The efficacy and safety of new potassium binders on renin–angiotensin–aldosterone system inhibitor optimization in heart failure patients: a systematic review and meta-analysis

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Abstract

Guideline-directed medical therapy (GDMT) has improved outcomes in patients with heart failure, including the use of reninangiotensin-aldosterone system inhibitors, which can hinder the excretion of potassium, resulting in hyperkalaemia. New potassium binders (NPBs) can prevent this adverse effect; however, the efficacy and safety of NPB for this indication have not been fully established. We conducted a systematic review and meta-analysis synthesizing randomized controlled trials (RCTs), which were retrieved by systematically searching PubMed, Web of Science, Scopus, and Cochrane through 26 April 2023. The risk of bias assessment was conducted, following Cochrane's updated Risk of Bias 2 assessment tool. We used the fixed-effects model to pool dichotomous data using risk ratio (RR) and continuous data using mean difference (MD), with a 95% confidence interval (CI) (PROSPERO ID: CRD42023426113). We included six RCTs with a total of 1432 patients. NPB was significantly associated with successful mineralocorticoid receptor antagonist (MRA) optimization [RR: 1.13 with 95% CI (1.02-1.25), P = 0.02], decreased patients with MRA at less than the target dose [RR: 0.72 with 95% CI (0.57–0.90), P = 0.004], and decreased hyperkalaemic episodes [RR: 0.42 with 95% CI (0.24–0.72), P = 0.002]. However, there was no difference between NPB and placebo regarding angiotensin-converting enzyme inhibitor (ACEi)/angiotensin receptor blocker (ARB)/angiotensin receptor/neprilysin inhibitor (ANRi) optimization [RR: 1.02 with 95% CI (0.89–1.17), P = 0.76] and serum potassium change [MD: -0.31 with 95% CI (-0.61 to 0.00), P = 0.05], with an acceptable safety profile except for the increased incidence of hypokalaemia with NPB [RR: 1.57 with 95% CI (1.12-2.21), P = 0.009]. NPB has been shown to improve GDMT outcomes by enhancing MRA optimization and reducing hyperkalaemic episodes. However, there are limited data on the effects of NPB on ACEi/ARB/ANRi optimization. Future RCTs should investigate ACEi/ARB/ANRi optimization and conduct head-to-head comparisons of NPB (patiromer and sodium zirconium cyclosilicate).

Keywords New potassium binders; Patiromer; Heart failure; Hyperkalaemia; Review; Meta-analysis

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Introduction

Heart failure (HF) is a complex cardiovascular condition characterized by the heart's inability to pump blood to meet the body's metabolic demands adequately. It can be categorized into two main types, HF with reduced ejection fraction (HFrEF) and HF with preserved ejection fraction (HFpEF).¹ This chronic and progressive condition affects millions of people worldwide, and its prevalence is estimated to increase by 46% from 2012 to 2023.² HF is a severe disease that requires

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the use of multiple medications to improve patient outcomes. Despite advances in HF management, it remains a major cause of hospitalization and mortality.

Guideline-directed medical therapy (GDMT) has been shown to improve outcomes in patients with HF, including the use of angiotensin-converting enzyme inhibitors (ACEis), angiotensin receptor blockers (ARBs), and mineralocorticoid receptor antagonists (MRAs), which are known as renin–angiotensin– aldosterone system inhibitors (RAASis). RAASis can hinder the excretion of potassium, resulting in elevated blood potassium levels, a condition known as hyperkalaemia. Hyperkalaemia is a common and serious complication of HF and is often caused by impaired renal function due to decreased renal blood flow or the use of nephrotoxic medications.³ This electrolyte imbalance can restrict the optimal use of RAASis, which are key components of GDMT.

To address this limitation, new potassium binders (NPBs), including patiromer and sodium zirconium cyclosilicate (SZC), have emerged as a class of medications that can reduce serum potassium levels by binding to potassium in the gastrointestinal tract, thereby preventing its absorption. Recent studies have suggested that NPB may be effective in preventing hyperkalaemia in patients with HF receiving RAASi therapy, enabling the optimization of GDMT.^{4–9} However, the efficacy and safety of NPB for this indication have not been fully established.

Accordingly, we have undertaken a systematic review and meta-analysis to evaluate the use of NPB for GDMT optimization in HF patients who developed hyperkalaemia while receiving RAASi therapy. This comprehensive analysis aims to provide important insights into the role of NPB in the management of HF and to inform clinical practice guidelines for the treatment of this condition. By assessing the available evidence, we can better understand the potential benefits and risks of utilizing NPB in this specific patient population, ultimately improving the care and outcomes for individuals with HF and hyperkalaemia.

Methodology

Protocol registration

This study was conducted under the guidelines outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement,¹⁰ and the Cochrane Handbook for Systematic Reviews and Meta-Analyses,¹¹ and prospectively registered in PROSPERO with ID: CRD42023426113.

Data sources and search strategy

A comprehensive search was conducted in major electronic databases such as MEDLINE (PubMed), Embase, Scopus,

Web of Science, and Cochrane Central Register of Controlled Trials (CENTRAL). The search was not limited by language or time restrictions. The details of the search strategy, including the keywords and the results of the search, can be found in Supporting Information, *Table S1*.

Eligibility criteria and study selection

Three reviewers (A.A., A.M.A., and I.G.) independently screened studies for inclusion based on pre-specified PICOS eligibility criteria: population (P): HF patients with current or a history of hyperkalaemia; intervention (I): NPB, including patiromer and SZC; comparator (C): placebo; outcome (O): the primary outcome was MRA optimization defined as patients with MRA at guidelines target dose, and the second-ary outcomes included MRA at <50% of the target dose, hyperkalaemic episodes, ACEi/ARB/angiotensin receptor/ neprilysin inhibitor (ANRi) optimization, change in serum potassium, and safety outcomes; and study design (S): randomized controlled trials (RCTs). Any conflict between the two reviewers was resolved by discussion and consensus; if a consensus could not be reached, a third reviewer (M.A.) was consulted to make the final decision.

The following were excluded: animal studies, pilot studies, case–control studies, case reports, case series, cohort studies, single-arm clinical trials, *in vitro* studies, book chapters, editorials, press articles, and conference abstracts.

Data extraction

Four reviewers (A.A., A.B., A.M.A., and I.G.) independently used a pre-designed extraction sheet to extract the following data: summary characteristics (study design, country, total participants, potassium binder intervention details, control, main inclusion criteria, follow-up duration, and primary outcome), baseline characteristics [number of participants in each group, age, gender, basal metabolic index (BMI), serum potassium, left ventricular ejection fraction (LVEF), glomerular filtration rate (GFR), systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate, and comorbidities], and efficacy and safety outcomes data. Any conflict was resolved by discussion.

Risk of bias and quality assessment

Four reviewers (A.A., A.B., A.M.A., and I.G.) independently utilized the Cochrane Risk of Bias 2 (RoB2) tool¹² to assess the quality of the included studies. The domains evaluated included the risk of bias stemming from the randomization process, deviations from the intended intervention, missing outcome data, measurement of the outcome, and selection of reported results. In the case of any disagreements, the

reviewers engaged in discussions and reached a consensus. To appraise the quality of evidence, two reviewers (M.A. and B.A.) utilized the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) guidelines.^{13,14} The evaluation was carried out for each outcome, and the decisions made were justified and documented. Any discrepancies were settled through discussion.

Statistical analysis

The statistical analysis was conducted using the RevMan v5.3 software.¹⁵ To combine the results of dichotomous outcomes, we used the risk ratio (RR), and for continuous outcomes, we used the mean difference (MD), both with a 95% confidence interval (CI), employing the fixed-effects model. We used the χ^2 and l^2 tests to evaluate heterogeneity, where the χ^2 test determines if heterogeneity exists and the l^2 test evaluates the extent of heterogeneity. As per the Cochrane Handbook (Chapter 9),¹⁶ we considered an alpha level below 0.1 for the χ^2 test to denote significant heterogeneity, while the l^2 test was interpreted as follows: 0-40% indicated not significant, 30-60% indicated moderate 50-90% heterogeneity, and indicated substantial heterogeneity.

Meta-regression was conducted to explore the potential sources of heterogeneity in the included studies. The following variables were considered as potential covariates: LVEF, GFR, baseline potassium, and age. A random-effects model was used to estimate the meta-regression coefficients. Finally, trial sequential analysis (TSA) was performed to assess the reliability and conclusiveness of the meta-analysis findings. TSA incorporates both the information size and the cumulative *z* curve to determine if the available evidence is sufficient and robust. The required information size (RIS) was calculated based on the anticipated intervention effect, diversity-adjusted RIS (DARIS), and diversity-adjusted information size (DAIS). Monitoring boundaries were applied to control the risks of Type I and Type II errors. TSA was conducted using the Trial Sequential Analysis software.¹⁷

Results

Search results and study selection

After searching five electronic databases, we retrieved 1181 records, excluding 558 duplicates via Covidence. Then we screened 623 abstracts, leaving 31 full texts. After the full-text screening, we included six RCTs (*Figure 1*).

