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CLINICAL ARTICLE



A meta-analysis investigating the efficacy and adverse events linked to sacubitril-valsartan in various heart failure subtypes

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Abstract

Background: Sacubitril-valsartan, an inhibitor of the angiotensin receptor neprilysin (ARNi), has been purported to exhibit superiority over angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) in individuals diagnosed with heart failure.

Hypothesis: This paper gives an updated meta-analysis comparing the efficacy and safety of sacubitril-valsartan to that of standard treatment for different types of heart failure.

Results: The meta-analysis comprised a total of nine randomized controlled trials (RCTs), incorporating data from a substantial sample size of 15 939 patients. The study observed a decrease in overall mortality and mortality related to cardiovascular causes among patients in the heart failure with reduced ejection fraction (HFrEF) category who were treated with sacubitril-valsartan. However, no statistically significant variation in this outcome was seen among patients with heart failure with preserved ejection fraction and HFmrEF. Patients who were administered sacubitril-valsartan had a notably elevated likelihood of experiencing hypotension. Nevertheless, no significant disparities were observed in terms of other adverse events among the various treatment groups.

Conclusion: Current meta-analysis provide support for use of sacubitril-valsartan in decreasing mortality in patients with HFrEF. However, more numbers of studies are required to draw a definite conclusion on other benefits associated with sacubitril-valsartan use over standard treatment of ACE inhibitors and ARBs.

KEYWORDS

ACE Inhibitors, heart failure, HFpEF, HFrEF, sacubitril-valsartan

1 | INTRODUCTION

The American Heart Association and the American College of Cardiology describe heart failure (HF) as "a complicated clinical illness that can emerge from any anatomical or functional cardiac problem that limits the ventricle's capacity to fill with or evacuate blood.^{*n*1,2} Dyspnea, tiredness, and indicators of volume overload, such as peripheral edema, are all symptoms. Heart failure (HF) can be attributed to a multitude of reasons, encompassing systemic illnesses, diverse cardiac abnormalities, and certain hereditary conditions.³

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Globally, an estimated 64.3 million people have HF, with numbers expected to climb as the population ages and new therapies for hypertension, diabetes, and other conditions become accessible.^{2,4,5} It is projected that HF will have an impact on a population of around 8 million individuals in the United States by the year 2030, which would represent approximately 3% of the total population.⁴ The incidence of HF is significantly higher in the elderly population, as evidenced by the fact that individuals aged 65 and above make up 80% of hospitalizations related to HF and 90% of deaths associated with HF.^{6,7}

The rising frequency of HF places a considerable financial strain on healthcare systems, as it is linked to both direct and indirect medical expenditures. Based on a study conducted in 2012, it was determined that the annual economic cost of HF amounted to \$108 billion.⁸ According to a comprehensive study conducted in 2020, the yearly median overall medical expenses for HF patients were \$24 383 per patient, including HF-specific hospitalization costs (\$15 879 per patient). Furthermore, individuals with HF with reduced ejection fraction (HFrEF) had greater expenditures than those with heart failure with preserved ejection fraction (HFpEF).⁹

HF is categorized into different subtypes according to the left ventricular ejection fraction (LVEF). These subtypes include heart failure with reduced ejection fraction (HFrEF) where the LVEF LVEF \leq 40%, HFpEF where the LVEF LVEF \geq 50%, and heart failure with mildly reduced ejection fraction (HFmEF) where the LVEF ranges from 41% to 49%.^{3,10} In addition, the New York Heart Association (NYHA) classification system categorizes individuals into four groups according to their level of physical activity limitations in relation to heart failure: Classes I, II, III, and IV. These classes are characterized by increasing severity of symptoms and greater physical restrictions, with Class I representing the mildest and Class IV the most severe.^{11,12}

The renin-angiotensin-aldosterone system (RAAS) plays a significant role in the pathophysiology of HF. Angiotensin II is the primary outcome of this cascade, and it exerts several systemic effects that first serve as compensatory mechanisms but subsequently exacerbate the heart failure situation.^{13,14} The strategic focus on components of the renin-angiotensin-aldosterone system (RAAS) has yielded significant decreases in both morbidity and mortality. Angiotensin converting enzyme (ACE) inhibitors are pharmacological agents that inhibit the enzymatic conversion of angiotensin I to angiotensin II. On the other hand, angiotensin receptor blockers (ARBs) are drugs that specifically block the angiotensin II receptors, known as AT1 receptors, which are present in the heart, blood vessels, and kidneys. This blockade leads to the dilation of blood vessels and an enhancement in blood flow.^{15,16} The activation of the natriuretic peptide system (NPS), which operates in opposition to the renin-angiotensin-aldosterone system (RAAS) and has favorable effects on the pathophysiology of HF, also occurs during episodes of HF, resulting in elevated levels of brain natriuretic peptide (BNP) and NT-proBNP. The NPS pathway elicits vasodilation, natriuresis, decreased blood pressure, and reduced sympathetic tone, concurrently leading to a decrease in aldosterone levels. The degradation of

natriuretic peptides by neprilysin renders a pharmacological inhibitor of this enzyme beneficial.^{17,18}

Sacubitril-valsartan represents a novel class of medication known as angiotensin receptor neprilysin inhibitors (ARNIs), which can serve as a viable alternative to angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs). In the PARADIGM-HF research,¹⁹ it was shown that individuals diagnosed with LVEF < 40% (HFrEF) and New York Heart Association (NYHA) class II-IV who received sacubitril-valsartan exhibited significant decreases in all-cause mortality, cardiovascular mortality, and initial hospitalization due to heart failure as compared to those treated with enalapril. This led to the initiation of several more trials that aimed to compare the efficacy and safety of sacubitril-valsartan with that of ACE inhibitors and ARBs. Recent clinical trials have also shown that sacubitril/valsartan improves left ventricular systolic and diastolic function in patients with HFrEF and end-stage kidney disease indicating its efficacy in patients with advanced stage kidney disease that have the highest likelihood for heart failure.²⁰ Furthermore. analysis of PARAGON-HF and PARAGLIDE-HF trials that included patients hospitalized for HF showed a significant reduction in occurrence of cardiovascular and renal events when EF > 40%.²¹

This study presents a thorough and up-to-date meta-analysis of clinical studies aimed at evaluating the safety and effectiveness of sacubitril-valsartan in comparison to RAAS inhibitors (ACE inhibitors or ARBs) as standalone treatments for patients diagnosed with heart failure.

2 | METHODS

2.1 | Search strategy

In November 2021, a comprehensive literature search was performed on MEDLINE (PubMed), Scopus, Embase, Web of Science, and the Cochrane Register of Controlled Trials (CENTRAL). The researcher employed a variety of search phrases, including sacubitril-valsartan, LCZ696, ARNI, valsartan, angiotensin converting enzyme (ACE) inhibitors, HF, and angiotensin receptor blockers (ARBs), in different combinations. Furthermore, a thorough compilation of search phrases, which encompassed Medical Subject Headings (MeSH) terms, was employed. The titles and abstracts of research deemed possibly relevant were thoroughly reviewed, and afterwards, the complete text versions of the relevant papers were carefully examined. Additional papers were identified through the process of cross-referencing the reference lists of the pertinent research.

The author conducted a thorough examination of pertinent sources to identify studies that were directly relevant to the topic at hand. The primary focus of data collection for this study involved obtaining whole papers from various sources, while abstracts were utilized to gather adequate information for the subsequent metaanalysis. In accordance with the established inclusion criteria, obsolete references were omitted while valuable studies were incorporated. The researcher independently collected event data that included relevant variables.

2.2 | Study selection or inclusion/exclusion criteria

Randomized controlled studies (RCT) that compared sacubitrilvalsartan were included in patients with HF with reduced ejection fraction (HFrEF, LVEF \leq 40%), those with preserved ejection fraction (HFpEF,—LVEF \geq 50%), and those with mildly preserved ejection fraction (HFmrEF, LVEF 41%–49%). The comparator treatment in the studies was ACE inhibitors or ARBs. All studies reporting mortality (all-cause or cardiovascular), HF hospitalization events, and adverse events (hypotension, hyperkalaemia, worsening renal function, and angioedema) were included. Exclusion criteria were nonrandomized studies, studies with placebo comparators, with participants without heart failure, and those published in languages other than English.

2.3 | Data extraction and quality assessment

After identifying the articles that fulfilled the inclusion criteria, the data was extracted using a predetermined data extraction form. The form encompassed the following elements: the author of the study, the name of the trial, the type of heart failure experienced by the participants, their New York Heart Association (NYHA) class, the drug used for comparison, mortality rates (including all-cause mortality and cardiovascular mortality), hospitalizations due to heart failure, and any adverse events reported (such as hypotension, hyperkalemia, worsening renal function, and angioedema). The selected trials included a definition of hypotension, which encompassed either clinical hypotension or a systolic blood pressure (SBP) measurement below 90 mm Hg.

The methodological rigor of the papers included in the analysis was evaluated by employing the Cochrane Collaboration's risk of bias assessment.²² This instrument incorporates several criteria, namely randomization, allocation concealment, blinding, and completeness of follow-up. The risk of bias for each item was assessed and categorized as high, low, or uncertain.

2.4 | Quantitative data synthesis

The meta-analysis was conducted using Review Manager (RevMan, Version 5. Copenhagen: The Nordic Cochrane Center, The Cochrane Collaboration. 2020). The risk ratio and its corresponding 95% confidence interval were computed based on the absolute participant counts in both the intervention and control groups.

The researchers performed meta-analyses utilizing a randomeffects model, specifically the Mantel-Haenszel method. To evaluate the variability among the studies included in the analysis, the l^2 statistic was employed. The l^2 values were categorized as follows: values below 25% indicated low heterogeneity, values between 25% and 50% indicated moderate heterogeneity, and values exceeding 50% indicated high heterogeneity.²³ Forest plots were generated, and a statistically significant result was seen with a p < .05. Furthermore, subgroup analyses were performed to examine the association between the type of heart failure (HFrEF, HFpEF, and HFmrEF) and the specific side effects. A funnel plot was employed to investigate the presence of publication bias, wherein the log risk ratio for each study was plotted against its corresponding standard error.

3 | RESULTS

3.1 | Identification of studies

Searching the database generated 1740 results, of which 1592 were vetted based on title and abstract. Irrelevant records (n = 1393) were eliminated, and 199 RCTs were evaluated for eligibility. However, 190 RCTs were removed for a variety of reasons, including inadequate comparator, trial design, result, and reviews. Figure S1 depicts the selection procedure.

3.2 | Study characteristics

In total, 9 RCTs totaling 15 939 participants met the inclusion criteria (sacubitril-valsartan intervention group: 7963 participants and Control group (ACE inhibitors or ARBs): (7976 participants). The studies included male and female participants (>18 years of age). Six trials were conducted in participants with HFrEF, two trials in patients with HFpEF and HFmrEF, and one trial in participants with HFrEF and HFmrEF. The features of the studies included in the meta-analysis are shown in Table 1.

3.3 | Characteristics of intervention group

Sacubitril-valsartan was administered orally in eight trials at a dose of 200 mg bid (sacubitril 97 mg and valsartan 103 mg). In one trial (PARALLEL-HF) sacubitril-valsartan was administered at a dose of 100 mg bid. Five trials used enalapril as a comparator at a dose of 10 mg bid, and the PARALLEL-HF trial used enalapril in a dose of 5 mg bid. In the remaining three trials, valsartan was used as a comparator at a dose of 160 mg bid. The follow-up periods of the trials ranged from approximately 3 months to 35 months. Supporting Information S4: Table 1 outlines information of the intervention and control groups.

3.4 | Bias assessment

Figure S2 depicts the findings of the risk of bias assessment. Overall, the risk of bias was low in most areas. The risk of bias from randomization, allocation concealment, and detection bias categories, on the other hand, remained unclear. Although the funnel plot for outcome of all-cause mortality looked symmetrical (Figure S3), the number of studies included was low (n = 8 trials) which is usually regarded as insufficient to ascertain publication bias.

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TABLE 1 Characteristics of trials included in the meta-analysis.

References	Trial name	Trial design	NYHA class ^a	HF class ^b
Owen et al. ²⁴	AWAKE-HF	Randomized, double-blind	Class II-III	HFrEF
Desai et al. ²⁵	EVALUATE-HF	Randomized, parallel	Class I-III	HFrEF
Piepoli et al. ²⁶	OUTSTEP-HF	Randomized, double-blind, prospective	Class II-IV	HFrEF
McMurray et al. ¹⁹	PARADIGM-HF	Randomized, double-blind	Class II-IV	HFrEF
Tsutsui et al. ²⁷	PARALLEL-HF	Randomized, double-blind	Class II-IV	HFrEF
Solomon et al. ²⁸	PARAGON-HF	Randomized, double-blind	Class II-IV	HFpEF and HFmrEF
Solomon et al. ²⁹	PARAMOUNT	Randomized, double-blind	Class II-III	HFpEF and HFmrEF
Velazquez et al. ³⁰	PIONEER-HF	Randomized, double-blind	Class I-IV	HFrEF
Kang et al. ³¹	PRIME-HF	Randomized, double-blind	Class II-III	HFrEF and HFmrEF

Abbreviation: HFpEF, heart failure with preserved ejection fraction.

^aNYHA, New York Heart Association.

^bHF, heart failure class, HFrEF (LVEF ≤ 40%), HFmrEF (LVEF 41%-49%), and HFpEF (LVEF ≥ 50%).

3.5 | Efficacy and safety outcomes

Supporting Information S4: Table 2 shows the results for mortality (all-cause and cardiovascular mortality) and HF hospitalization for the trials and Supporting Information S4: Table 3 shows the adverse effects reported for the intervention and control groups for the trials reporting these outcomes. The most reported adverse events were hypotension and hyperkalaemia. The values in the tables represent the number of participants experiencing the event divided by the total number of participants in the group.

