outcome of CVD and HFH in patients with HFrEF and NYHA class III/IV, followed by OM. Indeed, VICTORIA and GALACTIC-HF trials had the greater representation of NYHA class III/IV population, compared to the other RCTs. In particular, the VICTORIA trial is the only large RCT who enrolled a consistent number of patients with worsening HF with positive results [2, 25].

The idea that women are protected from CV disease is misleading, considering that HF represents one of the most important causes of mortality and hospitalization for them [30]. Women represent about 40% of patients affected by HFrEF with a more heterogeneous etiopathogenesis, since they are less prone to develop ischemic HF, but more exposed to pathologies such as peripartum cardiomyopathy or chemo- and radiotherapy-induced dilated cardiomyopathy [30, 31]. Also, response to therapy may be more heterogeneous. Our results suggest that empagliflozin caused a statistically significant reduction in the primary endpoint in women as compared to the other therapies.

Since the publication of PARADIGM-HF, sacubitril/valsartan was added to the HFrEF disease-modifying drugs and became the primary choice for renin-angiotensin-aldosterone system inhibition in HF. It is part of the "four pillars" of HFrEF therapy, alongside beta-blockers, mineralocorticoid receptor antagonists, and SGLT2is [2]. Nevertheless, it has been noted that the number of patients treated with sacubitril/valsartan is still limited in real-world clinical practice [32]. Also, in the main RCTs patients treated with ARNIs are