Characteristics of included studies

Six RCTs^{4–9} with a total of 1432 patients were included in our analysis; 737 received NPB, and 695 received placebo. The summary and baseline characteristics are outlined in *Tables 1* and *2*.

Risk of bias and certainty of evidence

All the included studies showed an overall low risk of bias (*Figure 2*). Only OPAL-HK⁴ showed a high risk of bias mainly due to the lack of double blinding. Certainty of evidence is outlined in a GRADE evidence profile (*Table 3*).

Efficacy outcomes

NPB was significantly associated with successful MRA optimization [RR: 1.13 with 95% CI (1.02–1.25), P = 0.02], decreased patients with MRA at less than the target dose [RR: 0.72 with 95% CI (0.57–0.90), P = 0.004], and decreased hyperkalaemic episodes [RR: 0.42 with 95% CI (0.24–0.72), P = 0.002]. However, there was no difference between NPB and placebo regarding ACEi/ARB/ANRi optimization [RR: 1.02 with 95% CI (0.89–1.17), P = 0.76] and serum potassium change [MD: -0.31 with 95% CI (-0.61 to 0.00), P = 0.05] (*Figure 3* and *Table 3*).

Our results were homogenous in MRA optimization $(l^2 = 0\%, P = 0.41)$, MRA at less than the target dose $(l^2 = 0\%, P = 0.55)$, and ACEi/ARB/ANRi optimization $(l^2 = 0\%, P = 0.9)$. However, it was heterogeneous in hyperkalaemic episodes $(l^2 = 77\%, P = 0.002)$ and serum potassium change $(l^2 = 90\%, P = 0.0001)$. Heterogeneity was not resolved by sensitivity analysis in hyperkalaemia. However, in serum potassium change analysis, after excluding Anker *et al.*, heterogeneity was resolved and decreased from $l^2 = 90\%$ to $l^2 = 36\%$ (Supporting Information, *Table S2*).

Safety outcomes

There was no difference between NPB and placebo regarding all-cause mortality [RR: 1.22 with 95% CI (0.68–2.21), P = 0.51], any adverse events [RR: 1.04 with 95% CI (0.88–1.23), P = 0.64], any serious adverse events [RR: 0.96 with 95% CI (0.71–1.31), P = 0.81], any adverse event leading to drug discontinuation [RR: 0.90 with 95% CI (0.49–1.65), P = 0.74], and gastrointestinal disorders [RR: 1.97 with 95% CI (0.59–6.57), P = 0.27]. However, NPBs were significantly associated with the incidence of hypokalaemia [RR: 1.57 with 95% CI (1.12–2.21), P = 0.009] (*Figure 4* and *Table 3*).

Figure 1 PRISMA flow chart of the screening process.



Our results were homogenous in all-cause mortality ($l^2 = 0\%$, P = 0.66), any adverse events ($l^2 = 42\%$, P = 0.13), any serious adverse events ($l^2 = 0\%$, P = 0.55), any adverse event leading to drug discontinuation ($l^2 = 0\%$, P = 0.72),

and hypokalaemia ($l^2 = 0\%$, P = 0.45). However, it was heterogeneous in gastrointestinal disorders ($l^2 = 87\%$, P = 0.00001) and heterogeneity was not resolved by sensitivity analysis (Supporting Information, *Table S2*).

			NPB					
		Sample			Frequency of	Treatment	Primary	Follow-up
Study ID	Study design	size	Drug	Dose	administration	duration	outcome	duration
Anker <i>et al.</i> , 2015 (HARMONIZE) ⁸	Double-blind, multicentre RCT	87	SZC	5 g (<i>n</i> = 18), 10 g (<i>n</i> = 18), or 15 g (<i>n</i> = 25)	Once daily	4 weeks	Mean potassium change	4 weeks
Butler <i>et al.</i> , 2022	Double-blind,	878	Patiromer	3.4 g	Up to three t	27 weeks	Mean potassium change	27 weeks
(DIAMOND)	multicentre RCT				imes daily			
Pitt e <i>t al.</i> , 2011	Double-blind,	104	Patiromer	15 g	Twice daily	4 weeks	Mean potassium change	4 weeks
(PEARL-HF) ²	multicentre RCT							
Pitt <i>et al.</i> , 2015	Single-blind,	49	Patiromer 8	.4–52.4 g/day titrated		8 weeks	Mean potassium change	2 weeks
(OPAL-HK) ⁴	multicentre RCT		according 1	o severity of hyperkalaemia				
Rossignol <i>et al.</i> , 2020	Double-blind,	132	Patiromer	1.2 g	Once daily	12 weeks	MRA optimization	12 weeks
(AMBER) ⁶	multicentre RCT							
Tardif <i>et al.</i> , 20 <u>2</u> 2	Double-blind,	182	SZC	5 g	Once daily	12 weeks	MRA optimization	12 weeks
(PRIORITIZE-HF) ⁷	multicentre RCT							
MRA, mineralocorticoid receptor a	antagonist; NPB, n	ew pot	assium binde	r; RCT, randomized controlled trial; SZC, sodiu	um zirconium cyc	closilicate.		

Table 1 Summary characteristics of the included RCTs

LVEF showed a significant effect ($\beta = -0.105$, P = 0.0094) when tested as a moderator for hyperkalaemia (Supporting Information, *Table S3* and *Figure S1*). However, none of the rest models showed a significant association as shown in Supporting Information, *Table S3* and *Figures S2–S18*. Also, heterogeneity in hyperkalaemia was resolved in a meta-regression model based on LVEF (Supporting Information, *Figure S19*).

Trial sequential analysis

The TSA results revealed that the available evidence surpassed the RIS and reached the trial sequential monitoring boundary, indicating robust conclusions. These findings strongly suggest that NPB can significantly reduce the incidence of hyperkalaemia and improve MRA optimization in HF patients (*Figure 5*).

Discussion

Our meta-analysis, involving six RCTs with a total of 1432 patients, found that NPB improved MRA optimization, reduced patients receiving suboptimal MRA, and the incidence of hyperkalaemia episodes compared with placebo. NPB also showed potential risks of hypokalaemia without any increase in the rates of other adverse events. This indicates that the use of NPB was effective in decreasing hyperkalaemia in patients with HF. However, there were no significant differences in ACEi/ARB/ANRi optimization and serum potassium change between the two groups.

The 2021 European Society of Cardiology, the 2021 American College of Cardiology expert consensus decision pathway, and the 2020/2021 Kidney Disease: Improving Global Outcomes clinical practice guidelines have all recognized the efficacy of NPB in managing hyperkalaemia in patients with HF and/or chronic kidney disease.^{18–20} These guidelines recommend the use of NPB to facilitate the initiation and optimization of guideline-directed RAASi therapy. The implementation of GDMT in HF patients is often suboptimal, particularly when it comes to MRA.^{21,22} This challenge may be attributed to the increased risk of hyperkalaemia associated with MRA.^{23,24} Hyperkalaemia has been linked to MRA discontinuation and dose reduction^{25,26} and has been identified as a predictor of receiving <50% of the target dose.²⁷ Sequentially, discontinuing or not starting RAASi is associated with a significant risk of 1 year mortality (~41%) and HF readmission (potentially exceeding 64%).²⁸ Scicchitano et al. reported a notable 75% mortality rate in HFrEF patients who stopped MRA over 65 months.²⁹ This challenging effect