3.6 | Meta-analysis results

In patients with HFrEF, all-cause mortality was considerably lower in the sacubitril-valsartan group than in the ACE inhibitors/ARBs group (RR: 0.85 [0.78, 0.93], $l^2 = 0\%$, p = .0004). There was no significant difference between sacubitril-valsartan and ACE inhibitors/ARBs for the outcome of all-cause mortality in patients with HFpEF and HFmrEF (RR: 0.97 [0.85, 1.11], $l^2 = 0\%$, p = .67). There was no significant subgroup effect (p = .23), indicating that the ejection fraction did not influence the efficacy of sacubitril-valsartan (Figure 1).

When cardiovascular mortality was used as the outcome, patients with HFrEF benefited from the use of sacubitril-valsartan (RR: 0.82 [0.74, 0.90], $l^2 = 0\%$, *p* < .0001) (Figure 2).

Sacubitril-valsartan did not cause a decrease in hospitalization events for participants with HFrEF (RR: 0.81 [0.59, 1.12], $l^2 = 65\%$, p = .20). Whereas it caused a significant decrease in hospitalizations for participants with HFpEF and HFmrEF (RR: 0.86 [0.79,0.93], $l^2 = 0\%$, p = .0004). In addition, there was no significant effect of ejection fraction on hospitalization events (p = .82) (Figure 3).

Adverse events such as hypotension were significantly higher in the sacubitril-valsartan group compared to ACE inhibitors or ARBs (RR: 1.53 [1.28, 1.84], l^2 = 31%, p < .00001). Other adverse events such as hyperkalaemia, worsening of renal function, and angioedema were similar between the two groups (Figure 4).

4 | DISCUSSION

The current study provides up-to-date and useful information on the safety and effectiveness of sacubitril-valsartan against RAAS inhibitors in patients with different ejection fractions categorized according to the universal classification for HF.¹⁰ The studies included in this meta-analysis are all multicentre, randomized, double-blind trials with an active comparator group with a low to moderate risk of bias across most domains. This study provides comprehensive evidence on the primary efficacy outcomes (mortality and hospitalization events) and adverse effects of sacubitril-valsartan versus ACE inhibitors/ARBs.

In patients with HFrEF, sacubitril-valsartan showed significant advantages in terms of lowering all-cause and cardiovascular mortality. In individuals with HFpEF or HFmrEF, however, there was no significant impact. Among the studies in patients with HFrEF, only results from the PARADIGM-HF study showed a reduction in all-cause mortality when sacubitril-valsartan was used compared to enalapril. This might be due to the PARADIGM-HF trial's 27-month follow-up term, which is longer than the other trials' follow-up periods, which range from 2 to 12 months. Solomon et al.³² utilized data from two studies with varied patient criteria in terms of LVEF, namely the PARADIGM-HF trial (LVEF eligibility ≤40%) and PARAGON-HF (LVEF eligibility ≥45%), to find a substantial reduction in all-cause mortality and cardiovascular mortality in the HFrEF groups. This study evaluated data and outcomes using different categories of ejection fraction and showed that patients with ejection fraction lower than normal (mid-range, borderline, or mildly reduced ejection fraction) would be expected to benefit from sacubitrilvalsartan versus RAAS inhibition. Diminished responses to sacubitrilvalsartan among patients with LVEF ≥ 50% and LVEF 41-49%%, may

	6.1	,	ACEIA	DD		Dick Datio	Dick Patio
Study or Subgroup	5-v Events	Total	Events	Total	Weight M-H. Random, 95% Cl		M-H Random 95% CI
16.1.1 HFrEF	Liento	Total	Lyong	Total	Weight		
AWAKE-HE	0	69	1	70	0.1%	0.34 (0.01.8.16)	
EVALUATE-HF	1	231	1	232	0.1%	1.00 [0.06, 15,96]	
OUTSTEP-HF	1	309	4	310	0.1%	0.25 [0.03, 2.23]	
PARADIGM-HF	711	4187	835	4212	69.0%	0.86 [0.78, 0.94]	
PIONEER-HF	10	440	15	441	0.9%	0.67 [0.30, 1.47]	
Subtotal (95% CI)		5236		5265	70.2%	0.85 [0.78, 0.93]	•
Total events	723		856				
Heterogeneity: Tau ² =	0.00; Ch	i ² = 1.93	2, df = 4 (P = 0.7	5); I ² = 0%	, ,	
Test for overall effect:	Z = 3.51	(P = 0.0	1004)				
16.1.2 HFpEF and HFn	nrEF						
PARAGON-HF	342	2407	349	2389	29.6%	0.97 [0.85, 1.12]	+
PARAMOUNT	1	149	2	152	0.1%	0.51 [0.05, 5.57]	
Subtotal (95% CI)		2556		2541	29.7%	0.97 [0.85, 1.11]	•
Total events	343		351				
Heterogeneity: Tau ² =	0.00; Ch	z = 0.28	B, df = 1 (P = 0.6	0); I ² = 0%	,	
Test for overall effect:	Z=0.43	(P = 0.6	17)				
16.1.3 HFrEF and HFm	Iref						
PRIME-HF	1	60	0	58	0.1%	2.90 [0.12, 69.81]	
Subtotal (95% CI)		60		58	0.1%	2.90 [0.12, 69.81]	
Total events	1		0				
Heterogeneity: Not ap	plicable						
Test for overall effect:	Z = 0.66	(P = 0.5	i1)				
Total (95% CI)		7852		7864	100.0%	0.89 [0.82, 0.96]	+
Total events	1067		1207				
Heterogeneity: Tau ² =	0.00; Ch	r = 5.10	6, df = 7 (P = 0.6	4); I ² = 0%		
Test for overall effect:	Z = 3.16	(P = 0.0	Eavours S-V Eavours ACEi/ARB				
Test for subgroup diffe	erences:	Chi ² = 3	2.97, df=	2 (P =	0.23), I ² =	32.6%	

FIGURE 1 Forest plot of trials included in the meta-analysis (*n* = 8) using a random-effects model for all-cause mortality outcome. Risk ratios and 95% confidence intervals are shown. ACEi/ARB, angiotensin converting enzyme inhibitors and angiotensin receptor blockers; S-V, sacubitril-valsartan.

	Sacubitril-valsartan		ACE inhibitor/ARB			Risk Ratio	Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl	
14.1.1 HFrEF								
PARADIGM-HF	558	4187	693	4212	60.4%	0.81 [0.73, 0.90]		
PARALLEL-HF	13	111	11	112	3.5%	1.19 [0.56, 2.55]		
Subtotal (95% CI)		4298		4324	63.9%	0.82 [0.74, 0.90]	•	
Total events	571		704					
Heterogeneity: Tau ² =	0.00; Chi ² = 0.9	8, df = 1	(P = 0.32); I ²	= 0%				
Test for overall effect:	Z = 3.91 (P < 0.0	0001)						
14.1.2 HFpEF and HFn	nrEF							
PARAGON-HF	204	2407	212	2389	36.1%	0.96 [0.79, 1.15]	• •	
Subtotal (95% CI)		2407		2389	36.1%	0.96 [0.79, 1.15]	•	
Total events	204		212					
Heterogeneity: Not ap	plicable							
Test for overall effect:	Z = 0.49 (P = 0.6	62)						
Total (95% CI)		6705		6713	100.0%	0.87 [0.75, 1.01]	•	
Total events	775		916					
Heterogeneity: Tau ² = 0.01; Chi ² = 3.15, df = 2 (P = 0.21); l ² = 36%								
Test for overall effect: Z = 1.87 (P = 0.06)								
Test for subgroup differences: Chi ² = 2.17, df = 1 (P = 0.14), l ² = 53.8%								

FIGURE 2 Forest plot of trials included in the meta-analysis (*n* = 3) using a random-effects model with cardiovascular mortality outcome. Risk ratios and 95% confidence intervals are shown. ACEi/ARB, angiotensin converting enzyme inhibitors and angiotensin receptor blockers; S-V, sacubitril-valsartan.

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	GAN	BIGE								
	S-V	,	ACEI/A	RB		Risk Ratio	Risk Ratio			
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl			
17.1.1 HFrEF										
PARADIGM-HF	537	4187	658	4212	40.8%	0.82 [0.74, 0.91]				
PARALLEL-HF	25	111	20	112	3.5%	1.26 [0.75, 2.13]	-+			
PIONEER-HF	35	440	61	441	6.0%	0.58 [0.39, 0.85]				
Subtotal (95% CI)		4738		4765	50.2%	0.81 [0.59, 1.12]	•			
Total events	597		739							
Heterogeneity: Tau ² =	0.05; Ch	i² = 5.6	8, df = 2 (P = 0.0	6); l² = 65	i%				
Test for overall effect:	Z = 1.27	(P = 0.2)	20)							
47.4.0 UE+EE UE+										
17.1.2 HEPEE and HEN	ILF									
PARAGON-HF	690	2407	797	2389	48.6%	0.86 [0.79, 0.94]				
PARAMOUNT	4	149	6	152	0.6%	0.68 [0.20, 2.36]				
Subtotal (95% CI)	co.(2000	000	2941	4 9. 270	0.00[0.79, 0.95]	•			
Total events	0.00.04	2 0 4	803 4 -46 - 4 4	n _ o 7	43, 17 - 00	,				
Heterogeneity: Tau ² = 0.00; Chi ² = 0.14, df = 1 (P = 0.71); I ² = 0%										
Test for overall effect.	Z = 3.94	(P = 0.0	1004)							
17.1.3 HFrEF and HFm	IFEF									
PRIME-HF	3	60	5	58	0.5%	0.58 [0.15, 2.32]				
Subtotal (95% CI)		60		58	0.5%	0.58 [0.15, 2.32]				
Total events	3		5							
Heterogeneity: Not ap	plicable									
Test for overall effect:	Z = 0.77	(P = 0.4)	14)							
Total (95% Cl)		7354		7364	100.0%	0.83 [0.75, 0.92]	•			
Total events	1294		1547							
Heterogeneity: Tau ² = 0.00; Chi ² = 6.70, df = 5 (P = 0.24); P = 25%										
Test for overall effect:	Z = 3.60	(P = 0.0)	0003)				Favours S-V Favours ACEI/ARB	00		
Test for subgroup diff	erences:	Chi ² =	0.41, df=	2 (P =	0.82), I ² =	: 0%				

FIGURE 3 Forest plot of trials included in the meta-analysis (*n* = 6) using a random-effects model with HF hospitalization outcome. Risk ratios and 95% confidence intervals are shown. ACEi/ARB, angiotensin converting enzyme inhibitors and angiotensin receptor blockers; S-V, sacubitril-valsartan.

be related to factors such pathological processes in patients with higher LVEF range and possible amyloid deposition.³² However, there were only two trials for patients with HFpEF and HFmrEF indicating that the meta-analysis results are not reliable indicators of efficacy in this LVEF category. The results of the meta-analysis are reliable for the HFrEF category as the number of studies is sufficient and heterogeneity values low ($l^2 = 0\%$) indicating the uniform participant and trial characteristics inspite of one of the trials that used valsartan as the comparator group (PRIME-HF).

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HF hospitalization events were not significantly different between the sacubitril-valsartan and RAAS inhibitor groups for patients with HFrEF. However, there was a significant decrease in hospitalization events for patients with HFpEF and HFmrEF who received sacubitrilvalsartan treatment. The two studies, PARADIGM-HF and PIONEER-HF that showed a significant reduction in hospitalizations for patients receiving sacubitril-valsartan both used enalapril (10 mg bid) as the comparator group. With regard to the other studies, the dose of sacubitril-valsartan and enalapril was lower in the PARALLEL-HF trial and valsartan was used as the comparator in PRIME-HF trial which could have led to insignificant differences in hospitalization events. Contrary to the effects seen in HFrEF patients, patients with HFpEF and HFmrEF benefited from the use of sacubitril-valsartan.