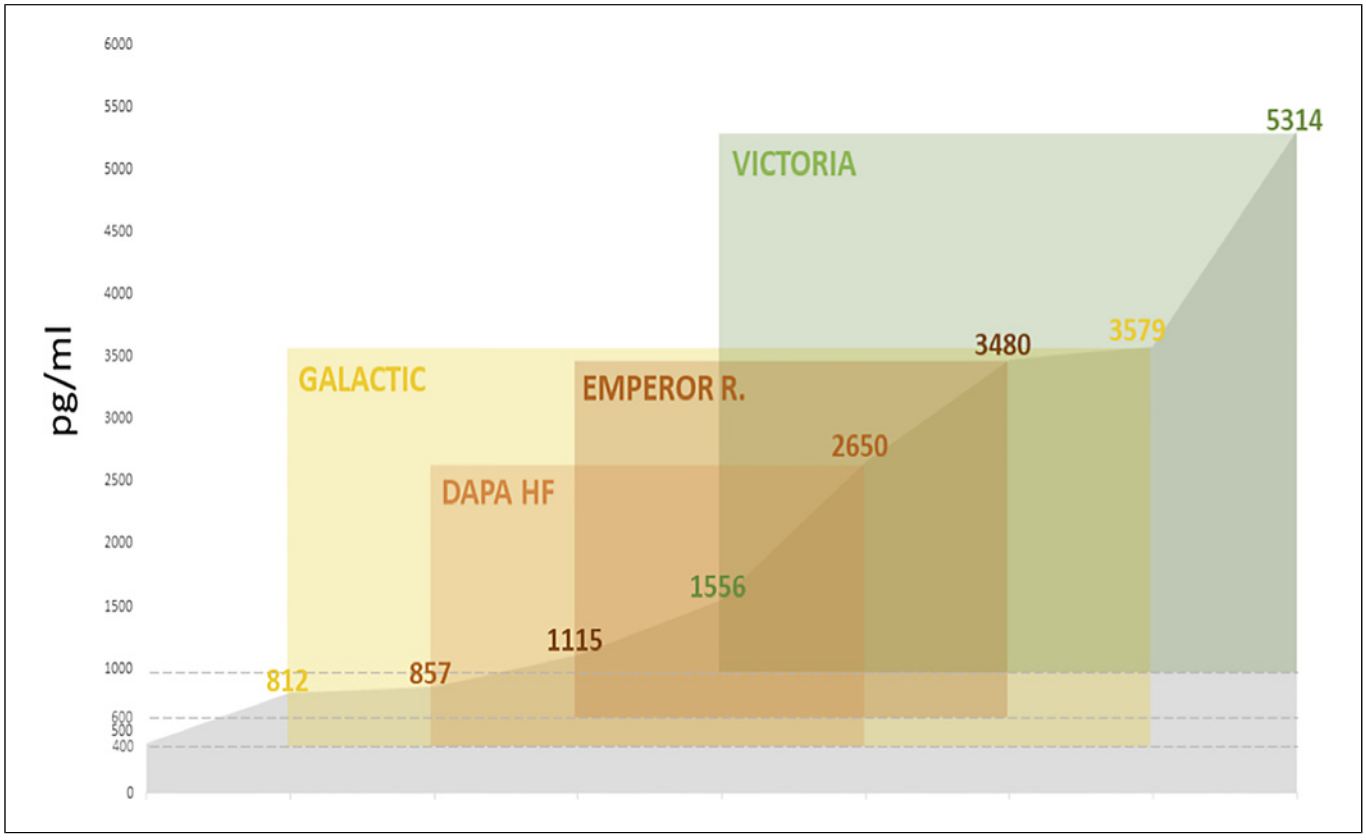

Fig. 5. Q1/Q3 N-terminal pro-B-type natriuretic peptide (NT-pro-BNP) cutoff from different trials [3–7]. Modern therapies for HFrEF.

underrepresented. We analyzed the effects of dapagliflozin, empagliflozin, vericiguat, and OM in patients already treated with sacubitril/valsartan. In this subgroup of patients, empagliflozin was the only drug that significantly reduced the risk of events associated with the primary endpoint. Dapagliflozin, OM, and vericiguat did not reach statistical significance, but they determined a reduction in adverse events risk, suggesting that the use of these molecules in association with sacubitril/valsartan should be implemented in clinical practice [25].

Clinical Heterogeneity

RCTs for emerging HFrEF therapies enrolled populations with different risk profiles. In this specific analysis, we included studies with differences in temporal closeness of the acute event [3–7] and the median value of NT pro-BNP plasma values at the time of randomization. Figure 5 shows a very small Q1/Q3 overlap area between data of the analyzed trials, highlighting the different risk profile of the study population. As mentioned above, the VICTORIA trial enrolled patients with higher baseline values of NT-pro-BNP and a narrow interquartile range, i.e., patients with worsening HF who themselves have a poor prognosis. Data on quartiles of NT-pro-BNP levels in the PARADIGM-HF are missing.

In our analysis, all five drugs showed a clinical benefit as regards reduction in the primary composite endpoint of CV death and hospitalization due to HF. When considering absolute risk reduction, events related to the primary endpoint were reduced in a range between 2.1% and 5.2% in the overall population, resulting in very low NNTs (Table 2). For this reason, despite the mentioned differences in risk profile, data on drug efficacy are consistent and should be contextualized in the subpopulation included in the RCTs.

Study Limitations

We could not analyze several data in some specific subgroups as they were not reported in literature; we did not use data on sacubitril/valsartan to study patients with CAD as they were not reported in the PARADIGM-HF trial. In the population with CKD, it should be considered that different equations were used among trials for the evaluation of GFR: modification of diet in renal disease

equation in VICTORIA, PARADIGM-HF, and GALACTIC-HF trials; CKD Epidemiology Collaboration (CKD-EPI) equation in DAPA-HF and EMPEROR-Reduced. In conclusion, although further specific studies are required to confirm our results, our analysis underlines the efficacy of new HFrEF therapies also in specific subgroups of patients, demonstrating the need for their full implementation in clinical practice.

Statement of Ethics

A statement of ethics is not applicable because this study is based exclusively on published literature.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

C.L. and P.S.: conceptualization, methodology, and revising the manuscript; M.V.M.: conceptualization, methodology, data curation, data analysis, and drafting of the manuscript; M.P.: conceptualization, methodology, and drafting of the manuscript; S. T., A.D.A., and G.S.: drafting of the manuscript; N.P., L.D.L., C.C., F.S., R.B., F.M., and C.D.V.: revising the manuscript; and C.R.: supervisor.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its online supplementary material files. Further inquiries can be directed to the corresponding author.

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