	Serum p	otassium, me	an (SD) Age	(years), mean ((SD)	eGFR,	nean (SD)	SBI	^o , mean (SD)	
Study ID	NPB	Plac	ebo NPB		Placebo	NPB	Placebo			Placebo
Anker <i>et al.</i> , 2015 (HARMONIZE) ⁸	5 g 4.42, 10 4.36, 15	g g	5 g 66.6	(32.9), 10 g (31.3), 15 g	65.3 (29)	NA	NA	AN		AA
Butler <i>et al.</i> , 2022 (DIAMOND) ⁹ Pitt <i>et al.</i> , 2011 (PEARL-HF) ⁵	4.69 (0.3) 4.69 (0.3)	() 4.65	(0.3) 66.6 (0.1) 68 (9	(1.00) (10.0) (c 11)	67.1 (9.9 68 (11) 76 E (8.3) 62.6 (2 84 (35	(2.6) 63.5 (2) (2.6) 78 (32) (32) 78 (32)	(1.4) 12 (1.4) 12 (1.2)	5 (12) 8 (13)	124 (13) 128 (12)
Ressigned et al., 2012 (OPAL-TIN) Rossigned et al., 2020 (AMBER) ⁶ Tardif et al., 2022 (PRIORITIZE-HF) ⁷	4.73 (0.2 4.73 (0.2 4.85 (0.3	(2) 4.70 (7) 4.87 (7) 4.87	7 (0.33) 72.9 72.9 72.9 72.9 72.9 72.9 72.9 72.9	(10.4) (10.4) (8.8)	6.0/ 0.07 69.4 (9.9 71.0 (8.1) 34.6 (() 34.6 (() 40.0 (1	c) 1.65 (11) (1) 37.3 (8) (1.0) 42.7 (1	1.5) NA	3.2 (6.4)	145.1 (6.8) NA
	der, New		Association, SBP, S		ressure; >U, st	andard devlat	5			
Table 2 (continued)										
			Comorbidities, N	(%)						
	LVEF, mean	(SD)	DM		HTN		CKD		AF	
Study ID	NPB	Placebo	NPB	Placebo	NPB	Placebo	NPB	Placebo	NPB	Placebo
Anker et al., 2015 (HARMONIZE) ⁸	NA	NA	5 g 13 (72.2), 10 g 16 (88.9), 15 g	18 (69.2)	NA	NA	5 g 12 (66.7), 10 g 15 (83.3), 15 g	19 (73.1)	NA	NA
Butler et al., 2022 (DIAMOND) ⁹ Pitt et al. 2011 (PEARI-HE) ⁵	33.5 (5.8) 40 (12)	33.5 (5.7) 41 (12)	17 (68.0) 182 (41.5) 15 (27)	174 (39.6) 18 (37)	406 (92.5) NA	396 (90.2) NA	18 (72.0) 439 (100) 27 (50)	439 (100) 20 (63)	160 (36.4) NA	181 (41.2) NA

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			Comorbidities, N	(%)						
	LVEF, mean	(SD)	DM		HTN		CKD		AF	
Study ID	NPB	Placebo	NPB	Placebo	NPB	Placebo	NPB	Placebo	NPB	Placebo
Anker <i>et al.</i> , 2015 (HARMONIZE) ⁸	NA	AN	5 g 13 (72.2), 10 g 16 (88.9), 15 g 17 (68.0)	18 (69.2)	NA	NA	5 g 12 (66.7), 10 g 15 (83.3), 15 g 18 (72 0)	19 (73.1)	NA	AN
Butler <i>et al.</i> , 2022 (DIAMOND) ⁹ Pitt <i>et al.</i> , 2011 (PEARL-HF) ⁵ Pitt <i>et al.</i> , 2015 (OPAL-HK) ⁴ Rossignol <i>et al.</i> , 2020 (AMBER) ⁶ Tardif <i>et al.</i> , 2022 (PRIORITIZE-HF) ⁷	33.5 (5.8) 40 (12) NA 48 (11) 33.8 (5.8)	33.5 (5.7) 41 (12) NA 50 (8) 33.9 (6.1)	182 (41.5) 15 (27) NA 24 (38) 40 (43.5)	174 (39.6) 18 (37) NA 33 (48) 42 (46.7)	406 (92.5) NA NA 63 (100) 86 (93.5)	396 (90.2) NA NA 69 (100) 85 (94.4)	439 (100) 27 (50) NA NA	439 (100) 30 (63) NA NA NA	160 (36.4) NA NA 9 (14) 42 (45.7)	181 (41.2) NA NA 12 (17) 42 (46.7)

	NYHA class,	(%) N						
	_		=		≡		≥	
study ID	NPB	Placebo	NPB	Placebo	NPB	Placebo	NPB	Placebo
Anker <i>et al.</i> , 2015 (HARMONIZE) ⁸	NA	NA	NA	NA	NA	NA	NA	NA
sutler <i>et al.</i> , 2022 (DIAMOND) ⁹	10 (2.3)	4 (0.9)	221 (50.3)	251 (57.4)	208 (47.4)	178 (40.7)	0	4 (0.9)
itt <i>et al.</i> , 2011 (PEARL-HF) ⁵	2 (4)	1 (2)	29 (53)	28 (57)	24 (44)	20 (41)	0	0
bitt <i>et al.</i> , 2015 (OPAL-HK) ⁴	NA	NA	NA	NA	NA	NA	NA	NA
łossignol <i>et al</i> ., 2020 (AMBER) ⁶	11 (18)	11 (16)	41 (65)	55 (80)	11 (18)	3 (4)	0	0
ardif et al., 2022 (PRIORITIZE-HF) ⁷	NA	NA	61 (66.3)	57 (63.3)	31 (33.7)	33 (36.7)	NA	NA
AF, atrial fibrillation; CKD, chronic kidne wailable: NPB new potassium binder: 1	ey disease; DM, di	abetes mellitus; eC	SFR, estimated glom	erular filtration rate	; HTN, hypertension;	: LVEF, left ventricula	ır ejection fract	ion; NA, not

Table 2 (continued)

can be managed by adding NPB to aid in continuing and reaching RAASi target doses as higher plasma potassium levels are also associated with increased risks of all-cause mortality, cardiovascular death, HF-related death, and sudden cardiac death, even when considering other influencing factors.²⁹

In our meta-analysis, NPBs significantly reduced suboptimal MRA doses and optimized MRA dosage. However, no effect was observed on ACEi/ARB/ANRi optimization. ACEi/ARB/ANRi optimization was reported by only two trials; hence, this outcome is underpowered. Furthermore, Tardif et al. implied that trial investigators (who were blinded from the treatment allocation) may have been concerned with renal function, hyperkalaemia, or hypotension related to initiation or up-titration of ACEi/ARB/ANRi.7 This can explain the lack of benefit upon ACEi/ARB/ANRi optimization in the context of the current underpowered available data for this outcome.

Furthermore, our analysis revealed a significant reduction in the incidence of hyperkalaemia. Hyperkalaemia, defined as a serum potassium level exceeding 5.0 mmol/L,³⁰ is a common occurrence in patients with HF. Its reported incidences range between 3.1% and 16.6%.³¹ This electrolyte imbalance poses a significant risk to a patient's health and is associated with a worsened prognosis, particularly in HF patients.^{32,33} NPB works by binding to potassium in the gastrointestinal tract and preventing its absorption. Patiromer exchanges calcium ions for potassium ions in the colon, promoting potassium excretion through faeces. SZC selectively traps potassium ions in exchange for sodium and hydrogen ions in the gut. Both binders effectively lower serum potassium levels, helping manage hyperkalaemia and optimize treatment outcomes, particularly in conditions like HF.34 Additionally, both patiromer and SZC were found to be safe in the treatment of hyperkalaemia,³⁵ which has been supported in our analysis.

Our analysis revealed no significant effect of NPB on all-cause mortality. Although mitigating RAASi discontinuation or the negative effects of hyperkalaemia can improve hard cardiovascular outcomes over the long term,⁹ our analysis revealed no significant effect of NPB on all-cause mortality. Butler et al. attributed this effect to a lack of sufficient power to detect significant differences in hard cardiovascular outcomes.9 Furthermore, most of the included trials were more underpowered and with less follow-up duration^{4–8} compared with DIAMOND,⁹ which can justify the lack of NPB effect on all-cause mortality. Additionally, Tardif et al. found no significant differences in hospitalization rates between SZC and placebo,⁷ and Butler et al. found no substantial difference in cardiovascular hospitalization, HF exacerbation, cardiovascular death, or overall mortality.⁹ Nevertheless, Butler et al. reported that patiromer significantly reduced hyperkalaemia-related morbidity.9 Finally, NPB might have the potential to mitigate the adverse effects and mortality associated with hyperkalaemia in HF patients. Further large-scale RCTs are still necessary to explore the effect on hard outcomes.



Figure 2 Quality assessment of the risk of bias in the included trials. The upper panel presents a schematic representation of risks (low = green, unclear = yellow, and high = red) for specific types of biases of each of the studies in the review. The lower panel presents risks (low = red, unclear = yellow, and high = red) for the subtypes of biases of the combination of studies included in this review.

Although the NPB mechanism of action may lead to gastrointestinal adverse events such as diarrhoea, constipation, nausea or vomiting, and electrolyte imbalances, including hypomagnesaemia,³⁴ our study did not find any significant difference in the risk of gastrointestinal disorders. However, NPB was significantly associated with an increased incidence of hypokalaemia, which may be because most patients can be additionally on loop or thiazide diuretics for hypertension management. In the included RCTs, most patients who experienced hypokalaemia had serum potassium levels ranging from 3.0 to 3.5 mEg/L. None of the patients in PRIORITIZE-HF had serum potassium levels below 3.0 mEq/ L, indicating severe hypokalaemia.⁷ However, in DIAMOND, one patient in each treatment arm had severe hypokalaemia. but they did not provide a specific definition for severe hypokalaemia.⁹

Moreover, dyskalaemia, which encompasses both hypokalaemia and hyperkalaemia, is prevalent in patients with HF due to the underlying HF condition itself, associated comorbidities, and the medications used for HF management. A recent large observational study revealed that within 1 year, 24.4% of patients encountered at least one hyperkalaemia event, with 10.2% reporting moderate to severe hyperkalaemia.³⁶ Also, 20.3% of patients experienced at least one episode of hypokalaemia, while 3.7% of them encountered severe hypokalaemia.³⁶ This indicates that dyskalaemia is a normal phenomenon in HF patients, and as long as NPB does not significantly increase severe hypokalaemia, they can be considered safe with a recommendation to monitor serum potassium level.