Sacubitril-valsartan was shown to have a considerably greater rate of hypotension (either symptomatic or SBP < 90 mm Hg) than RAAS inhibitors. This is in line with a meta-analysis of the effects of sacubitril-valsartan against ARBs, which found that sacubitrilvalsartan reduced systolic and diastolic blood pressures significantly.³³ The moderate heterogeneity seen with subgroup analysis of hypotension could be attributed to different comparators, followup times, and LVEF of participants in the different trials. The higher incidence of hypotension in the sacubitril-valsartan group can be attributed to the natriuretic potential of sacubitril which is an ARNi. Dose adjustment of sacubitril-valsartan, blood pressure monitoring, and adjustment of concomitant diuretic use may help reduce hypotension incidence. Other adverse events such as hyperkalaemia, worsening renal function, and angioedema were not significantly different between sacubitril-valsartan and comparator groups. In case of hyperkalaemia, two large trials, PARADIGM-HF and PARAGON-HF showed a significantly lower incidence of hyperkalaemia in the sacubitril-valsartan group. Although, the comparators and the HF class was different between these trials, the follow-up time in both was relatively longer. In addition, heterogeneity values for all analysis of adverse events outcomes were moderate to high as the trials different in participant characteristics and comparators. Overall,

Study out Subgroup Events Total Weight M.H., Random, 95% C1 M.H., Random, 95% C1 EVALUATE-HF 9 231 4 233 1.5% 2.27 (p. 7, 7, 72) CVALUATE-HF 9 231 4 233 1.5% 2.27 (p. 7, 7, 72) PARADON-HF 112 2.167 5.98 4.21 (p. 10, 3.58) ++++++++++++++++++++++++++++++++++++		Sacubitrily	aleartan	ACE inhibit	ore/ARRe		Risk Ratio	Risk Ratio		
10.1.1 Mpotension 2011 4 233 1.8% 2.27 [0.71, 7.27] OUTSTEP-HF 43 309 20 310 4.9% 2.16 [1.30, 3.56] PARADIOM-HF 112 4167 5.9 4.21 6.8% 1.41 [1.02, 161] + PARADIOM-HF 111 5 112 2.2% 2.62 [0.97, 11] + PARADUMT 28 149 27 152 5.1% 1.06 [0.66, 1,71] + PARAULEL-HF 13 111 5 112 2.2% 2.62 [0.97, 11] + PARAUCH-HF 260 1 58 0.5% 1.30 [0.18, 20.7] + PARAUTE-HF 2 80 1 58 0.74 [0.66, 0.9] +	Study or Subaroup	Events	Total	Events	Total	Weight	M-H. Random, 95% Cl	M-H. Random, 95% Cl		
$ \begin{array}{c} EvALURE + H & 9 & 231 & 4 & 233 & 18\% & 277 (0.7, 7.27) \\ PARADONH + F & 112 & 4187 & 59 & 4212 & 68\% & 191 (140, 2.61) \\ PARADONH + F & 112 & 4187 & 59 & 4212 & 68\% & 1.91 (140, 2.61) \\ PARADONH + F & 112 & 4187 & 59 & 4212 & 68\% & 1.91 (140, 2.61) \\ PARADON + F & 310 & 110 & 5112 & 2.2\% & 262 (0.97, 7.11) \\ PARADON + F & 13 & 111 & 5 & 112 & 2.2\% & 126 (0.65, 1.71) \\ PONEER + H & 2 & 60 & 1 & 56 & 0.5\% & 1.39 (0.65, 1.71) \\ PONEER + H & 2 & 60 & 1 & 56 & 0.5\% & 1.39 (0.80, 2.07) \\ Subtal (95\% C) & T294 & T7907 & 3.4\% & 1.24 (0.80, 1.84) \\ Hetrogonehy \; Tat^* = 0.02, Ch^* = 0.19, H = 31\% \\ Test for overall effect Z = 4.22 (P = 0.0001) \\ Tat = ents & Tat^* = 0.23 & Cat^* = \mathsf{Cat$	10.1.1 Hypotension	Liono	Total	Lionto	Total		in rig raine rig con or			
DUTSTEP-HF 43 309 20 310 45% 216 [130 556] PARADIONHF 112 4187 59 4212 65% 1421 140,261] PARADONHF 300 2407 257 2399 78% 147[127,170] PARADUNT 28 149 27 152 5.1% 1.06 [0.66,171] PARADONHF 28 149 27 152 5.1% 1.53 [1.28,1.84] Total events 653 429 Heterogenety: Tau*-0 02, Ch*= 10.8, d*= 21 78% Test for overall effect Z = 4.52 (P < 0.00001) PARADONHF 181 4187 2236 4212 75% 0.77 (0.64,0.33) PARADONHF 181 4187 2236 4212 75% 0.77 (0.64,0.33) PARADONHF 181 4187 2236 4212 75% 0.77 (0.84,0.33) PARADONHF 181 4187 2237 5% 0.77 (0.86,0.62,1.27) PARADONHF 194 4187 100 4212 5% 0.58 (0.76,1.27) PARADONHF 97 2407 109 2399 7.7% 0.98 (0.76,1.27) PARADONHF 97 2407 109 2399 7.7% 0.88 (0.76,1.01) PARADONHF 94 44167 100 4212 5.5% 0.75% 0.97 (0.18,0.71,13) PARADONHF 94 44167 100 4212 5.5% 0.97 (0.18,0.71,13) PARADONHF 94 4417 100 4212 5.5% 0.97 (0.14,6.64) PARADONHF 94 4417 100 4212 3.2% 0.88 (0.76,1.04) PARADONHF 94 4417 100 4212 3.2% 0.98 (0.76,1.04) PARADONHF 94 4417 100 4212 3.2% 0.98 (0.76,1.04) PARADONHF 14 4207 4238 1.93% 0.88 (0.76,1.04) PARADONHF 14 4207 4238 1.93% 0.84 (0.01,8.21) PARADONHF 14 4207 4238 1.93% 0.84 (0.01,8.21) PARADONHF 14 4207 4238 1.93% 0.84 (0.01,8.21) PARADONHF 14 4207 4238 1.95% 0.97 (0.14,6.64) PARADONHF 14 4207 4238 1.95% 0.97 (0.14,6.64) PARADONHF 14 4207 4238 0.9% 0.97 (0.14,6.64) PARADONHF 14 4207 4238 0.9% 0.97 (0.14,6.64) PARADONHF 14 4207 4238 0.9% 0.9% 0.97 (0.14,6.64) PARADONHF 14 4207 4238 0.9% 0.9% 0.88 (0.76,1.04) PARADONHF 1	EVALUATE-HF	9	231	4	233	1.8%	2.27 [0.71, 7.27]			
PARADONH=F 112 4187 59 4212 6.8% 1.91[140,261] PARADON=F 380 2407 257 2389 79% 1.471(12,17.0) PARADON=F 380 2407 257 2389 79% 1.471(12,17.0) PARADON=F 380 2407 257 2389 79% 1.471(12,17.0) PARADON=F 280 149 27 152 25% 262(097,711) PONEER+F 2 80 158 440 56 441 6.4% 1.18(0.85,171) PONEER+F 2 80 158 440 56 441 6.4% 1.18(0.85,171) Total events 653 429 Heterogenethy Tau ² 0.02, Ch ² 1.019, d = 70 = 0.18; F = 31% Test for overall effect Z = 45.20 + 0.0001) PARADON HF 181 4187 2.33 5.4% 1.24(0.86,1.71) PARADON HF 181 4187 2.36 4212 7% 0.77 (0.40,03) PARADON HF 181 4187 2.36 4212 7% 0.57 (0.40,03) PARADON HF 181 4187 2.36 4212 7% 0.57 (0.40,03) PARADON HF 181 4187 2.37 428 Heterogenethy Tau ² 0.05, Ch ² = 1.43, df = 7 (P = 0.04), F = 52% Total events 372 428 Heterogenethy Tau ² 0.05, Ch ² = 1.43, df = 7 (P = 0.04), F = 52% Total events 272 306 Heterogenethy Tau ² 0.02, df = 6 (P = 0.04), F = 52% Total events 272 306 Heterogenethy Tau ² 0.02, df = 6 (P = 0.99), P = 0% Total events 272 306 Heterogenethy Tau ² 0.02, df = 6 (P = 0.99), P = 0% Total events 34 272 306 Heterogenethy Tau ² 0.03, df = 6 (P = 0.99), P = 0% Total events 34 27 (P = 0.99), P = 0% Total events 34 27 (P = 0.99), P = 0% Total events 34 27 (P = 0.99), P = 0% Total events 34 27 (P = 0.99), P = 0% Total events 123 (P = 0.70) Total events 123 (P = 0.70) Tota	OUTSTEP-HF	43	309	20	310	4.9%	2.16 [1.30, 3.58]			
PARALLEL.HF 13 101 0 257 2389 79% 147 127, 170 +	PARADIGM-HF	112	4187	59	4212	6.6%	1.91 [1.40, 2.61]			
PARALLEL-HF 13 111 5 112 2.2% 242 [0.87, 7.11] PARAMOUNT 28 149 27 152 2.5% 10.6 [0.6, 6, 7, 71] PIONEER-HF 66 440 56 441 8.4% 1.18 [0.85, 1.64] PIONEER-HF 2 60 158 0.5% 1.30 [1.8, 0.75] Subtoal (95% C) 7894 7907 35.4% 1.53 [1.28, 1.84] Total events 653 429 Heterogenety, Tau ² = 0.02, Ch ² = 10.19, df = 7 (P = 0.19), P = 31% Test for overall effect Z = 1.6 2 (P < 0.00001) 10.12 Hyperkalaemia EVALUATE-HF 37 231 30 233 5.4% 1.24 [0.80, 1.94] OUTSTEP-HF 22 309 11 310 3.5% 201 [0.89, 407] PARADOIM-HF 151 4197 236 4212 7.6% 0.77 [0.64, 0.93] 4 PARADOIM-HF 75 2366 10 2367 6.8% 0.77 [0.64, 0.93] 4 PARADOIM-HF 75 240 (D 1 2.07 6.8% 0.77 [0.64, 0.93] 4 PARADOIM-HF 75 240 (D 1 2.07 6.8% 0.77 [0.64, 0.93] 5 PARADOIM-HF 75 240 (D 2 56 0.5% 0.88 [0.57, 1.72] PIONEER-HF 51 44.0 41 441 5.9% 0.25 [0.27, 2.73] PIONEER-HF 51 44.0 2 58 0.5% 0.88 [0.57, 1.27] PIONEER-HF 51 44.0 2 58 0.5% 0.88 [0.57, 1.27] Subtoal (95% C) 7.873 7.785 31.7% 0.98 [0.76, 1.27] 5 Subtoal (95% C) 7.873 7.785 31.7% 0.88 [0.67, 1.15] 6 PARADOIM-HF 97 2407 109 2389 7.0% 0.88 [0.67, 1.15] 7 PARADOIM-HF 97 2407 109 2389 7.0% 0.88 [0.67, 1.15] 7 PARADOIM-HF 97 2407 109 2389 7.0% 0.88 [0.67, 1.05] 7 PARADOIM-HF 94 4187 108 4212 0.5% 0.088 [0.87, 1.15] 7 PARADOIM-HF 94 201 7 108 212 0.5% 0.088 [0.87, 1.15] 7 PARADOIM-HF 94 210 7 109 2139 7.0% 0.88 [0.87, 1.04] 7 PARADICHE-HF 0 0 410 65 441 65% 0.38 (0.87, 1.05] 7 PARADICHE-HF 0 140 6 141 12 0% 0.05 (0.09, 2.70] 7 PARADICHE-HF 0 200 C) F385 7597 2587 0.038 [0.76, 1.01] 7 PARADICHE-HF 0 200 C) F385 7597 2587 0.038 [0.74, 5.04] 7 PARADICHE-HF 0 200 C) F385 7597 2587 0.038 [0.74, 5.04] 7 PARADICHE-HF 0 410 6 1412 0.05% 112 (0.48, 113) 7 PARADICHE-HF 0 200 C) F38 30834 100.0% 1.18 [0.99, 110] 7 PARADICHE-HF 0 200 C) F39 27 575 7597 2587 0.038 [0.76, 1.05] 7 PARADICHE-HF 0 1410 6 1412 0.05% 112 (0.99, 1.05] 7 PARADICHE-HF 0 200 C) F38 30834 100.0% 1.28 [0.84, 113] 7 PARADICHE-HF 0 200 C) F39 20 C = 0.00001), F =	PARAGON-HF	380	2407	257	2389	7.9%	1.47 [1.27, 1.70]	+		
PARAMOUNT 28 149 27 152 51% 1.06 (0.6, 7.1) PIONEER-HF 66 440 56 441 84% 1.19 (0.5, 1.6) PRINE-HF 2 60 1 59 0.5% 1.93 (0.12, 0.75) Stutbat (95% C1) 7894 7907 35.4% 1.33 (1.2, 0.75) 1.53 (1.2, 1.84] Total events 653 429 Heterogenety: Tau*2 0.02; Ch ² = 0.109; J ² = 7 (P = 0.18); J ² = 31% Testfor overall effect Z = 4.62 (P < 0.00001) 10.12 Myoerkalaemia EVALUATE-HF 75 2366 101 2367 6.8% 0.74 (0.55, 0.99) PARADION-HF 181 4187 236 4212 7.6% 0.77 (0.84, 0.93) PARADON-HF 75 2366 101 2367 6.8% 0.74 (0.55, 0.99) PARADON-HF 75 149 6 152 1.8% 0.65 (0.27, 2.73) PARADLE, HF 0 111 1 112 0.3% 0.36 (0.25, 5.19) Stutbat (95% C1) 7873 7895 31.7% 0.88 (0.81, 0.55, 5.19) PARADON-HF 12 1.80 2 53 0.5% 0.48 (0.05, 5.19) PARADON-HF 12 0.05; Ch ² = 1.44, 9; (F = 7 (P = 0.04); P = 52% Testfor overall effect Z = 0.15 (P = 0.89) 10.13 Worsening renal function EVALUATE-HF 2 111 4 112 1.0% 0.56 (0.61, 1.27) PARADON-HF 97 2407 109 2399 7.0% 0.88 (0.81, 1.15) PARADON-HF 97 2407 109 2399 7.0% 0.88 (0.81, 0.15) PARADON-HF 97 2407 109 2398 7.0% 0.88 (0.81, 1.15) PARADON-HF 97 2407 109 2398 7.0% 0.88 (0.81, 1.15) PARADON-HF 97 2407 109 2398 7.0% 0.89 (0.81, 0.15) PARADON-HF 97 2407 109 2398 7.0% 0.89 (0.76, 1.27) PARADON-HF 97 2407 109 2398 7.0% 0.89 (0.81, 0.15) PARADON-HF 97 2407 109 2398 7.0% 0.89 (0.76, 1.04) PARADON-HF 97 2407 109 2398 1.0% 0.31 (0.61, 8.21) PARADON-HF 97 2407 109 2398 1.0% 0.31 (0.71, 0.82) PARADON-HF 97 2407 109 2398 1.0% 0.34 (0.01, 8.21) PARADON-HF 97 2407 109 2398 1.0% 0.34 (0.01, 8.21) PARADON-HF 97 2407 109 2398 1.0% 0.34 (0.01, 8.21) PARADON-HF 14 2407 4 239 1.0% 0.34 (0.01, 8.21) PARADON-HF 14 2407 4 2.23 0.5% 0.38 (0.76, 1.04) PARADICH-HF 0 0.80 0 5.8 Notestmable Subtotal (95% C1) 7.436 7.445 6.0% 1.25 (0.40, 3.95] Total events 34 2.21 Heterogenety: Tau* = 0.02; ch ² = 0.05), H	PARALLEL-HF	13	111	5	112	2.2%	2.62 [0.97, 7.11]			