Multiple previous meta-analyses investigated NPB for HF. Carvalho *et al.* and Montagnani *et al.* are in line with our findings regarding MRA optimization.^{37,38} Also, Carvalho *et al.* showed the same findings regarding all other outcomes,³⁸ with Montagnani *et al.* focusing on MRA optimization only.³⁷ However, none of them reported pooled analysis on ACEi/ ARB/ANRi optimization. Also, our review is the first to provide certainty of evidence assessment, following GRADE guidelines, and TSA, assessing the reliability and conclusiveness of our findings. Therefore, our review adds to the available

Calinity assessment Manual consistency Inducation Manual consistency Manual consist	Table 3 GRADE evidence profile						
Raticipants (rudies) follow-upRisk of biasInconsistencyIndirectinesPublicationOreal decisionARA optimization (50 mg/day)Not seriousNot seriousNot seriousNot seriousNot seriousOreal decisionOreal decision12.200ARA optimization (50 mg/day)Not seriousNot seriousNot seriousNot seriousNot seriousNot seriousNot seriousNot serious12.200Max less than the target doseNot seriousNot seriousNot seriousNot seriousNot seriousNot serious12.201Max less than the target doseNot seriousNot seriousNot seriousNot seriousNot serious12.201Max less than the target doseNot seriousNot seriousNot seriousNot seriousSerious*None12.201Max devise eventNot seriousNot seriousNot seriousNot seriousSerious*NoneSerious*12.201Not seriousNot seriousNot seriousNot seriousNoneSerious*Serious*None12.201Not seriousNot seriousNot seriousNot seriousNoneSerious*NoneSerious*12.201Not seriousNot seriousNot seriousNot seriousNoneSerious*NoneSerious*12.201Not seriousNot seriousNot seriousNot seriousNoneSerious*Serious*Serious*Serious*12.202Not seriousNot seriousNot seriousNot serious<	Certainty assessment						
	Participants (studies) follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence
(4 RCD) (4 RCD)Not serious (4 RCD)Not serious (4 RCD)Not serious (4 RCD)Not serious (4 RCD)Not serious (4 RCD)Not serious 	MRA optimization (50 mg/day)	Mot corious	Not sorious	Not corious	Corious ^a	Nono	
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(4 RC3) (10 CC)	MRA at less than the target dose	Not serious	Not serious	Not serious	Verv serious ^b	anoN	
Hyperlalaemia (serum potassium >55 mEqU) (3 RTS)Not serious' (serious')Not serious' (serious')Not serious' 	(4 RCTs)						Low
(5 CT) Activity Not serious Not serious Not serious Very low ACE(ARBANR) optimization Not serious Not serious Not serious Not serious Very low (2 RCTs) Serious Not serious Not serious Not serious Not serious Not serious Very low 3 RCTs) Serious Not serious Not serious Not serious Not serious None 0000 4 RCTs) Not serious Not serious Not serious Not serious None 0000 4 RCTs) Not serious Not serious Not serious Not serious None 0000 4 RCTs) Not serious Not serious Not serious Not serious None 0000 4 RCTs) Not serious Not serious Not serious None 0000 4 RCTs) Not serious Not serious Not serious None 0000 4 RCTs) Not serious Not serious None 0000 0000 4 RCTS) Any serious Not serious None 0000 0000 4 RCTS)<	Hyperkalaemia (serum potassium >5.5 mt 1248	Eq/L) Not serious	Vany sarious ^c	Not serious	Sarious ^a	andM	
ACEI(ARB[A/RR]) $ACEI(ARB[A/RR])$ $ACEI(ARB[A/RR])$ $ACEI(ARB[A/RR])$ $ACEI(ARB[A/RR])$ $ACEI(ARB[A/RR])$ $ACEI(ARB[A/RR])$ $ACEI(ARB[A/RR])$ $ACIDBODDBODDBODDACDDACDDACDDACDDACDDACDDACDDACDDACDDACDDACDDACDDACDDACDDACDDACDDACDDACDDACDDACDDACDDACDDACDDACDDACDDACDDACDDACDDACDDACDDACDDACDDACDDACDDACDDACDDACDDACDDACDDACDDACDDACDDACDDACDDACDDACDDACDDACDDACDDACDDACDDACDDACDDACDDACDDACDDACDDACDDACDDACDDACDDACDDACDDACDDACDDACDDACDDACDDACDDACDDACDDACDDACDDACDDACDDACDDACDDACDDACDDACDDACDDACDDACDDACDDACDDACDDACDDACDDACDDACDDACDDACDDACDDACDDACDDACDDACDDACDDACDDACDDACDDACDDACDDACDDACDDACDDACDDACDDACDDACDDACDDACDDACDDACDDACDDACDDACDDACDD$	(5 RCTs)			1001 301 1003	20100		Very low
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6 KCIS)	1431	Not serious	Very serious	Not serious	Not serious	None	00 ⊕⊕ .
	(6 RCIS)						Low

^aConfidence interval does not exclude the risk of appreciable benefit/harm. ^{1b}Confidence interval does not exclude the risk of appreciable benefit/harm, and the number of events is <300 events. $2c_1^2 > 75\%$. $3d_1^2 > 50\%$.

ESC Heart Failure 2024; **11**: 28–43 DOI: 10.1002/ehf2.14588

Certainty assessment	Summary of findings				
	Study event rates (%)			Anticipated absolute effects	
Participants (studies) follow-up	With (comparison)	With (intervention)	Relative effect (95% CI)	Risk with (comparison)	Risk difference with (intervention)
MRA optimization (50 mg/day) 1290 (4 RCTs)	321/644 (49.8%)	364/646 (56.3%)	RR 1.13 (1.02–1.25)	498 per 1000	65 more per 1000 (from 10 more to 125 more)
MRA at less than the target dose 1290 (4 RCTs)	145/644 (22.5%)	104/646 (16.1%)	RR 0.72 (0.57–0.90)	225 per 1000	63 fewer per 1000 (from 97 fewer to 23 fewer)
Hyperkalaemia (serum potassium >5. 1248 (5 RC15)	.5 mEq/L) 166/604 (27.5%)	102/644 (15.8%)	RR 0.42 (0.24–0.72)	275 per 1000	159 fewer per 1000 (from 209 fewer to 77 fewer)
ALEI/AKB/AINKI OPUIMIZAUON 1054 (2 RCTs)	225/526 (42.8%)	230/528 (43.6%)	RR 1.02 (0.89–1.17)	428 per 1000	9 more per 1000 (from 47 fewer to 73 more)
Serum potassium change (at the late: 1060 (3 RCTs)	st endpoint) 509	551	I	The mean serum potassium change (at the latest endpoint) was 0	MD 0.31 lower (0.61 lower to 0)
All-Gause mortairty 1240 (4 RCTs)	19/620 (3.1%)	23/620 (3.7%)	RR 1.22 (0.68–2.21)	31 per 1000	7 more per 1000 (from 10 fewer to 37 more)
Any adverse events 1431 (6 RCTs)	443/695 (63.7%)	469/736 (63.7%)	RR 1.04 (0.88–1.23)	637 per 1000	25 more per 1000 (from 76 fewer to 147 more)
Any serious adverse events 1431 (6 RCTs)	74/695 (10.6%)	70/736 (9.5%)	RR 0.96 (0.71–1.31)	106 per 1000	4 fewer per 1000 (from 31 fewer to 33 more)
Any adverse event leading to drug dis 1250 (5 RCT)	scontinuation 22/605 (3.6%)	20/645 (3.1%)	RR 0.90 (0.49–1.65)	36 per 1000	4 fewer per 1000 (from 19 fewer to 24 more)
dastrointestinal disorders 1821 (6 RCTs)	46/1085 (4.2%)	65/736 (8.8%)	RR 1.97 (0.59–6.57)	42 per 1000	41 more per 1000 (from 17 fewer to 236 more)
пурокаlаетпа 1431 (6 RCTs)	46/695 (6.6%)	83/736 (11.3%)	RR 1.57 (1.12–2.21)	66 per 1000	38 more per 1000 (from 8 more to 80 more)
ACEi, angiotensin-converting enzyme	inhibitor; ANRi, angiotens	in receptor/neprilysin inhi	bitor; ARB, angiotensin recep	otor blocker; Cl, confidence inter	val; GRADE, Grading of Recom-

Table 3 (continued)

mendations Assessment, Development, and Evaluation; MD, mean difference; MRA, mineralocorticoid receptor antagonist; RCTs, randomized controlled trials; RR, risk ratio. ^aConfidence interval does not exclude the risk of appreciable benefit/harm. ^{cf2} > 75%. ^{df2} > 50%.

ESC Heart Failure 2024; **11**: 28–43 DOI: 10.1002/ehf2.14588

Figure 3 Forest plots of the efficacy outcomes. (A) Mineralocorticoid receptor antagonist (MRA) optimization, (B) MRA at less than the target dose, (C) hyperkalaemia (potassium >5.5 mEq/L), (D) angiotensin-converting enzyme inhibitor/angiotensin receptor blocker/angiotensin receptor/neprilysin inhibitor optimization, and (E) serum potassium change. CI, confidence interval; M-H, Mantel–Haenszel; NPB, new potassium binder.



(C)

	NPE	3	Place	bo		Risk Ratio		Risk	Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI		M-H, Rand	om, 95% Cl	
Anker et al. 2015 (HARMONIZE)	7	61	16	26	19.4%	0.19 [0.09, 0.40]				
Butler et al. 2022 (DIAMOND)	61	439	85	439	28.4%	0.72 [0.53, 0.97]				
Pitt et al. 2011 (the PEARL-HF)	4	55	12	49	14.2%	0.30 [0.10, 0.86]				
Pitt et al. 2015 (OPAL-HK)	2	26	11	21	10.3%	0.15 [0.04, 0.59]	-			
Rossignol et al. 2020 (AMBER)	28	63	42	69	27.8%	0.73 [0.52, 1.02]		-		
Total (95% CI)		644		604	100.0%	0.42 [0.24, 0.72]		•		
Total events	102		166							
Heterogeneity: Tau ² = 0.25; Chi ² =	17.55, df	= 4 (P	= 0.002);	$ ^2 = 77^{\circ}$	%			01	10	100
Test for overall effect: Z = 3.15 (P =	: 0.002)						0.01	Favors (NBP)	Favors (Placebo)	100

(D)

	NPE	3	Place	bo		Risk Ratio		Risk F	latio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, Fixed	I, 95% CI	
Butler et al. 2022 (DIAMOND)	217	439	212	439	94.2%	1.02 [0.89, 1.17]			<u> </u>	
Tardif et al. 2022 (PRIORITIZE-HF)	13	89	13	87	5.8%	0.98 [0.48, 1.99]	•			
Total (95% CI)	220	528	225	526	100.0%	1.02 [0.89, 1.17]				
Heterogeneity: Chi ² = 0.02, df = 1 (P=	230 1 ² (0.90 =	= 0%	220				L		15	
Test for overall effect: $Z = 0.30$ ($P = 0$.	76)						Favo	ors [Placebo]	Favors [NPB]	2

(E) Mean Difference NPB Placebo Mean Difference Study or Subgroup Mean SD Total Mean SD Total Weight IV, Random, 95% CI IV, Random, 95% CI Anker et al. 2015 (HARMONIZE) 4.6 0.38 61 5.2 0.5 26 31.7% -0.60 [-0.81, -0.39] Butler et al. 2022 (DIAMOND) 0.03 0.4 439 0.13 0.4 439 37.2% -0.10 [-0.15, -0.05] Tardif et al. 2022 (PRIORITIZE-HF) -0.27 0.62 -0.02 0.52 31.1% -0.25 [-0.48, -0.02] 51 44 Total (95% CI) 551 509 100.0% -0.31 [-0.61, 0.00] Heterogeneity: Tau² = 0.06; Chi² = 20.69, df = 2 (P < 0.0001); l² = 90% -2 2 ή Test for overall effect: Z = 1.96 (P = 0.05) Favors [NPB] Favors [Placebo]

Figure 4 Forest plots of the safety outcomes. AE, adverse event; CI, confidence interval; M-H, Mantel-Haenszel; NPB, new potassium binder.