PIONEER-HF 0 66 440 56 441 0.4% 1.18 (0.85, 16.4) PIONEER-HF 2 60 1 59 0.5% 1.30 (18, 20, 75) Subtol (95% C) 7894 7907 35.4% 1.53 (1.28, 1.84) Heterogenety, Tau" = 0.02, Ch" = 10.19, df = 7 (P = 0.18), P = 31% Test for overall effect Z = 0.5 (Ch" = 7 (P = 0.18), P = 31% Test for overall effect Z = 0.5 (Ch" = 1.5	PARAMOUNT	28	149	27	152	5.1%	1.06 [0.66, 1.71]			
$\begin{array}{c c c c c c c c c c c c c c c c c c c $	PIONEER-HF	66	440	56	441	6.4%	1.18 [0.85, 1.64]			
Subtact (95% C) 7984 7907 35.4% 1.53 [1.28, 1.84] Heterogeneity, Tat ² = 0.02, Ch7 = 10.19, df = 7 (P = 0.18); P = 31% Test for overall effect Z = 4.52 (P < 0.00001) 10.12 Hyperkalaemia EVALUATE-HF 37 2.31 30 233 5.4% 1.24 [0.80, 1.94] OUTSTEP-HF 22 309 11 310 35% 2010 9.9, 4.07] PARADOM-HF 181 4187 236 4212 7.6% 0.77 [0.40, 0.33] PARADOM-HF 75 2386 101 2.357 6.8% 0.77 [0.40, 0.33] PARADOM-HF 75 2486 101 2.357 6.8% 0.77 [0.40, 0.33] PARADOM-HF 151 440 41 441 5.9% 1.25 [0.40, 1.84] PARADOM-HF 51 440 41 441 5.9% 1.25 [0.40, 1.84] PARADOM-HF 151 440, df = 7 (P = 0.04); P = 52% Test for overall effect Z = 0.15 (P = 0.86) 10.13 Worsening renafiltation PARADOM-HF 37 240 Heterogeneity, Tat ² = 0.05; Ch7 = 14.49, df = 7 (P = 0.04); P = 52% Test for overall effect Z = 0.15 (P = 0.89) 10.13 Worsening renafiltation EVALUATE-HF 12 231 14 233 3.3% 0.86 [0.41, 1.83] PARADOM-HF 37 2407 108 2.389 7.0% 0.080 [0.67, 1.51] PARADOM-HF 37 2407 108 2.389 7.0% 0.080 [0.67, 1.52] PARADOM-HF 37 2407 108 2.398 7.5% 0.38 [0.67, 1.51] PARADOM-HF 37 2407 108 2.398 7.5% 0.38 [0.67, 1.15] PARADOM-HF 37 2407 108 2.398 7.5% 0.38 [0.67, 1.28] PARADOM-HF 47 2.403 (P = 0.98); P = 0.8 Test for overall effect Z = 1.33 (P = 0.06); P = 50% Test for overall effect Z = 1.33 (P = 0.06); P = 50% Test for overall effect Z = 1.32 (P = 0.00); P = 65 % Test for overall effect Z = 1.32 (P = 0.00); P = 50% Test for overall effect Z = 1.32 (P = 0.00); P = 50% Test for overall effect Z = 1.32 (P = 0.00); P = 50% Test for overall effect Z = 1.32 (P = 0.00); P = 50% Test for overall effect Z = 1.32 (P = 0.00); P = 50% Test for overall effect Z = 1.32 (P = 0.00); P = 50% Test for overall effect Z = 1.32 (P = 0.00); P = 50% Test for overall effect Z = 1.32 (P = 0.00); P = 50% Test for overall effect Z = 1.32 (P = 0.00); P = 50% Test for overall effect Z = 1.32 (P = 0.00)	PRIME-HF	2	60	1	58	0.5%	1.93 [0.18, 20.75]			
Total events 653 429 Test for overall effect $Z = 4.52 (P = 0.10), P = 31\%$ Test for overall effect $Z = 4.52 (P = 0.0001)$ 10.12 hyperkalaemia EVALUATE-HF 37 231 30 233 54% 1.24 [0.80, 1.94] OUTSTEP-HF 22 309 11 310 3.5% 2.01 [0.94, 4.07] PARADIOMH 181 4187 236 4.212 76% 0.77 [0.54, 0.93] PARADIOMH 181 4187 236 4.212 76% 0.77 [0.54, 0.93] PARADAONHF 175 2386 101 2367 6.8% 0.74 [0.55, 0.99] PARADAONHF 151 440 41 441 5.9% 1.25 [0.41, 1.83] PARADAONHF 51 440 41 441 5.9% 1.25 [0.41, 1.83] PARADAONHF 51 440 41 441 5.9% 0.45 [0.07, 2.73] Total events 372 428 10.13 Worsening renal function EVALUATE-HF 12 231 14 233 3.3% 0.88 [0.76, 1.27] Total events 372 428 10.13 Worsening renal function EVALUATE-HF 12 231 14 233 3.3% 0.88 [0.87, 1.15] PARADIONH F 97 2407 109 2399 7.0% 0.88 [0.88, 1.15] PARADIONH F 97 2407 109 2399 7.0% 0.88 [0.87, 1.15] PARADIONH F 97 2407 109 2399 7.0% 0.88 [0.87, 1.15] PARADIONH F 97 2407 109 2399 7.0% 0.88 [0.87, 1.15] PARADIONH F 97 2407 109 2399 7.0% 0.88 [0.87, 1.15] PARADIONH F 97 2407 109 2399 7.0% 0.88 [0.87, 1.15] PARADIONH F 97 2407 109 2399 7.0% 0.88 [0.87, 1.15] PARADIONH F 97 2407 109 2399 7.0% 0.88 [0.87, 1.15] PARADIONH F 97 2407 109 2399 7.0% 0.88 [0.87, 1.15] PARADIONH F 97 2407 109 2399 7.0% 0.88 [0.87, 1.15] PARADIONH F 97 2407 109 2399 7.0% 0.88 [0.87, 1.15] PARADIONH F 97 2407 109 2399 7.0% 0.88 [0.87, 1.15] PARADIONH F 97 2407 109 2390 7.0% 0.88 [0.87, 1.15] PARADIONH F 97 2407 109 2390 7.0% 0.88 [0.87, 1.15] PARADIONH F 97 2407 109 2390 7.0% 0.88 [0.87, 1.15] PARADIONH F 91 4417 10 4212 3.2% 1.38 [0.89, 0.16, 0.41] PARADIONH F 19 44187 10 4212 3.2% 1.91 [0.89, 4.11] PARADIONH F 114 2407 4 2303 1.9% 3.47 [1.15, 1.04] PARADIONH F 114 2407 4 2303 1.9% 3.47 [1.15, 1.04] PARADIONH F 114 2407 4 2339 1.9% 3.47 [1.15, 1.04] PARADIONH F 114 2407 4 2389 1.9% 3.47 [1.15, 1.04] PARADIONH F 114 2407 4 2389 1.9% 3.47 [1.15, 1.04] PARADIONH F 114 2407 4 2389 1.9% 3.47 [1.15, 1.04] PARADIONH F 114 2407 4 2389 1.9% 3	Subtotal (95% CI)		7894		7907	35.4%	1.53 [1.28, 1.84]	•		
Heterogeneity: Tau ² = 0.02; Chi ² = 10.19; i ² = 31% Test for overall effect $Z = 4.2$ (P = 0.19; i ² = 31% Test for overall effect $Z = 4.2$ (P = 0.00001) 10.1.2 Hyperkalaemia EVALUATE-HF 37 231 30 233 5.4% 1.24 (0.80, 1.94) OUTSTEP.HF 22 309 11 310 3.5% 2.01 (0.99, 4.07) PARADIOM-HF 75 2386 101 2.37 6.8% 0.77 (0.64, 0.93) PARADICHF 75 2386 101 2.37 6.8% 0.77 (0.64, 0.93) PARADICHF 75 2386 101 2.37 6.8% 0.77 (0.64, 0.93) PARADICHF 75 144 9 6 152 1.8% 0.58 (0.57, 73) PARADICHF 75 1440 41 441 5.9% 1.25 (0.84, 1.84) PIONEER-HF 51 440 41 441 5.9% 1.25 (0.84, 1.84) PIONEER-HF 51 440 41 441 5.9% 1.25 (0.84, 1.84) PIONEER-HF 51 440 41 471 5.9% 1.25 (0.84, 1.84) PIONEER-HF 51 440 41 97 1.09 2.389 10.76, 1.27] Subtotal (95% Ci) 77873 7783 7885 31.7% 0.98 (0.61, 1.83) PARADICHF 12 221 14 223 3.3% 0.86 (0.41, 1.83) PARADICHF 14 9.49 (f = 7 (P = 0.04); P = 52% Test for overall effect Z = 0.15 (P = 0.04); P = 52% Test for overall effect Z = 0.15 (P = 0.04); P = 52% Test for overall effect Z = 0.15 (P = 0.99); P = 0% Test for overall effect Z = 0.13 (P = 0.09); P = 0% Test for overall effect Z = 0.13 (P = 0.09); P = 0% Test for overall effect Z = 0.13 (P = 0.09); P = 0% Test for overall effect Z = 1.43 (P = 0.05); P = 0.95; Te 55% Test for overall effect Z = 0.38 (P = 0.05); P = 59% Test for overall effect Z = 1.82 (P = 0.07) Total events 34 21 Heterogeneity: Tau ² = 0.03; (P = 7.30; d = 3 (P = 0.00); P = 59% Test for overall effect Z = 1.82 (P = 0.07) Total events 131 1141 Heterogeneity: Tau ² = 0.03; (P = 0.05); P = 59% Test for overall effect Z = 1.82 (P = 0.07) Total events 1331 1184 Heterogeneity: Tau ² = 0.38 (P = 0.07) Total events 1331 1184 Heterogeneity: Tau ² = 0.38 (P = 0.07) Total events 1331 1184 Heterogeneity: Tau ² = 0.27 (P = 0.05); P = 50% Test for overall effect Z = 1.82 (P = 0.07) Total events 1331 1184 Heterogeneity: Tau ² = 0.28 (P = 0.07) Total events 1331 1184 Heterogeneity: Tau ² = 0.28 (P = 0.07) Total events 1331 1184 Heteropeneity: Tau ²	Total events	653		429						
10.1.2 Hyperkalaemia EVALUNTE-HF 37 231 30 233 5.4% 1.24 [0.80, 1.94] OUTSTEP-HF 22 309 11 310 3.5% 2.01 [0.99, 4.07] PARADIGM-HF 181 1187 236 4212 7.6% 0.77 [0.64, 0.03] PARADONHF 75 2386 101 2367 6.8% 0.74 [0.55, 0.99] PARALLEL+F 0 111 1 112 0.3% 0.34 [0.01, 8.17] PARADIGM-HF 5 1440 61 52 18.8% 0.86 [0.27, 2.73] POINEER-HF 1 60 2 58 0.5% 0.48 [0.05, 5.19] Stubtotal (5% (C) 7873 7885 31.7% 0.98 [0.67, 1.57] Test for orenall effect Z = 0.15 (P = 0.86) 114 12 1.0% 0.58 [0.67, 1.51] PARADIGM-HF 97 2407 198 23.3% 0.88 [0.67, 1.51] PARADIGM-HF 97 2417 1.83 0.39 [0.67, 1.28] 0.39 [0.67, 1.28] PARADIGM-HF 97 2414 53.8 0.39 [0.67, 1.28]	Heterogeneity: Tau ² =	0.02; Chi ² = 1	10.19, df = 7	7 (P = 0.18);	l² = 31%					
10.1.2 Hyperkalaemia EVALUATE-HF 37 231 30 233 5.4% 1.24 [0.80, 1.94] VISTEP-HF 22 309 11 310 3.5% 0.27 [0.64, 0.33] PARADON-HF 75 236 111 112 0.3% 0.37 [0.64, 0.33] PARADON-HF 75 236 111 112 0.3% 0.34 [0.01, 8.17] PARADON-HF 75 149 6 152 18% 0.98 [0.27, 27] PARADON-HF 1 40 41 441 59% 1.25 [0.84, 1.84] PIONEER-HF 1 60 2 58 0.5% 0.49 [0.05, 519] Subtotal (95% C) 7873 7885 31.7% 0.98 [0.76, 1.27] Total events 372 428 125 111 112 10% 0.88 [0.61, 1.183] PARADON-HF 97 20.15 (P = 0.88) 0.88 [0.61, 1.183] 0.48 [0.05, 2.16] 0.48 [0.06, 2.16] 0.41 [0.12 0.41 [0.12 0.43 [0.07, 1.04] 0.41 [0.12 0.43 [0.07, 1.04] 0.41 [0.12 0.43 [0.07, 1.04] 0.41 [0.12 0.43 [0.01, 8.21] <td>Test for overall effect:</td> <td>Z = 4.62 (P <</td> <td>0.00001)</td> <td></td> <td></td> <td></td> <td></td> <td></td>	Test for overall effect:	Z = 4.62 (P <	0.00001)							
$ \begin{array}{c ccccccccccccccccccccccccccccccccccc$	10.1.2 Hyperkalaemia	a								
OUTSTEP.HP 22 300 310 370 3	EVALLIATE-HE	- 37	231	30	222	5 4 %	1 24 (0 80 1 94)			
PARADIOM-HF 121 4187 236 4212 7.6% 0.077 [0.64, 0.3] + PARADIOM-HF 75 2366 101 2367 6.8% 0.77 [0.64, 0.3] + PARALLEL-HF 0 111 1 112 0.3% 0.34 [0.01, 8.17] PARALLEL-HF 0 111 1 112 0.3% 0.34 [0.01, 8.17] PARALOWNT 5 1440 41 441 5.9% 0.48 [0.05, 5.19] POINEER-HF 51 440 41 441 5.9% 0.48 [0.05, 1.27] Total events 372 428 4212 6.9% 0.48 [0.05, 1.18] PRIME-HF 12 231 14 233 3.3% 0.88 [0.61, 1.18] PARADIOHHF 94 4187 108 4212 6.9% 0.88 [0.61, 1.18] PARADIOHHF 97 2407 109 2389 7.0% 0.88 [0.61, 1.28] - PARADIOHHF 94 4187 10 4212 5.9% 0.39 [0.76, 1.24] - PARADIOH 97 2407	OUTSTEP-HE	22	201	11	310	3.5%	2 01 (0 00, 1.04)			
PARAJON-LFP 75 2366 101 2367 6.8% 0.74 [0.55, 0.98] PARAJOL-LE-LFP 0 111 1 112 0.3% 0.34 [0.01, 8.17] PARAMOUNT 5 149 6 152 1.8% 0.05 [0.27, 2.73] PIONEER-NF 51 440 41 441 5.9% 0.125 [0.84, 184] PIME-LFF 1 60 2 58 0.5% 0.04 [0.05, 5.19] Subtotal (95% CI) 7873 7885 31.7% 0.98 [0.76, 1.27] Total events 372 428 10.1 Worsening renal function EVALUATE-LFF 1 2 21 14 233 3.3% 0.86 [0.41, 1.83] PARAJOIM-HF 97 2407 108 4212 6.9% 0.88 [0.67, 1.15] PARAJOIM-HF 97 2407 109 2389 7.0% 0.88 [0.67, 1.15] PARAJOIM-HF 97 2407 109 2389 7.0% 0.88 [0.67, 1.28] PARAJOIM-HF 97 2407 109 2389 7.0% 0.88 [0.67, 1.28] PARAJOUNT 5 149 4 152 1.5% 1.28 [0.36, 4.66] PARAJOUNT 5 149 4 152 1.5% 0.50 [0.09, 2.70] PARAJOUNT 5 149 4 152 1.5% 0.58 [0.67, 1.28] PIONEER-NF 6 00 440 65 441 6.5% 0.039 [0.76, 1.04] Total events 272 306 Heterogeneity: Tau" = 0.00; Chi" = 0.82, df = 6 (P = 0.99); P = 0% Test for overail effect Z = 1.43 (P = 0.15) 10.1.4 Angioedema EVALUATE-HF 0 111 0 112 2.3% 1.34 [0.01, 8.21] PARAJOU-HF 14 2407 4 2389 1.9% 3.47 [1.15, 10.54] PARAJOU-HF 13 4.16 (P = 0.05); P = 59% Test for overail effect Z = 1.82 (P = 0.00); P = 59% Test for overail effect Z = 1.82 (P = 0.07) Total (95% CI) 30788 30834 100.0% 1.18 [0.99, 1.40] Total events 1331 1184 Heterogeneity Tau" = 0.70; P = 20.53, df = 3 (P = 0.0001); P = 85% Test for overail effect Z = 1.82 (P = 0.07) Favours [experimental] Favours [control]	PARADIGM-HE	181	4187	236	4212	7.6%	0.77 [0.64 0.93]	-		