66.1 All-Cause Mortality Definer et J. 2022 (MANOND) 2 4.39 5.1% 1.38 [D.73, 2.58] Pite et J. 2022 (PRIORTIZ-HF) 1 91 1.00 0.5% 0.39 [D.02, 0.57] Taroff et J. 2022 (PRIORTIZ-HF) 1 91 1.00 0.5% 0.39 [D.02, 0.57] Taroff et J. 2022 (PRIORTIZ-HF) 1 91 0.00 0.5% 0.39 [D.02, 0.57] Taroff et J. 2022 (PRIORTIZ-HF) 1 91 0.00 0.5% 0.39 [D.02, 0.57] 6.2.2 Any Adverse Events Arker et J. 2015 (PARMONDZ) 22 65 5.5% 1.52 [D.65, 2.71] Pite et J. 2022 (DRIORTIZ-HF) 30 51 48 0.5% 1.52 [D.65, 2.71] Pite et J. 2022 (DRIORTIZ-HF) 30 65 6.5 1.52 [D.65, 1.51] 1.02 Tardif et J. 2022 (PRIORTIZ-HF) 4.09 4.43 Heterogenetity Taure 0.02, Chill = S61, 1.55 1.00 0.00 [D.67, 1.31] Tardif et J. 2022 (DRIORTIZ-HF) 22 24 1.0% 0.39 [D.66, 1.32] Pite at J.2015 (DRIAL-HF) 2.55 2.49 1.0% 0.29 [D.67, 1.31] Subtotal (B^5% CI) 7.41	Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
Buller et al. 2022 (DMANCHO) 22 4 39 16 4 39 51% 1.38 [0.73, 2.58] First al. 2015 (OMANCHO) 22 6 31 60 0.4% 0.27 [0.15, 0.48] Tradied al. 2022 (DMANCHO) 23 19 620 6.4% 1.22 [0.36, 2.71] Subtradied al. 2020 (MARCHO) 32 0 19 0.05, 0.7 0.38 Tradie et al. 2016 (Chirl Carlor 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1,	6.6.1 All-Cause Mortality							
The star 2015 (CPAL-Hi) 0 0 27 1 22 0.4% 0.27 (D01, 6.41) sessing of al. 2020 (PRIORITZE-HP) 1 91 1 80 0.5% 0.39 (D02, 75.57) Tradit example to 200: CPF=1.58, df=3 (P=0.65); f= 0.56 test for version of al. 2020 (PRIORITZE-HP) 1 92 1 9 26 5.6% 1.52 (D.65, 2.71) the star at 2.015 (CPALHON DIZE) 32 61 9 26 5.6% 1.52 (D.65, 2.71) the star at 2.015 (CPALHON DIZE) 32 61 9 26 5.6% 1.72 (D.65, 2.71) the star at 2.015 (CPALHON DIZE) 32 61 9 26 5.6% 1.72 (D.65, 2.71) the star at 2.015 (CPALHON DIZE) 32 61 9 26 5.6% 1.72 (D.65, 2.71) the star at 2.015 (CPALHON DIZE) 32 61 9 26 5.6% 1.72 (D.65, 2.71) the star at 2.015 (CPALHON DIZE) 32 61 9 26 5.6% 1.72 (D.65, 2.71) the star at 2.015 (CPALHON DIZE) 32 61 9 26 5.6% 1.72 (D.65, 2.71) the star at 2.015 (CPALHON DIZE) 32 61 9 26 5.6% 1.72 (D.65, 2.71) the star at 2.015 (CPALHON DIZE) 32 61 9 26 5.6% 1.72 (D.65, 2.71) the star at 2.015 (CPALHON DIZE) 32 61 9 26 5.6% 1.72 (D.65, 2.71) the star at 2.015 (CPALHON DIZE) 32 61 9 26 5.6% 1.72 (D.65, 2.71) the star at 2.015 (CPALHON DIZE) 32 61 9 26 5.6% 1.72 (D.65, 2.71) the star at 2.015 (CPALHON DIZE) 44 52 43 (D.65, 2.71) the star at 2.015 (CPALHON DIZE) 44 50 42 26 (D.67, 1.32) the star at 2.015 (CPALHON DIZE) 44 51 422 (D.65, 2.71) the star at 2.015 (CPALHON DIZE) 44 51 42 (D.65, 2.51) the star at 2.015 (CPALHON DIZE) 5 4 61 0 26 Not estimable the star 2.015 (CPALHON DIZE) 5 6 140 0 0.29 (D.71, 1.31) the star 2.015 (CPALHON DIZE) 5 61 40 0 0.42 (D.71, 1.31) the star 2.015 (CPALHON DIZE) 5 61 40 0 0.42 (D.71, 1.31) the star 2.015 (CPALHON DIZE) 5 61 40 0 0.42 (D.71, 1.31) the star 2.015 (CPALHON DIZE) 5 61 40 0 2.63 (D.44, 0.33 (D.64, 1.52) the star 2.015 (CPALHON DIZE) 4 61 0 26 Not estimable the star 2.015 (CPALHON DIZE) 4 61 0 26 Not estimable the star 2.015 (CPALHON DIZE) 4 61 0 26 Not estimable the star 2.015 (CPALHON DIZE) 4 61 0 26 0.5% 1.48 (D.63, 1.44) (D.64, 2.50) the star 2.015 (CPALHON DIZE) 4 61 0 26 0.5% 1.48 (D.63, 1.44) (D.64, 2.50) the star 2.015 (CPALHON DIZE) 4 61 0 26 0.5% 1.48	Butler et al. 2022 (DIAMOND)	22	439	16	439	5.1%	1.38 [0.73, 2.58]	+
The segment of al. 2020 (AMBER) 0 6 83 1 66 0.4% 0.38 [0.02, 6.79] and of al. 2020 (AMBER) 1 9 1 60, 0 - 50 (- 0.06); $F = 0.5$ Final varies 2 0.00; $Ch^{-2} = 1.50$, $dr = 3$ ($P = 0.66$); $F = 0.5$ Final varies 2 0.00; $Ch^{-2} = 1.50$, $dr = 3$ ($P = 0.66$); $F = 0.5$ Final varies 2 0.00; $Ch^{-2} = 1.50$, $dr = 3$ ($P = 0.66$); $F = 0.5$ Final varies 2 0.00; $Ch^{-2} = 0.00$; $Dr = 0.50$; $P = 0.5$ Final varies 2 0.00; $Ch^{-2} = 0.50$; $P = 0.50$	Pitt et al. 2015 (OPAL-HK)	0	27	1	22	0.4%	0.27 [0.01, 6.41]	
Tardif et al. 2022 (PRIORITZE-HP) 1 91 1 90 0.5% 0.09(0.06, 15.57) Total events 2 3 19 Heard and the approximate the approx	Rossignol et al. 2020 (AMBER)	0	63	1	69	0.4%	0.36 [0.02, 8.79]	
Subtolal (9% C) 620 620 6.4% 1.22 (0.68, 2.21) Heterogeneity: Tar = 0.0; Ch ² = 0.5; df = 2 (e^{-} 0.6; f^{-} 0.6% Test for overall effect Z = 0.5 (e^{-} 0.6; df = 2 (e^{-} 0.6; f^{-} 0.6% Heterogeneity: Tar = 0.0; Ch ² = 0.5; df = 2 (e^{-} 0.6; f^{-} 0.6% Heterogeneity: Tar = 0.0; Ch ² = 0.5; df = 2 (e^{-} 0.6%; f^{-} 0.6% Heterogeneity: Tar = 0.0; Ch ² = 0.5; df = 2 (e^{-} 0.6%; f^{-} 0.6% Heterogeneity: Tar = 0.0; Ch ² = 0.5; df = 2 (e^{-} 0.6%; f^{-} 0.6% Heterogeneity: Tar = 0.0; Ch ² = 0.5; df = 2 (e^{-} 0.13); f^{-} 42% Test for overall effect Z = 0.46 (e^{-} 0.64) 6.6.3 Any Serious Adverse Events Adver + at .2015 (CHARMONUE) 0 443 Heterogeneity: Tar = 0.0; Ch ² = 0.51, df = 2 (e^{-} 0.55; ff = 0.% Test for overall effect Z = 0.24 (e^{-} 0.64) 6.6.3 Any Serious Adverse Events Adver + at .2015 (CHARMONUE) 0 443 Heterogeneity: Tar = 0.0; Ch ² = 0.50; df = 0 (e^{-} 0.56; f^{-} 0.% Test for overall effect Z = 0.24 (e^{-} 0.64) 6.6.4 Any AE Leading to Drug Discontinuation Anker + at .2015 (CHARMONUE) 0 41 439 Heterogeneity: Tar = 0.0; Ch ² = 0.50; df = 0 (e^{-} 0.55; f^{-} 0.% Test for overall effect Z = 0.23 (e^{-} 0.72; Z = 0.72; e^{-} 0% Test for overall effect Z = 0.24 (e^{-} 0.65); f^{-} 0.% Test for overall effect Z = 0.24 (e^{-} 0.65); f^{-} 0.% Test for overall effect Z = 0.23 (e^{-} 0.72; f^{-} 0.% Test for overall effect Z = 0.23 (e^{-} 0.72; f^{-} 0.% Test for overall effect Z = 0.23 (e^{-} 0.72; f^{-} 0.% Test for overall effect Z = 0.23 (e^{-} 0.40001); f^{-} 1.5% 1.57 (0.55) (0.54 (e^{-} 0.5001); f^{-} 0.% Test for overall effect Z = 0.23 (e^{-} 0.0001); f^{-} 0.5% Test for overall effect Z = 0.23 (e^{-} 0.41 (e^{-} 0.41 (e^{-} 0.5%; 1.44 (e^{-} 0.41 (e^{-} 0.4	Tardif et al. 2022 (PRIORITIZE-HF)	1	91	1	90	0.5%	0.99 [0.06, 15.57]	
Total events 23 19 Heterogeneity: Tare 100; Chef 156; df = 3 ($\mathcal{P} = 0.50$); $\mathcal{P} = 0.50$;	Subtotal (95% CI)		620		620	6.4%	1.22 [0.68, 2.21]	*