PARALLEL-IHF 0 111 1 112 0.3% 0.34 [0.01, 8.17] PARALLEL-IHF 1 140 6 122 1.8% 0.85 [0.27, 27.3] PARADIONT 5 149 6 152 1.8% 0.85 [0.27, 27.3] PARADION-HF 1 140, 0f = 7 (P = 0.04), P = 52% Total events 372 428 Heterogeneity Tau ² = 0.5; (P = 0.48), of = 7 (P = 0.04), P = 52% Test for overall effect Z = 0.15 (P = 0.48), of = 7 (P = 0.04), P = 52% Test for overall effect Z = 0.15 (P = 0.48), of = 7 (P = 0.04), P = 52% Test for overall effect Z = 0.15 (P = 0.48), of = 7 (P = 0.04), P = 52% Test for overall effect Z = 0.15 (P = 0.48), of = 7 (P = 0.04), P = 52% Test for overall effect Z = 0.15 (P = 0.48), of = 7 (P = 0.04), P = 52% Test for overall effect Z = 0.15 (P = 0.48), of = 7 (P = 0.04), P = 52% Test for overall effect Z = 0.15 (P = 0.48), of = 7 (P = 0.48), P = 0.57 (P = 0.48), P = 0.57 (P = 0.48), P = 0.58, O = 0.57 (P = 0.48), P = 0.58, O = 0.59 (P = 0.48), P = 0.58, O = 0.59 (P = 0.48), P = 0.58, O = 0.59 (P = 0.48), P = 0.58, O = 0.59 (P = 0.48), P = 0.58, O = 0.59 (P = 0.48), P = 0.58, O = 0.59 (P = 0.48), P = 0.58, O = 0.59 (P = 0.48), P = 0.58, O = 0.59 (P = 0.48), P = 0.58, O = 0.59 (P = 0.48), P = 0.58, O = 0.59 (P = 0.48), P = 0.58, O = 0.59 (P = 0.48), P = 0.58, O = 0.59 (P = 0.48), P = 0.58, O = 0.59 (P = 0.58), P = 0.59, P = 0.58, O = 0.59 (P = 0.58), P = 0.59, P = 0.58, O = 0.59 (P = 0.58), P = 0.59, P = 0.58, O = 0.59 (P = 0.58), P = 0.59, P = 0.58, O = 0.59 (P = 0.58), P = 0.59, P = 0.58, O = 0.59 (P = 0.58), P = 0.59, P = 0.58, O = 0.59 (P = 0.58), P = 0.59, P = 0.58, O = 0.59 (P = 0.58), P = 0.58, O = 0.59 (P = 0.58), P = 0.59, P = 0.58, O = 0.59 (P = 0.58), P = 0.59, P = 0.58, O = 0.59 (P = 0.58), P = 0.59, P = 0.58, O = 0.59 (P = 0.58), P = 0.59, P = 0.58, O = 0.59 (P = 0.061), P = 0.59, P = 0.58, O = 0.59 (P = 0.59, P = 0.58), P = 0.59, P = 0.58, O = 0.59 (P = 0.59), P = 0.59, P = 0.58, O = 0.59 (P = 0.50), P = 0.59, O = 0.59 (P = 0.58), P = 0.59, O = 0.59 (P = 0.50), P = 0.59, O = 0.59 (P = 0.50), P = 0.59, O = 0.59 (P = 0.50), P = 0.59, O = 0.59 (P = 0.58), P = 0.59, O = 0.	PARAGON-HE	75	2386	101	2367	6.8%	0.74 [0.55 0.99]			
PARAMOUNT 5 149 6 152 1.8% 0.85 [0.27, 2.73] PIONEER-HF 51 440 41 441 5.9% 1.25 [0.84, 1.84] PIME-HF 1 60 2 58 0.5% 0.48 [0.05, 5.19] Subtotal (95% Ct) 7873 7885 31.7% 0.98 [0.76, 1.27] Total events 372 428 Heterogeneity: Tau ² = 0.05; Chi ² = 14.49, df = 7 (P = 0.04); P = 52% Test for overall effect Z = 0.15 (P = 0.88) 10.1.3 Worsening renal function EVALUATE-HF 1 2 231 14 233 3.3% 0.86 [0.41, 1.83] PARADIOM-HF 94 4187 108 4212 6.9% 0.88 [0.68, 1.15] PARADOM-HF 97 2407 109 2389 7.0% 0.89 [0.76, 1.04] PARAMOUNT 5 149 4 152 1.5% 1.28 [0.35, 465] PIONEER-HF 2 60 2 58 0.7% 0.97 [0.14, 6.64] Subtotal (9% Ct) 7585 7597 26.8% 0.97 [0.14, 6.64] Subtotal (9% Ct) 7585 7597 26.8% 0.39 [0.76, 1.04] PARADIOM-HF 14 2407 4 2389 1.9% 3.47 [1.15, 1.054] PARADIOM-HF 14 2407 4 2389 1.9% 3.47 [1.15, 1.054] PARADIOM-HF 14 2407 4 2389 1.9% Not estimable PIONEER-HF 0 111 0 112 Not estimable PIONEER-HF 1 440 6 441 0.6% 0.17 [0.02, 1.38] PRME-HF 0 60 0 56 Not estimable PIONEER-HF 1 1440 6 441 0.6% 0.17 [0.02, 1.38] PRME-HF 0 60 0 56 Not estimable PIONEER-HF 1 1440 6 441 0.6% 0.17 [0.02, 1.38] PRME-HF 0 60 0 56 Not estimable PIONEER-HF 1 1440 6 441 0.6% 0.17 [0.02, 1.38] PRME-HF 0 60 0 56 Not estimable PIONEER-HF 1 1440 6 441 0.8% 0.17 [0.02, 1.38] PRME-HF 0 60 0 56 Not estimable PIONEER-HF 1 1440 6 441 0.6% 1.18 [0.99, 1.40] Total events 334 21 Heterogeneity. Tau ² = 0.07, 0H ² = 30.5, df = 3 (P = 0.0001); P = 68% Test for overall effect Z = 1.38 (P = 0.07) Total events 1331 1184 Heterogeneity. Tau ² = 0.07, 0H ² = 30.58, df = 3 (P = 0.0001); P = 68, 4% Test for overall effect Z = 1.82 (P = 0.07) Favours [experimental] Favours [control]	PARALLEL-HE	0	111	1	112	0.3%	0.34 [0.01 8.17]			
PIONEER-HF 51 440 41 441 5.9% 1.25 [0.84, 1.84] PRIME-HF 1 60 2 58 0.5% 0.48 [0.05, 5.19] Total events 372 428 Heterogenety. Tau* 50.50, ch* 14.49, df = 7 ($P = 0.04$); $P = 52\%$ Test for overall effect Z = 0.15 ($P = 0.88$) 10.1.3 Worsening renal function EVALUATE-HF 12 231 14 233 3.3% 0.88 [0.67, 1.15] PARADIOM-HF 94 4187 108 4212 6.9% 0.88 [0.67, 1.15] PARADIOM-HF 97 2407 109 2389 7.0% 0.88 [0.68, 1.15] PARADIOM-HF 97 2407 109 2389 7.0% 0.88 [0.81, 1.5] PARADIOM-HF 12 6.0 2 58 0.7% 0.97 [0.14, 6.64] Subtotal (95% CI) 7585 7597 26.8% 0.89 [0.76, 1.04] Total events 272 306 Heterogeneity: Tau* = 0.00, Ch* = 0.82, df = 6 (P = 0.99); P = 0% Test for overall effect Z = 1.43 (P = 0.15) 10.1 Angloedema EVALUATE-HF 0 231 1 233 0.3% 0.34 (0.01, 8.21] PARADIOM-HF 14 2407 4 2389 1.9% 0.34 [10.18, 8.41] PARADIOM-HF 14 4207 4 2389 1.9% 0.34 [0.01, 8.21] PARADIOM-HF 14 4207 4 2389 1.9% 0.34 [0.01, 8.21] PARADICH-HF 0 6 60 0 5 8 Notestimable Subtotal (95% CI) 7436 7445 6.0% 1.25 [0.40, 3.95] Total events 34 21 Heterogeneity. Tau* = 0.00, Ch* = 0.50, df = 20 6 P < 0.0001); P = 65% Test for overall effect Z = 1.82 (P = 0.07) Est for subroup differences: Ch* = 2.053, df = 20 (P < 0.0001); P = 654%.	PARAMOUNT	5	149	6	152	1.8%	0.85 [0.27, 2.73]			
PRIME-HF 1 1 60 1 7873 7885 31.7% 0.38 [0.05, 5.19] Subtotal (95% Ct) 7873 7873 7885 31.7% 0.38 [0.05, 5.19] Otal events 372 428 Heterogeneity: Tau" = 0.05, Ch"= 1.4.49, d" = 7 (P = 0.04); P = 52% Test for overall effect Z = 0.15 (P = 0.88) 10.1.3 Worsening renal function EVALUATE-HF 1 2 231 14 233 3.3% 0.86 [0.41, 1.83] PARADIOM-HF 94 4187 108 4212 6.9% 0.88 [0.68, 1.15] PARADIOM-HF 94 4187 108 4212 6.9% 0.88 [0.61, 1.15] PARADIOM-HF 97 2407 109 2389 7.0% 0.88 [0.61, 1.15] PARADIOM-HF 92 111 4 112 1.0% 0.50 [0.09, 2.70] PARADIOM-HF 2 0.15 (P = 0.89; P = 0.85; P = 0.00; P = 6.95; P = 0.85; P = 0.00; P = 0.85; P = 0.85; P = 0.85; P = 0.85; P = 0.00; P = 0.85; P = 0.85; P = 0.85; P = 0.85; P = 0.00; P = 0.85; P = 0.00; P = 0.	PIONEER-HE	51	440	41	441	5.9%	1 25 [0 84 1 84]			
Subiotal (95% CI) 7873 7885 31.7% 0.98 [0.76, 1.27] Total events 372 428 Heterogeneity: Tau* 0.05; Ch* 14.49, df = 7 (P = 0.04); P = 52% Test for overall effect Z = 0.15 (P = 0.88) 10.1.3 Worsening renal function EVALUATE-HF 12 231 14 233 3.3% 0.86 [0.41, 1.83] PARADIGM-HF 94 4187 108 4212 6.9% 0.88 [0.67, 1.15] PARAOON-HF 97 2407 109 2389 7.0% 0.88 [0.68, 1.16] PARAOUNT 5 149 4 152 1.5% 1.28 [0.35, 4.66] PIONEER-HF 60 440 65 441 6.5% 0.93 (0.57, 1.28] PIME-HF 2 60 2 58 0.7% 0.97 [0.14, 6.64] Subtotal (95% CI) 7585 7597 26.8% 0.89 [0.76, 1.04] PARADIGM-HF 19 4187 10 4212 3.2% 1.91 [0.89, 4.11] PARADIGM-HF 19 4.187 10 4212 3.2% 1.91 [0.89, 4.11] PARADIGM-HF 19 4.187 10 4212 3.2% 1.91 [0.89, 4.11] PARADIGM-HF 19 4.187 10 4.212 3.2% 1.91 [0.89, 4.11] PARADIGM-HF 19 4.187 10 4.212 3.2% 1.91 [0.89, 4.11] PARADIGM-HF 19 4.187 10 4.212 3.2% 1.91 [0.89, 4.11] PARADIGM-HF 10 5.00 5.8 Not estimable Subtotal (95% CI) 7436 7445 6.0% 1.25 [0.40, 3.95] Total events 1331 1184 Heterogeneity: Tau* = 0.03; (Ch* = 8.059, df = 2.8 (P = 0.0001); P = 68% Test for overail effect Z = 1.82 (P = 0.0000); P = 68% Test for overail effect Z = 0.53	PRIME-HE	1	60	2	58	0.5%	0.48 (0.05, 5.19)			
Total events 372 428 Heterogeneity: Tau ² = 0.05, Ch ² = 14.49, df = 7 (P = 0.04), P = 52% Test for overail effect Z = 0.15 (P = 0.88) 10.1.3 Worsening renal function EVALUATE-HF 12 231 14 233 3.3% 0.86 [0.41, 1.83] PARADOM-HF 94 4187 108 4212 6.9% 0.88 [0.67, 1.15] PARADOM-HF 97 2407 109 2389 7.0% 0.88 [0.67, 1.15] PARAMOUNT 5 149 4 152 1.5% 1.28 [0.5, 66] PIONEER-HF 60 440 65 441 6.5% 0.93 [0.67, 1.28] PRIME-HF 2 60 2 58 0.7% 0.97 [0.14, 6.64] Subtotal (65% cl) 7585 7597 26.8% 0.89 [0.76, 1.04] Total events 272 306 Heterogeneity: Tau ² = 0.00, Ch ² = 0.82, df = 6 (P = 0.99); P = 0% Test for overail effect Z = 1.43 (P = 0.15) 10.1.4 Angioedema EVALUATE-HF 0 111 0 112 Not estimable PIONEER-HF 1 4400 6 441 0.6% 0.17 [0.02, 1.38] PARADOM-HF 14 2407 4 2389 1.9% 3.47 [1.15, 10.54] PARADOM-HF 14 2407 4 2389 1.9% 3.47 [1.15, 10.54] PARADOM-HF 14 2407 4 2389 1.9% 3.47 [1.5, 10.54] PARADOM-HF 14 2407 4 2389 1.9% 3.47 [1.5, 10.54] PARADOM-HF 14 2407 4 2389 1.9% 3.47 [1.5, 10.54] PARADOM-HF 1 4 2407 4 2389 1.9% 3.47 [1.5, 10.54] PARADOM-HF 1 4 2407 4 2389 1.9% 3.47 [1.5, 10.54] PARADOM-HF 1 4 2407 4 2389 1.9% 3.47 [1.5, 10.54] PARADOM-HF 1 4 2407 4 2389 1.9% 3.47 [1.5, 10.54] PARADOM-HF 1 4 2407 4 2389 1.9% 3.47 [1.5, 10.54] PARADOM-HF 1 4 2407 4 2389 1.9% 3.47 [1.5, 10.54] PARADOM-HF 1 4 2407 4 2389 1.9% 3.47 [1.5, 10.54] PARADOM-HF 1 4 2407 4 2389 1.9% 3.47 [1.5, 10.54] PARADOM-HF 1 4 2407 4 2389 1.9% 3.47 [1.5, 10.54] PARADOM-HF 1 4 2407 4 2389 1.9% 3.47 [1.5, 10.54] PARADOM-HF 1 1 440 6 441 0.6% 0.17 [0.0, 1.38] PARADOM-HF 1 1 440 7 4 238 7.445 6.0% 1.25 [0.40, 3.95] Total events 3 3 1 1184 Heterogeneity: Tau ² = 0.73 (Ch ² = 7.38, df = 3 (P = 0.000); P = 68% Test for overail effect Z = 0.38 (P = 0.07) Favours [experimental] Favours [control] Favours [experimental] Favours [control]	Subtotal (95% CI)		7873	~	7885	31.7%	0.98 [0.76, 1.27]	★		
Heterogeneity: Tau ² = 0.05; Chi ² = 14.49, df = 7 (P = 0.04); P = 52% Test for overall effect Z = 0.15 (P = 0.08) 10.13 Worsening renal function EVALUATE: HF 12 231 14 233 3.3% 0.86 [0.41, 1.83] PARADIGM-HF 97 2407 109 2389 7.0% 0.88 [0.67, 1.15] PARAQON-HF 97 2407 109 2389 7.0% 0.88 [0.68, 1.15] PARAQON-HF 97 2407 109 2389 7.0% 0.88 [0.68, 1.15] PARALLEL-HF 2 111 4 112 1.0% 0.50 [0.09, 2.70] PARAMOUNT 5 149 4 152 1.5% 1.28 [0.35, 4.66] PRIME-HF 60 440 65 441 6.5% 0.93 [0.67, 1.28] PRIME-HF 60 440 65 441 6.5% 0.93 [0.67, 1.04] POINEER-HF 60 440 65 441 6.5% 0.93 [0.76, 1.04] Total events 272 306 Heterogeneity: Tau ² = 0.00; Chi ² = 0.82, df = 6 (P = 0.99); P = 0% Test for overall effect Z = 1.43 (P = 0.15) 10.14 Angiodema EVALUATE: HF 0 231 1 233 0.3% 0.34 [0.01, 8.21] PARADIGM-HF 19 4187 10 4212 3.2% 1.91 [0.89, 4.11] PARAGON-HF 14 2407 4 2389 1.9% 3.47 [1.15, 10.54] PARADIGM-HF 19 4187 10 4212 3.2% 1.91 [0.89, 4.11] PARADIGM-HF 19 4187 10 4212 3.2% 1.91 [0.80, 4.11] PARADIGM-HF 19 4187 10 4212 3.2% 1.91 [0.90, 4.13] PARADIGM-HF 19 4187 10 4212 3.2% 1.91 [0.90, 4.13] PARADIGM-HF 19 4407 4 2.98 1.95 3.047 [0.02, 1.38] PARADIGM-HF 19 4407 4 2.95 9.0000; P = 59% Test for overall effect Z = 0.38 (P = 0.000); P = 59% Test for overall effect Z = 1.52 (P = 0.0001); P = 68% Test for overall effect Z = 1.52 (P = 0.0001); P = 68% Test for overall effect Z = 0.53, df = 3 (P = 0.0001); P = 684%	Total events	372		428						
Test for overall effect. $Z = 0.15$ (P = 0.88) 10.1.3 Worsening renal function EVALUATE-HF 12 231 14 233 3.3% 0.86 [0.41, 1.83] PARADIOM-HF 94 4187 108 4212 6.9% 0.88 [0.67, 1.15] PARALEL-HF 2 111 4 112 1.0% 0.50 [0.09, 2.70] PARAMONT 5 149 4 152 1.5% 1.28 [0.35, 4.66] PIONEER-HF 60 440 65 441 6.5% 0.93 [0.67, 1.28] PRIME-HF 2 60 2 58 0.7% 0.97 [0.14, 6.64] Subtotal (95% CI) 7585 7597 26.8% 0.89 [0.76, 1.04] Total events 272 306 Heterogeneity: Tau ² = 0.09; Chi ² = 0.82; df = 6 (P = 0.09); P = 0% Test for overall effect Z = 1.43 (P = 0.15) 10.1.4 Angioedema EVALUATE-HF 0 231 1 233 0.3% 0.34 [0.01, 8.21] PARAGOM-HF 14 2407 4 2389 1.9% 3.47 [1.15, 10.54] PARAGOM-HF 14 2407 4 2389 1.9% 3.47 [1.15, 10.54] PARAGOM-HF 14 4407 4 2389 1.9% 3.47 [1.15, 10.54] PARAGOM-HF 14 4407 6 441 0.6% 0.17 [10.2, 1.38] Not estimable PIONEER-HF 0 60 0 58 Not estimable PIONEER-HF 1 440 6 441 0.6% 1.125 [0.40, 3.95] Total events 34 21 Heterogeneity: Tau ² = 0.70; Chi ² = 7.38, df = 3 (P = 0.06); P = 59% Test for overall effect Z = 1.52 (P = 0.07) Total events 1331 1184 Heterogeneity: Tau ² = 0.09; Chi ² = 80,59, df = 26 (P = 0.0001); P = 68% Test for overall effect Z = 1.52 (P = 0.07) Total events 1331 1184 Heterogeneity: Tau ² = 0.09; Chi ² = 0.053, df = 3 (P = 0.0001); P = 68% Test for overall effect Z = 1.52 (P = 0.07) Favours [experimental] Favours [control]	Heterogeneity: Tau ² =	0.05; Chi ² =	14.49, df = 7	7 (P = 0.04);	l² = 52%					
10.1.3 Worsening renal function EVALUATE-HF 12 231 14 233 3.3% 0.86 [0.41, 1.83] PARADIGM-HF 94 4187 108 4212 6.9% 0.88 [0.67, 115] PARADIGM-HF 97 2407 109 2389 7.0% 0.88 [0.67, 115] PARALLEL-HF 2 111 4 112 1.0% 0.50 [0.09, 2.70] PARALLEL-HF 2 111 4 152 1.5% 1.28 [0.35, 4.66] PIONEER-HF 60 440 65 441 6.5% 0.97 [0.14, 6.64] Subtotal (95% CI) 7585 7597 26.8% 0.39 [0.76, 1.04] 0.440 PARADIGM-HF 19 2.31 1 2.33 0.34 0.34 [0.01, 8.21] PARADIGM-HF 14 2407 4 2389 1.9% 3.47 [1.15, 10.54] PARADIGM-HF 14 2407 4 2389 1.9% 3.47 [1.15, 10.54] PARADIGM-HF 14 2407 4 2389 1.91 [0.88, 4.11] 1.12 PARADIGM-HF 14	Test for overall effect:	Z = 0.15 (P =	0.88)							
10.1.3 Worsening renal function EVALUATE-HF 12 231 14 233 3.3% 0.86 [0.41, 1.83] PARADIGM-HF 94 4187 108 4212 6.9% 0.88 [0.67, 1.15] PARADIGM-HF 97 2407 109 2389 7.0% 0.88 [0.67, 1.15] PARALEL-HF 2 111 4 112 1.0% 0.50 [0.08, 2.70] PARADIONT 5 149 4 152 1.5% 1.28 [0.35, 4.66] PINDE-HF 2 60 2 58 0.7% 0.87 [0.14, 6.64] Subtoal (95% CI) 7585 7597 26.8% 0.89 [0.76, 1.04] 0 Total events 272 306 Heterogeneity: Tau" = 0.00; Chi" = 0.82, df = 6 (P = 0.99); P = 0% Test for overall effect Z = 1.43 (P = 0.15) 10 110 0.34 [0.01, 8.21] 0.34 [0.01, 8.21] 0 PARADIGM-HF 19 4187 10 2389 1.9% 3.47 [1.15, 10.54] 0.34 [0.01, 8.21] 0 0 0 0 0 0 0 0 0 0 0 0 0 <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td>										
$ \begin{array}{c c c c c c c c c c c c c c c c c c c $	10.1.3 Worsening rer	nal function								
PARADIGM-HF 94 4187 108 4212 6.9% 0.88 [0.67, 1.15] PARAGON-HF 97 2407 109 2389 7.0% 0.88 [0.67, 1.15] PARALLEL-HF 2 111 4 112 1.0% 0.50 [0.09, 2.70] PARAMOUNT 5 149 4 152 1.5% 1.28 [0.35, 4.66] PIONEER-HF 60 440 65 441 6.5% 0.39 [0.76, 1.28] PIONEER-HF 2 2 60 2 58 0.7% 0.37 [0.14, 6.64] Subtotal (95% CI) 7585 7597 26.8% 0.89 [0.76, 1.04] Total events 272 306 Heterogeneity: Tau ² = 0.00; Chl ² = 0.82, df = 6 (P = 0.99); P = 0% Test for overall effect $Z = 1.43$ ($P = 0.15$) Total events 34 21 PARADIGM-HF 1 440 6 441 0.6% 0.17 [0.02, 1.38] PRIME-HF 0 60 0 58 Notestimable Subtotal (95% CI) 7436 7445 6.0% 1.25 [0.40, 3.95] Total events 34 21 Heterogeneity: Tau ² = 0.09; Chl ² = 80.59, df = 26 (P < 0.0001); P = 59% Test for overall effect $Z = 1.82$ ($P = 0.07$) Total events 1331 1184 Heterogeneity: Tau ² = 0.09; Chl ² = 80.59, df = 26 (P < 0.00001); P = 68% Test for overall effect $Z = 1.82$ ($P = 0.07$) Total events 1331 1184 Heterogeneity: Tau ² = 0.09; Chl ² = 80.59, df = 26 (P < 0.00001); P = 68% Test for overall effect $Z = 1.82$ ($P = 0.07$) Total events 1331 1184	EVALUATE-HF	12	231	14	233	3.3%	0.86 [0.41, 1.83]			
PARAGON-HF 97 2407 109 2389 7.0% 0.88 [0.68, 1.15] PARALEL-HF 2 111 4 112 1.0% 0.50 [0.09, 2.70] PARAMOUNT 5 149 4 152 1.5% 1.28 [0.35, 4.66] PIONEER-HF 60 440 65 441 6.5% 0.39 [0.76, 1.28] PRIME-HF 2 60 2 58 0.7% 0.89 [0.76, 1.04] PRIME-HF 2 60 2 58 0.7% 0.89 [0.76, 1.04] Total events 272 306 Heterogeneity: Tau ² = 0.00; Chi ² = 0.82, df = 6 (P = 0.99); l ² = 0% Test for overall effect: Z = 1.43 (P = 0.15) 10.1.4 Angioedema EVALUATE-HF 0 231 1 233 0.3% 0.34 [0.01, 8.21] PARADIGM-HF 19 4187 10 4212 3.2% 1.91 [0.89, 4.11] PARADIGM-HF 14 2407 4 2389 1.9% 3.47 [1.15, 10.54] PARALEL-HF 0 111 0 112 Not estimable PIONEER-HF 1 440 6 441 0.6% 0.17 [0.02, 1.38] PRIME-HF 0 60 0 58 Not estimable PIONEER-HF 1 440 6 7445 6.0% 1.25 [0.40, 3.95] Total events 34 21 Heterogeneity: Tau ² = 0.73; Chi ² = 7.38, df = 3 (P = 0.000); l ² = 59% Test for overall effect: Z = 1.82 (P = 0.07) Total events 1331 1184 Heterogeneity: Tau ² = 0.09; Chi ² = 80.59, df = 26 (P < 0.00001); l ² = 68% Test for overall effect: Z = 1.82 (P = 0.07) Total events 1331 1184 Heterogeneity: Tau ² = 0.09; Chi ² = 20.53, df = 26 (P < 0.00001); l ² = 68% Test for overall effect: Z = 1.82 (P = 0.07) Total events 1331 1184 Heterogeneity: Tau ² = 0.09; Chi ² = 20.53, df = 26 (P < 0.00001); l ² = 68%	PARADIGM-HF	94	4187	108	4212	6.9%	0.88 [0.67, 1.15]			
PARALLEL-HF 2 111 4 112 1.0% 0.50 [0.09, 2.70] PARAMOUNT 5 149 4 152 1.5% 1.28 [0.35, 4.66] PIONEER-HF 60 440 65 441 6.5% 0.33 [0.67, 1.28] PRIME-HF 2 60 2 58 0.7% 0.37 [0.14, 6.64] Subtotal (95% CI) 7585 7597 26.8% 0.89 [0.76, 1.04] Total events 272 306 Heterogeneity: Tau ² = 0.00; ChF = 0.82, df = 6 (P = 0.99); I ² = 0% Test for overall effect: Z = 1.43 (P = 0.15) 10.1.4 Angioedema EVALUATE-HF 0 231 1 233 0.3% 0.34 [0.01, 8.21] PARADIGM-HF 19 4187 10 4212 3.2% 1.91 [0.89, 4.11] PARADIGM-HF 14 2407 4 2389 1.9% 3.47 [1.15, 10.54] PARADIGM-HF 14 42407 4 2389 1.9% 3.47 [1.15, 10.54] PARALLEL-HF 0 111 0 112 Not estimable PIONEER-HF 1 4440 6 441 0.6% Not estimable PIONEER-HF 0 60 0 58 Not estimable Subtotal (95% CI) 7436 7445 6.0% 1.25 [0.40, 3.95] Total events 34 21 Heterogeneity: Tau ² = 0.03; ChF = 7.38, df = 3 (P = 0.006); I ² = 59% Test for overall effect: Z = 1.82 (P = 0.70) Total events 1331 1184 Heterogeneity: Tau ² = 0.09; ChF = 80.59, df = 26 (P < 0.00001); I ² = 68% Test for overall effect: Z = 0.53 df = 3 (P = 0.0001), I ² = 85.4%	PARAGON-HF	97	2407	109	2389	7.0%	0.88 [0.68, 1.15]			
PARAMOUNT 5 149 4 152 1.5% 1.28 [0.35, 4.66] PIONEER-HF 60 440 65 441 6.5% 0.93 [0.67, 1.28] PRIME-HF 2 60 2 58 0.7% 0.97 [0.14, 6.64] Subtotal (95% CI) 7585 7597 26.8% 0.89 [0.76, 1.04] Total events 272 306 Heterogeneity: Tau ² = 0.00; Chi ² = 0.82, df = 6 (P = 0.99); i ² = 0% Test for overall effect Z = 1.43 (P = 0.15) 10.1.4 Angioedema EVALUATE-HF 0 231 1 233 0.3% 0.34 [0.01, 8.21] PARADIGM-HF 19 4187 10 4212 3.2% 1.91 [0.89, 4.11] PARAOON-HF 14 2407 4 2389 1.9% 3.47 [1.15, 10.54] PARAALLEL-HF 0 111 0 112 Not estimable PIONEER-HF 1 440 6 441 0.6% 0.17 [10.02, 1.38] PRIME-HF 0 60 0 58 Not estimable PIONEER-HF 1 440 6 1421 0.6% 1.25 [0.40, 3.95] Total events 34 21 Heterogeneity: Tau ² = 0.73; Chi ² = 7.38, df = 3 (P = 0.000); i ² = 59% Test for overall effect Z = 0.38 (P = 0.70) Total events 1331 1184 Heterogeneity: Tau ² = 0.09; Chi ² = 80.59, df = 26 (P < 0.00001); i ² = 68% Test for overall effect Z = 1.82 (P = 0.07) Total events 1331 1184 Heterogeneity: Tau ² = 0.09; Chi ² = 20,53, df = 3 (P = 0.0001); i ² = 68% Test for overall effect Z = 1.82 (P = 0.07) Total events 1331 1184 Heterogeneity: Tau ² = 0.09; Chi ² = 80.59, df = 26 (P < 0.00001); i ² = 68% Test for overall effect Z = 1.82 (P = 0.07) Total events 1331 1184 Heterogeneity: Tau ² = 0.09; Chi ² = 20,53, df = 3 (P = 0.0001); i ² = 68%	PARALLEL-HF	2	111	4	112	1.0%	0.50 [0.09, 2.70]			
PIONEER-HF 60 440 65 441 6.5% 0.93 ($0.67, 1.28$) PRIME-HF 2 60 2 58 0.7% 0.97 ($0.14, 6.64$] Subtotal (95% CI) 7585 7597 26.8% 0.89 [$0.76, 1.04$] Total events 272 306 Heterogeneily: Tau ² = 0.00; Chi ² = 0.82, df = 6 (P = 0.99); P = 0% Test for overall effect Z = 1.43 (P = 0.15) 10.1.4 Angioedema EVALUATE-HF 0 231 1 233 0.3% 0.34 ($0.01, 8.21$] PARADIOM-HF 19 4187 10 4212 3.2% 1.91 ($0.89, 4.11$] PARAGON-HF 14 2407 4 2389 1.9% 3.47 ($1.15, 10.54$] PARALEL-HF 0 111 0 112 Not estimable PIONEER-HF 1 440 6 441 0.6% 0.17 ($0.02, 1.38$] PRIME-HF 0 60 0 58 Not estimable Subtotal (95% CI) 7436 7445 6.0% 1.25 ($0.40, 3.95$] Total events 34 21 Heterogeneity: Tau ² = 0.73; Chi ² = 7.38, df = 3 (P = 0.06); P = 59% Test for overall effect Z = 0.38 (P = 0.70) Total events 1331 1184 Heterogeneity: Tau ² = 0.09; Chi ² = 80.59, df = 26 (P < 0.00001); P = 68% Test for overall effect Z = 1.82 (P = 0.07) Total events 1331 1184 Heterogeneity: Tau ² = 0.09; Chi ² = 80.59, df = 26 (P < 0.00001); P = 85.4%	PARAMOUNT	5	149	4	152	1.5%	1.28 [0.35, 4.66]			
PRIME-HF 2 60 2 58 0.7% 0.97 [0.14, 6.64] Subtotal (95% CI) 7585 7597 26.8% 0.89 [0.76, 1.04] Total events 272 306 Heterogeneily: Tau ² = 0.00; Chi ² = 0.82, df = 6 (P = 0.99); I ² = 0% 0.89 [0.76, 1.04] Test for overall effect Z = 1.43 (P = 0.15) 0 10.1.4 Angioedema 2000 Chi ² = 0.231 1 233 0.3% 0.34 [0.01, 8.21] PARADIGM-HF 19 4187 10 4212 3.2% 1.91 [0.89, 4.11] PARALEL-HF 0 111 0 112 Not estimable PIONEER-HF 1 440 6 441 0.6% 0.17 [0.02, 1.38] PRIME-HF 0 60 0 58 Not estimable Subtotal (95% CI) 7436 7445 6.0% 1.25 [0.40, 3.95] Total events 1331 1184 1184 1.18 [0.99, 1.40] Heterogeneity: Tau ² = 0.09; Chi ² = 80.59, df = 26 (P < 0.00001); I ² = 68% 1.18 [0.99, 1.40] 1.00 1.00 Total events 1331 1184 166% 1.25 [0.40,	PIONEER-HF	60	440	65	441	6.5%	0.93 [0.67, 1.28]			
Subtoral (95% CI) 7585 7597 26.8% 0.89 [0.76, 1.04] Total events 272 306 Heterogeneity: Tau ² = 0.00; Chi ² = 0.82, df = 6 (P = 0.99); P = 0% Test for overall effect Z = 1.43 (P = 0.15) 10.1.4 Angioedema EVALUATE-HF 0 PARADIGM-HF 19 4187 10 4212 3.2% 1.91 [0.89, 4.11] PARADIGM-HF 14 2407 4 2389 1.9% 3.47 [1.15, 10.54] PARALLEL-HF 0 111 0 112 Not estimable PIONEER-HF 1 440 6 441 0.6% 0.17 [0.02, 1.38] PRIME-HF 0 60 0 58 Not estimable PIONEER-HF 1 440 6 441 0.6% Subtotal (95% CI) 7436 7445 6.0% 1.25 [0.40, 3.95]	PRIME-HF	2	60	2	58	0.7%	0.97 [0.14, 6.64]			