Heterogeneity: Tar = 0.00; Ch ⁺ = 1.50; df = 3 ($f = 0.60$); $f = 0.80$; $f = 0.80$; $f = 0.81$ anker et al. 2015 (HARMONIZE) 32 61 9 26 5.6% 1.52 (0.85, 2.71] Storburst al. 2020 (MARDND) 32 439 325 439 10.6% 0.98 [0.91, 1.07] The tal. 2015 (CHARMONIZE) 12 61 37 66 7.5% 0.98 [0.91, 1.07] The tal. 2015 (CHARMONIZE) 12 61 37 66 7.5% 0.98 [0.97, 1.30] The tal. 2015 (CHARMONIZE) 12 66 3 37 66 7.5% 0.98 [0.97, 1.30] The tal. 2015 (CHARMONIZE) 17 78 64 43 Heterogeneity: Tar = 0.02; Ch ⁺ = 0.81 ($d = 5.0^{\circ} = 0.13$); $f = 42\%$. Test for overall effect Z = 0.46 ($f = 0.64$) 66.5 Any Sections Adverse Events Anker et al. 2015 (CHARMONIZE) 10 61 0 26 Not estimable Builter et al. 2022 (CHARMONIZE) 10 61 0 26 Not estimable Builter et al. 2022 (CHARMONIZE) 10 61 0 26 Not estimable Builter et al. 2022 (CHARMONIZE) 10 61 0 26 Not estimable Builter et al. 2022 (CHARMONIZE) 10 61 0 26 Not estimable Builter et al. 2022 (CHARMONIZE) 10 61 0 26 Not estimable Builter et al. 2022 (CHARMONIZE) 10 61 0 26 Not estimable Builter et al. 2022 (CHARMONIZE) 10 61 0 26 Not estimable Builter et al. 2022 (CHARMONIZE) 10 61 0 26 Not estimable Builter et al. 2022 (CHARMONIZE) 10 61 0 26 Not estimable Builter et al. 2022 (CHARMONIZE) 10 61 0 26 Not estimable Builter et al. 2023 (CHARMONIZE) 10 61 0 26 Not estimable Builter et al. 2023 (CHARMONIZE) 10 61 0 26 Not estimable Builter et al. 2023 (CHARMONIZE) 10 61 0 26 Not estimable Builter et al. 2023 (CHARMONIZE) 10 61 0 26 Not estimable Builter et al. 2023 (CHARMONIZE) 12 605 7.5% 0.90 (D46, 1.65] Test for overall effect Z = 0.34 ($f = 0.72$); $f = 0.5$ Test for overall effect Z = 0.34 ($f = 0.72$); $f = 0.5$ Test for overall effect Z = 0.33 ($f = 0.74$) 65.6 Sastrotherein Bioneters Test for overall effect Z = 0.32 ($f = 0.74$) 65.6 Sastrotherein Bioneters Test for overall effect Z = 0.32 ($f = 0.74$) 65.6 Sastrotherein Bioneters Test for overall effect Z = 0.32 ($f = 0.74$); $f = 0.55$ Test for overall effect Z = 0.32 ($f = 0.74$); $f = 0.56$ Test for overal	Total events	23		19				
Test for overall effect $Z = 0.86 (P = 0.51)$ 56.2. Any Adverse Events Anker et al. 2016 (APAMNONLZ) 32 61 9 26 5.6% 1.52 [0.85, 2.71] Build et al. 2012 (APAMNONLZ) 32 61 9 26 5.6% 1.52 [0.85, 2.71] Filt et al. 2011 (the PEARL-HF) 15 27 14 22 8.6% 0.87 [0.55, 1.38] Filt et al. 2015 (OPAL-HK) 15 27 14 22 8.6% 0.87 [0.55, 1.38] Filt et al. 2015 (OPAL-HK) 15 27 14 22 8.6% 0.87 [0.55, 1.38] Filt et al. 2015 (OPAL-HK) 15 27 14 22 8.6% 0.87 [0.55, 1.38] Filt et al. 2012 (OPRORTIZE-HF) 43 91 47 90 8.7% 0.98 [0.57, 1.21] Total events 4.202 (PRORTIZE-HF) 43 91 47 90 8.7% 0.98 [0.57, 1.38] Filt et al. 2015 (OPAL-HK) 5 55 2 49 1.0% 0.88 [0.13, 6.09] Filt et al. 2015 (OPAL-HK) 2 55 2 49 1.0% 0.88 [0.13, 6.09] Filt et al. 2015 (OPAL-HK) 2 55 2 49 1.0% 0.88 [0.13, 6.09] Filt et al. 2015 (OPAL-HK) 0 67 1 22 0.4% 0.27 [0.01, 6.41] Filt et al. 2015 (OPAL-HK) 0 70 7 4 Heter al. 2015 (OPAL-HK) 0 27 1 22 0.4% 0.27 [0.01, 6.41] Filt et al. 2015 (OPAL-HK) 1 9 01 4.2% Statiotal (95% CI) 70 7 74 Heter al. 2015 (OPAL-HK) 1 9 01 0.2% Filt et al. 2015 (OPAL-HK) 1 2 0 02. (f = 4 P = 0.55), F = 0% Test for overall effect Z = 0.24 (P = 0.53) EAS A May Elocating to Drug Discontinueation Anker et al. 2016 (APAMONIZE) 0 0 1 0 26 Not estimable External effect Z = 0.24 (P = 0.53) EAS A May Elocating to Drug Discontinueation Anker et al. 2016 (APAMONIZE) 1 0 1 20 Statiotal (95% CI) 7.7% 0.90 [0.48, 11.60] Filt et al. 2017 (DPAL-HK) 1 2 0 2 Heterogeneity: Tat' = 0.00, Ch'' = 3.02, eff = 4 P = 0.72); F = 0% Test for overall effect Z = 0.37 (P = 0.72) EAS Eds Asynchemica Nather et al. 2015 (DPAL-HK) 1 2 0 2 Heterogeneity: Tat' = 0.00, Ch'' = 1.33, eff = 3 (P = 0.72); F = 0% Test for overall effect Z = 0.37 (P = 0.72); F = 0% Test for overall effect Z = 0.37 (P = 0.72); F = 0% Test for overall effect Z = 0.37 (P = 0.000); F = 6% Test for overall effect Z = 0.30 (P = 0.000); F = 6% Test for overall effect Z = 0.00 (DH); F = 6% Test for overall effect Z = 0.00 (OH); F = 6% Test for overall effect Z = 0.00 (P = 0	Heterogeneity: Tau ² = 0.00; Chi ² = 1.5	58, df = 3	(P = 0.8)	66); I ² = 0	%			
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	Test for overall effect: $Z = 0.66$ ($P = 0$.	51)						
nhar et al. 2015 (PARI-NUNDZE) 32 61 9 226 5.6 % 1.52 (B.85, 2.71) The start 2015 (CMANNON 2E) 320 439 10.6 % 0.58 (B.91, 1.07) The start 2015 (CPAL-HF) 30 55 15 49 6.5 % 0.37 (D.55, 1.38) Tradie tal. 2020 (AMBERD) 29 63 33 68 7.9 % 0.36 (D.57, 1.38) Tradie tal. 2020 (AMBERD) 49 63 32 64 39 10.6 % 0.58 (D.57, 1.38) Tradie tal. 2020 (AMBERD) 49 63 43 68 7.9 % 0.36 (D.57, 1.38) Tradie tal. 2015 (CPAL-HG) 49 61 0 26 Not estimable Budler et al. 2012 (CHARNON)2D 6 61 0 26 Not estimable Budler et al. 2022 (CHARNON)2D 5 4 439 58 439 8.1 % 0.33 (D.66, 1.32) The tal. 2015 (CPAL-HG) 0 27 1 220 0.4 % 0.16 (D.12, 97) Tradie tal. 2022 (CHARNON)2D 5 4 439 58 439 8.1 % 0.33 (D.66, 1.32) The tal. 2015 (CPAL-HG) 0 27 1 22 0.4 % 0.27 (D.01, 6.4) Tradie tal. 2022 (CHARNON)2D 7 7 4 74 The tal. 2015 (CPAL-HG) 0 27 1 22 0.4 % 0.16 (D.12, 97) Tradie tal. 2022 (CHARNON)2D 7 7 4 74 The tal. 2015 (CPAL-HG) 0 27 7 4 74 The tal. 2015 (CPAL-HG) 0 27 74 The tal. 2015 (CPAL-HG) 0 24 (P = 0.55); P = 0 % Test for overall effect Z = 0.24 (P = 0.52); P = 0 % Test for overall effect Z = 0.24 (P = 0.72); P = 0 % Test for overall effect Z = 0.33 (P = 0.72); P = 0 % Test for overall effect Z = 0.33 (P = 0.74) 6.6.5 GB 7 9% 0.36 (D.11, 21) Tradie events 20 (CPAL-HG) 1 22 2 0 0.5 % 0.34 (D.10, 1, 17) The tal. 20 (The PARL-HF) 1 2 55 2 49 0 0.1 ; M = 138 (D.16, 23, 156, 157) Tradie events 20 (CPAL-HG) 5 27 0 22 0.5 % 0.34 (D.10, 1, 17) The tal. 20 (The PARL-HF) 2 5 5 4 39 0 2.7 % 0.34 (D.10, 1, 17) Tradie events 20 (CPAL-HG) 5 27 0 22 0.5 % 0.34 (D.10, 1, 17) Tradie events 20 (CPAL-HG) 5 27 0 22 0.5 % 0.34 (D.10, 1, 17) Tradie events 20 (CPAL-HG) 5 27 0 22 0.5 % 0.34 (D.10, 1, 17) Tradie events 20 (CPAL-HG) 5 27 0 22 0.5 % 0.34 (D.10, 1, 17) Tradie events 20 (CPAL-HG) 5 27 0 22 0.5 % 0.34 (D.10, 1, 17) Tradie events 20 (CPAL-HG) 5 27 0 22 0.5 % 0.34 (D.10, 1	6.6.2 Any Adverse Events							