I otal events $2/2$ 306 Heterogeneity: Tau ² = 0.00; Chi ² = 0.82, df = 6 (P = 0.99); P = 0% Test for overall effect Z = 1.43 (P = 0.15) 10.1.4 Angioedema EVALUATE-HF 0 231 1 233 0.3% 0.34 [0.01, 8.21] PARADIGM-HF 19 4187 10 4212 3.2% 1.91 [0.89, 4.11] PARADIGM-HF 14 2407 4 2389 1.9% 3.47 [1.15, 10.54] PARADIGM-HF 14 2407 4 2389 1.9% 3.47 [1.15, 10.54] PARADIGM-HF 14 2407 4 2389 1.9% 3.47 [1.15, 10.54] PARADIGM-HF 14 440 6 441 0.6% 0.17 [0.02, 1.38] PRIME-HF 0 60 58 Not estimable Subtotal (95% CI) 7436 7445 6.0% 1.25 [0.40, 3.95] Total events 34 21 1.98 1.18 [0.99, 1.40] 1.01 1.0 Total (95% CI) 30788 30834 100.0% 1.18 [0.99, 1.40] 1.01 1.01 1.00 100 Fa	Subtotal (95% CI)		7585		7597	26.8%	0.89[0.76, 1.04]	•		
Heterogeneity: Tau" = 0.00; Chi" = 0.82, df = 6 (P = 0.99); P = 0% Test for overall effect: $Z = 1.43$ (P = 0.15) 10.14 Angioedema EVALUATE-HF 0 231 1 233 0.3% 0.34 [0.01, 8.21] PARADIGM-HF 19 4187 10 4212 3.2% 1.91 [0.89, 4.11] PARAGON-HF 14 2407 4 2389 1.9% 3.47 [1.15, 10.54] PARALLEL-HF 0 111 0 112 Not estimable PIONEER-HF 1 440 6 441 0.6% 0.17 [0.02, 1.38] PRIME-HF 0 60 0 58 Not estimable Subtotal (95% CI) 7436 7445 6.0% 1.25 [0.40, 3.95] Total events 34 21 Heterogeneity: Tau" = 0.73; Chi" = 7.38, df = 3 (P = 0.06); I" = 59% Test for overall effect: $Z = 0.38$ (P = 0.70) Total events 1331 1184 Heterogeneity: Tau" = 0.09; Chi" = 80.59, df = 26 (P < 0.00001); I" = 68% Test for overall effect: $Z = 1.82$ (P = 0.07) Test for subgroup differences: Chi" = 20.53, df = 3 (P = 0.0001), I" = 85.4%	Total events	272		306						
10.1.4 Angioedema EVALUATE-HF 0 231 1 233 0.3% 0.34 [0.01, 8.21] PARADIGM-HF 19 4187 10 4212 3.2% 1.91 [0.89, 4.11] PARADIGM-HF 14 2407 4 2389 1.9% 3.47 [1.15, 10.54] PARADLEL-HF 0 111 0 112 Not estimable PIONEER-HF 1 440 6 441 0.6% 0.17 [0.02, 1.38] PRIME-HF 0 60 0 58 Not estimable Subtotal (95% Cl) 7436 7445 6.0% 1.25 [0.40, 3.95] Total events 34 21 Heterogeneity: Tau ² = 0.73; Chi ² = 7.38, df = 3 (P = 0.06); I ² = 59% 1.18 [0.99, 1.40] Total (95% Cl) 30788 30834 100.0% 1.18 [0.99, 1.40] Total events 1331 1184 110 100 Heterogeneity: Tau ² = 0.09; Chi ² = 80.59, df = 26 (P < 0.0001); I ² = 68% 0.01 0.1 10 Test for overall effect: Z = 1.82 (P = 0.07) 10 10 10 100 Favours [experime	Heterogeneity: Tau-=	7-1 42 /P-	0.82, 01 = 6 0.15)	(P = 0.99); F	= 0%					
10.1.4 Angioedema EVALUATE-HF 0 231 1 233 0.3% 0.34 [0.01, 8.21] PARADIGM-HF 19 4187 10 4212 3.2% 1.91 [0.89, 4.11] PARAGON-HF 14 2407 4 2389 1.9% 3.47 [1.15, 10.54] PARALLEL-HF 0 111 0 112 Not estimable PIONEER-HF 1 440 6 441 0.6% 0.17 [0.02, 1.38] PRIME-HF 0 60 0 58 Not estimable PIONEER-HF 1 440 6 1.25 [0.40, 3.95] Total events 34 21 Heterogeneity: Tau ² = 0.73; Chi ² = 7.38, df = 3 (P = 0.06); I ² = 59% 1.25 [0.40, 3.95] Total events 1331 1184 Heterogeneity: Tau ² = 0.09; Chi ² = 80.59, df = 26 (P < 0.00001); I ² = 68% 1.18 [0.99, 1.40] Test for overall effect: Z = 1.82 (P = 0.07) 10 10 Test for subgroup differences: Chi ² = 20.53, df = 3 (P = 0.0001), I ² = 85.4% Favours [experimental] Favours [control]	restion overall ellect.	Z = 1.43 (F =	0.13)							
EVALUATE-HF 0 231 1 233 0.3% 0.34 [0.01, 8.21] PARADIGM-HF 19 4187 10 4212 3.2% 1.91 [0.89, 4.11] PARAGON-HF 14 2407 4 2389 1.9% 3.47 [1.15, 10.54] PARACULEL-HF 0 111 0 112 Not estimable PIONEER-HF 1 440 6 441 0.6% 0.17 [0.02, 1.38] PRIME-HF 0 60 0 58 Not estimable PIONEER-HF 1 440 6 441 0.6% 0.17 [0.02, 1.38] PRIME-HF 0 60 0 58 Not estimable Subtoal (95% CI) 7436 7445 6.0% 1.25 [0.40, 3.95] Total events 34 21 Heterogeneity: Tau ² = 0.73; Chi ² = 7.38, df = 3 (P = 0.06); l ² = 59% 1.18 [0.99, 1.40] Total (95% CI) 30788 30834 100.0% 1.18 [0.99, 1.40] Total events 1331 1184 100 10 100 100 100 100 Test fo	10.1.4 Angioedema									
PARADIGM-HF 19 4187 10 4212 3.2% 1.91 [0.89, 4.11] PARAGON-HF 14 2407 4 2389 1.9% 3.47 [1.15, 10.54] PARALLEL-HF 0 111 0 112 Not estimable PIONEER-HF 1 440 6 441 0.6% 0.17 [0.02, 1.38] PRIME-HF 0 60 0 58 Not estimable Subtoal (95% CI) 7436 7445 6.0% 1.25 [0.40, 3.95] Total events 34 21 Heterogeneity: Tau ² = 0.73; Chi ² = 7.38, df = 3 (P = 0.06); l ² = 59% 1.82 [0.40, 3.95] Total events 34 21 1184 1184 Heterogeneity: Tau ² = 0.09; Chi ² = 80.59, df = 26 (P < 0.00001); l ² = 68% 1.18 [0.99, 1.40] 0.01 0.1 10 Total events 1331 1184 1184 10 100 100 100 Test for subgroup differences: Chi ² = 20.53, df = 3 (P = 0.0001); l ² = 85.4% 54.4% 100 10 100 Favours [control]	EVALUATE-HF	0	231	1	233	0.3%	0.34 [0.01, 8.21]			
PARAGON-HF 14 2407 4 2389 1.9% 3.47 [1.15, 10.54] PARALLEL-HF 0 111 0 112 Not estimable PIONEER-HF 1 440 6 441 0.6% 0.17 [0.02, 1.38] PRIME-HF 0 60 58 Not estimable Subtotal (95% CI) 7436 7445 6.0% 1.25 [0.40, 3.95] Total events 34 21 Heterogeneity: Tau ² = 0.73; Chi ² = 7.38, df = 3 (P = 0.06); l ² = 59% 7445 6.0% 1.25 [0.40, 3.95] Total events 34 21 Heterogeneity: Tau ² = 0.73; Chi ² = 7.38, df = 3 (P = 0.06); l ² = 59% 1.18 [0.99, 1.40] 1.18 [0.99, 1.40] Total events 1331 1184 1184 1.18 [0.99, 1.40] 1.01 100 Test for overall effect: Z = 1.82 (P = 0.07) Test for subgroup differences: Chi ² = 20.53, df = 3 (P = 0.0001); l ² = 85.4% 1.20 100 100 Favours [experimental] Favours [control] Favours [control] Favours [control] 100	PARADIGM-HF	19	4187	10	4212	3.2%	1.91 [0.89, 4.11]			
PARALLEL-HF 0 111 0 112 Not estimable PIONEER-HF 1 440 6 441 0.6% 0.17 [0.02, 1.38] PRIME-HF 0 60 0 58 Not estimable Subtotal (95% Cl) 7436 7445 6.0% 1.25 [0.40, 3.95] Total events 34 21 Heterogeneity: Tau ² = 0.73; Chi ² = 7.38, df = 3 (P = 0.06); l ² = 59% 1.25 [0.40, 3.95] Total events 34 21 Heterogeneity: Tau ² = 0.73; Chi ² = 7.38, df = 3 (P = 0.06); l ² = 59% 1.25 [0.40, 3.95] Total (95% Cl) 30788 30834 100.0% Total events 1331 1184 Heterogeneity: Tau ² = 0.09; Chi ² = 80.59, df = 26 (P < 0.00001); l ² = 68% 1.18 [0.99, 1.40] Test for overall effect: $Z = 1.82$ ($P = 0.07$) 100 Test for subgroup differences: Chi ² = 20.53, df = 3 (P = 0.0001), l ² = 85.4% Favours [experimental]	PARAGON-HF	14	2407	4	2389	1.9%	3.47 [1.15, 10.54]			
PIONEER-HF 1 440 6 441 0.6% 0.17 [0.02, 1.38] PRIME-HF 0 60 0 58 Not estimable Subtotal (95% Cl) 7436 7445 6.0% 1.25 [0.40, 3.95] Total events 34 21 Heterogeneity: Tau ² = 0.73; Chi ² = 7.38, df = 3 (P = 0.06); I ² = 59% 1.25 [0.40, 3.95] Total events 34 21 Heterogeneity: Tau ² = 0.73; Chi ² = 7.38, df = 3 (P = 0.06); I ² = 59% 1.25 [0.40, 3.95] Total (95% Cl) 30788 30834 100.0% Total (95% Cl) 30788 30834 100.0% Total events 1331 1184 Heterogeneity: Tau ² = 0.09; Chi ² = 80.59, df = 26 (P < 0.00001); I ² = 68% 0.01 0.1 Test for overall effect: Z = 1.82 (P = 0.07) 100 100 Favours [experimental] Favours [control] Favours [control]	PARALLEL-HF	0	111	0	112		Not estimable			
PRIME-HF 0 60 0 58 Not estimable Subtotal (95% Cl) 7436 7445 6.0% 1.25 [0.40, 3.95] Total events 34 21 Heterogeneity: Tau ² = 0.73; Chi ² = 7.38, df = 3 (P = 0.06); I ² = 59% Test for overall effect: $Z = 0.38$ (P = 0.70) Total (95% Cl) 30788 30834 100.0% 1.18 [0.99, 1.40] Total events 1331 1184 Heterogeneity: Tau ² = 0.09; Chi ² = 80.59, df = 26 (P < 0.00001); I ² = 68% 1.18 [0.99, 1.40] Test for overall effect: $Z = 1.82$ ($P = 0.07$) Test for subgroup differences: Chi ² = 20.53, df = 3 (P = 0.0001); I ² = 85.4% Favours [experimental]	PIONEER-HF	1	440	6	441	0.6%	0.17 [0.02, 1.38]			
Subtotal (95% Cl) 7436 7445 6.0% 1.25 [0.40, 3.95] Total events 34 21 Heterogeneity: Tau ² = 0.73; Chi ² = 7.38, df = 3 (P = 0.06); I ² = 59% Test for overall effect: $Z = 0.38$ (P = 0.70) Total (95% Cl) 30788 30834 100.0% Total events 1331 1184 Heterogeneity: Tau ² = 0.09; Chi ² = 80.59, df = 26 (P < 0.00001); I ² = 68% 1.18 [0.99, 1.40] Test for overall effect: $Z = 1.82$ (P = 0.07) 100 Test for subgroup differences: Chi ² = 20.53, df = 3 (P = 0.0001), I ² = 85.4% Favours [experimental]	PRIME-HF	0	60	0	58		Not estimable			
Total events 34 21 Heterogeneity: Tau ² = 0.73; Chi ² = 7.38, df = 3 (P = 0.06); l ² = 59% Test for overall effect: Z = 0.38 (P = 0.70) Total (95% Cl) 30788 30834 100.0% Total events 1331 1184 Heterogeneity: Tau ² = 0.09; Chi ² = 80.59, df = 26 (P < 0.00001); l ² = 68% 0.01 0.1 Test for subgroup differences: Chi ² = 20.53, df = 3 (P = 0.0001), l ² = 85.4% Favours [experimental]	Subtotal (95% CI)		7436		7445	6.0%	1.25 [0.40, 3.95]			
Heterogeneity: Tau ² = 0.73; Chi ² = 7.38, df = 3 (P = 0.06); l ² = 59% Test for overall effect: Z = 0.38 (P = 0.70) Total (95% Cl) 30788 30834 100.0% 1.18 [0.99, 1.40] Total events 1331 1184 Heterogeneity: Tau ² = 0.09; Chi ² = 80.59, df = 26 (P < 0.00001); l ² = 68% 0.01 0.1 10 Test for subgroup differences: Chi ² = 20.53, df = 3 (P = 0.0001), l ² = 85.4% Favours [experimental] Favours [control]	Total events	34		21						
Test for overall effect: $Z = 0.38 (P = 0.70)$ Total (95% Cl) 30788 30834 100.0% 1.18 [0.99, 1.40] Total events 1331 1184 Heterogeneity: Tau ² = 0.09; Chi ² = 80.59, df = 26 (P < 0.00001); l ² = 68% 0.01 0.1 10 Test for subgroup differences: Chi ² = 20.53, df = 3 (P = 0.0001), l ² = 85.4% Favours [experimental] Favours [control]	Heterogeneity: Tau ² = 0.73; Chi ² = 7.38, df = 3 (P = 0.06); l ² = 59%									
Total (95% Cl) 30788 30834 100.0% 1.18 [0.99, 1.40] Total events 1331 1184 Heterogeneity: Tau ² = 0.09; Chi ² = 80.59, df = 26 (P < 0.00001); l ² = 68% 0.01 0.1 Test for subgroup differences: Chi ² = 20.53, df = 3 (P = 0.0001), l ² = 85.4% Favours [experimental]	Test for overall effect:	Z = 0.38 (P =	0.70)							
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Test for overall effect: $Z = 1.82$ ($P = 0.07$) Test for subgroup differences: $Chi^2 = 20.53$, $df = 3$ ($P = 0.0001$), $I^2 = 85.4\%$ Favours [experimental] Favours [control]	Hotorogeneity: Tou?-	100 Chiž – 1	20 50 df - 1	1104 06/₽∢0.000	1011-12-600	×.				
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	Test for subaroup diff	erences: Chi	² = 20.53. dt	f = 3 (P = 0.0	001), I ^z = 85	.4%		Favours [experimental] Favours [control]		

FIGURE 4 Forest plot of trials included in the meta-analysis (*n* = 10) using a random-effects model with adverse events outcome. Risk ratios and 95% confidence intervals are shown. ACEi/ARB, angiotensin converting enzyme inhibitors and angiotensin receptor blockers; S-V, sacubitril-valsartan.

there was no significant difference between the groups in terms of adverse event rates.

Although this meta-analysis provides insight into the efficacy and safety of sacubitril-valsartan in HF patients, there are some limitations. Most of trials were sponsored by a drug company which adds a potential source of bias in showing greater efficacy of the intervention. The numbers of studies were low, and all outcomes were not reported for each trial thus limiting the data and making it difficult to assess publication bias. It is recommended that at least 10 studies with results be included in a Funnel plot as the power of the

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test decreases with fewer studies.³⁴ Factors such as gender, age, HF type, baseline blood pressure, comparator, and follow-up time varied between the trials which may have potentially confounded the results. In some trials, the follow-up time was probably inadequate to capture long-term adverse events. Several clinical trials to assess the efficacy of sacubitril-valsartan are still ongoing and availability of these results will further strengthen and—add evidence in favor of sacubitril-valsartan usage. Furthermore, as new studies have shown the benefit of sacubitril-valsartan in patients with kidney failure and those with EF > 40%, additional studies in patients with these conditions will help strengthen evidence-based medicine for use of this combination treatment compared to other commonly prescribed cardiovascular drugs.²⁰

5 | CONCLUSION

In individuals with HFrEF, sacubitril-valsartan had a better impact than ACE inhibitors or ARBs in lowering all-cause and cardiovascular mortality. Even though there was no substantial improvement in patients with HFpEF and HFmrEF, the number of trials was insufficient to reach a definite conclusion. There was no substantial difference in the occurrences of additional adverse events between sacubitril-valsartan and RAAS inhibitors, other than hypotension. Additional data from ongoing clinical trials is expected to provide more information and provide a comprehensive summary on the benefits of sacubitril-valsartan.

AUTHOR CONTRIBUTIONS

Qing Ji developed the concept and designed the study and analyzed data, proofreading and final editing along with guarantor of the manuscript.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Upon reasonable request, the corresponding author will provide access to the requested information.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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