Buller et al. 2022 (DVMOND) 320 439 325 439 10.6%, 0.88 (0.91, 107) Pilt et al. 2017 (bPAL-HK) 15 27 14 22 6.8%, 0.87 (0.55, 1.39) Tardif et al. 2012 (PRIORITIZE-HF) 43 91 47 90 8.7%, 0.80 (0.67, 1.21) Total events 4302 (PRIORITIZE-HF) 43 91 47 90 8.7%, 0.80 (0.67, 1.21) Total events 4409 443 Total events 440 (P= 0.02, ChF = 31, df = 5 (P= 0.13), F = 42%, Test for overall effect Z = 0.44 (P= 0.64) 65.3 Any Serious Adverse Events Ander et al. 2012 (DMANDN) 54 439 58 439 61%, 0.83 (0.66, 3.22) Total events 400 (P= 0.64) 65.3 Any Serious Adverse Events Ander et al. 2012 (DMANDN) 54 439 58 439 61%, 0.83 (0.66, 3.22) Total events 400 (P= 0.64) 65.3 Any Serious Adverse Events Ander et al. 2012 (DMANDN) 54 439 58 439 61%, 0.83 (0.66, 3.22) Total events 400 (P= 0.84) 65.5 Adv, Set Leading to DMC (P) 50.5 (P= 0.42%, 1.38) Total events 70 74 Heterogeneity: Tau* = 0.00, ChF = 3.02, df = 4 (P = 0.55), P = 0%. Test for overall effect Z = 0.24 (P = 0.81) 6.6.5 Adv, AE Leading to Drug Discontinuation Anker et al. 2015 (PARMONDZE) 0 61 0 2 Total events 70 74 Heterogeneity: Tau* = 0.00, ChF = 3.02, df = 4 (P = 0.55), P = 0%. Test for overall effect Z = 0.23 (P = 0.72), P = 0%. Test for overall effect Z = 0.23 (P = 0.81) 6.6.5 Adv, AE Leading to Drug Discontinuation Anker et al. 2015 (PARMONDZE) 0 61 0 2 Total events 202 (2MANCND) 34 439 24 439 6.3% 1.04 (0.10, 4.24) Total events 202 (2MANCND) 34 439 24 439 6.3% 1.02 (0.49, 1.65) Total events 202 (2MANCND) 34 439 24 439 6.3% 1.02 (0.49, 1.65) Total events 202 (2MANCND) 34 439 24 439 6.3% 1.02 (0.49, 1.65) Total events 65 0 46 Heterogeneity: Tau* = 0.00, Ch* = 1.33, df = 5 (P = 0.45), P = 0%. Test for overall effect Z = 0.33 (P = 0.74) Heterogeneity: Tau* = 0.00, Ch* = 4.27, df = 5 (P = 0.45), P = 0%. Test overall effect Z = 2.60 (P = 0.72), P = 0%. Test overall effect Z = 2.60 (P = 0.72), P = 0%. Test overall effect Z = 2.60 (P = 0.72), P = 0%. Test overall effect Z = 2.60 (P = 0.00)), T = 60%. Test overall effect Z = 2.60 (P = 0.45), P =	Anker et al. 2015 (HARMONIZE)	32	61	9	26	5.6%	1.52 [0.85, 2.71]	
Pitt et al. 2015 (PAR-HARD) 30 55 15 49 6.5% 1.78 [1.10, 2.90] Pitt et al. 2015 (PAR-HARD) 15 2.7 14 22 6.8% 0.87 (D.55, 1.38] Pitt et al. 2015 (PAR-HARD) 29 63 33 69 7.9% 0.96 [0.67, 1.38] Pitt et al. 2015 (PAR-HARD) 29 63 439 64.1% 1.04 [0.08, 1, 2.2] Subtotal (P3% C) Chill = 8.61, dF 5 ($\mathcal{P} = 0.13$), $F = 42%$. Test for overall effect Z = 0.4 ($\mathcal{P} = 0.64$) 8.6.3 Any Serious Adverse Events Ankar et al. 2015 (PAR-HARD) 2 65 2 49 1.0% 0.98 [0.13, 20] Pitt et al. 2015 (DARANDALZE) 0 61 0 26 Not estimable Builder et al. 2020 (DMARDE) 1 26 20 (MARDER) 0 63 3 69 0.4% 0.27 [0.01, 6.41] Pitt et al. 2015 (DARANDALZE) 0 61 0 226 Not estimable Subtotal (P3% C) 77 1 22 0.4% 0.27 [0.01, 6.41] Pitt et al. 2015 (DARANDALZE) 0 61 0 226 Not estimable Subtotal (P3% C) 77 1 22 0.4% 0.27 [0.01, 6.41] Pitt et al. 2015 (DARANDALZE) 0 61 0 226 Not estimable Subtotal (P3% C) 77 38 095 14.0% 0.96 [0.71, 1.31] Pitt et al. 2015 (DARANDALZE) 0 61 0 226 Not estimable Subtotal (P3% C) 72 22 0.001 F = 3.02, dF = 4 ($\mathcal{P} = 0.55$), $P = 0$ % Test for overall effect Z = 0.24 ($\mathcal{P} = 0.55$), $P = 0$ % Test for overall effect Z = 0.24 ($\mathcal{P} = 0.55$), $P = 0$ % Test for overall effect Z = 0.24 ($\mathcal{P} = 0.55$), $P = 0$ % Test for overall effect Z = 0.24 ($\mathcal{P} = 0.57$), $P = 0$ % Test for overall effect Z = 0.23 ($\mathcal{P} = 0.72$), $P = 0$ % Test for overall effect Z = 0.23 ($\mathcal{P} = 0.72$), $P = 0$ % Test for overall effect Z = 0.23 ($\mathcal{P} = 0.72$), $P = 0$ % Test for overall effect Z = 0.23 ($\mathcal{P} = 0.72$), $P = 0$ % Test for overall effect Z = 0.23 ($\mathcal{P} = 0.72$), $P = 0$ % Test for overall effect Z = 0.23 ($\mathcal{P} = 0.72$), $P = 0$ % Test for overall effect Z = 0.23 ($\mathcal{P} = 0.72$), $P = 0$ % Test for overall effect Z = 0.23 ($\mathcal{P} = 0.72$), $P = 0$ % Test for overall effect Z = 0.23 ($\mathcal{P} = 0.72$), $P = 0$ % Test for overall effect Z = 0.21 ($\mathcal{P} = 0.72$), $P = 0$ % Test for overall effect Z = 0.21 ($\mathcal{P} = 0.72$), $P = 0$ % Test for overall effect Z = 0.20 ($\mathcal{P} = 0.81$) $A = 0.00$ $O = 0.4\%$ 4 39 0.01 (3.64) $A = 0.0$	Butler et al. 2022 (DIAMOND)	320	439	325	439	10.6%	0.98 [0.91, 1.07]	1
Pitt et al. 2015 (CPAL-HK) 15 27 14 22 6.8% 0.87 (0.57, 1.39) Tardif et al. 2022 (PRIORITZE-HF) 43 91 47 90 8.7% 0.90 (0.67, 1.31) Tardif et al. 2022 (PRIORITZE-HF) 45 91 47 90 8.7% 0.90 (0.67, 1.31) Total events 469 443 Total events 469 443 Test for overall effect $Z = 0.46$ ($P = 0.64$) 6.6.3 Any Serious Adverse Events Anker et al. 2015 (APAMINON)25 0 61 0 26 Not estimable Butler et al. 2012 (CMAROND) 54 439 58 439 8.1% 0.93 (0.6.6, 1.32) Pitt et al. 2014 (PAROND) 54 439 58 439 8.1% 0.93 (0.6.6, 1.32) Pitt et al. 2015 (CPAL-HK) 0 27 1 22 0.4% 0.16 (0.1, 2.97) Tardif et al. 2022 (CMAROEN) 7 6 695 4.0% 0.48 (0.1, 2.97) Tardif et al. 2022 (CMAROEN) 7 70 74 Heterogeneity: Tard = 0.00; Chr = 3.02, df = 4 ($P = 0.55$); $P = 0$ % Test for overall effect $Z = 0.34$ ($P = 0.81$) 56.4 Any AE Leading to Drug Discontinuation Anker et al. 2015 (CPAL-HK) 1 27 2 22 0.7% 0.41 (0.04, 4.20) Total events 70 74 Heterogeneity: Tard = 0.00; Chr = 3.02, df = 4 ($P = 0.55$); $P = 0$ % Test for overall effect $Z = 0.34$ ($P = 0.72$); $P = 0$ % Test for overall effect $Z = 0.34$ ($P = 0.72$); $P = 0$ % Test for overall effect $Z = 0.32$ ($P = 0.72$); $P = 0$ % Test for overall effect $Z = 0.32$ ($P = 0.72$); $P = 0$ % Test for overall effect $Z = 0.32$ ($P = 0.72$); $P = 0$ % Test for overall effect $Z = 0.32$ ($P = 0.72$); $P = 0$ % Test for overall effect $Z = 0.32$ ($P = 0.72$); $P = 0$ % Test for overall effect $Z = 0.32$ ($P = 0.72$); $P = 0$ % Test for overall effect $Z = 0.32$ ($P = 0.72$); $P = 0$ % Test for overall effect $Z = 0.32$ ($P = 0.72$); $P = 0$ % Test for overall effect $Z = 0.32$ ($P = 0.72$); $P = 0$ % Test for overall effect $Z = 0.32$ ($P = 0.72$); $P = 0$ % Test for overall effect $Z = 0.32$ ($P = 0.72$); $P = 0$ % Test for overall effect $Z = 0.32$ ($P = 0.72$); $P = 0$ % Test for overall effect $Z = 0.32$ ($P = 0.42$); $P = 0.5$ Test for overall effect $Z = 0.32$ ($P = 0.72$); $P = 0.5$ Test for overall effect $Z = 0.32$ ($P = 0.52$); $P = 0.5$ Test for overall effect $Z = 0.32$ ($P = 0.5$	Pitt et al. 2011 (the PEARL-HF)	30	55	15	49	6.5%	1.78 [1.10, 2.90]	
Rossignol et al. 2020 (AMBER) 29 63 33 69 7.9% 0.96 (0.67, 1.3) Tadif et al. 202 (AMBER) 736 695 46.1% 1.04 (0.88, 1.23) Subtolal (9% C) 736 695 46.1% 1.04 (0.88, 1.23) Total events 469 443 Heterogeneity: Tau*= 0.02, Chi*= 8.61, df= 5 ($\mathcal{P} = 0.13$); P= 42% Test for versal effect Z = 0.46 ($\mathcal{P} = 0.84$) 6.6.3 Any Serious Adverse Events 0.61 0.26 Not estimable Subtolal (9% C) 104, 255 2.49 1.0% 0.89 (0.16, 6.1) Rossignol et al. 2020 (AMBER) 0.63 36 90.4% 0.16 (0.01, 2.97) Subtolal (9% C) 70 74 74 1.0% 0.96 (0.71, 1.31) Fietal 2.015 (CHORITZE-HF) 14 91 90 4.2% 1.38 (0.55, 2.95) Subtolal (9% C) 70 74 1.0% 0.96 (0.71, 1.31) 1.0% 6.6.4 Any AE Leading to Drug Discontinuation Anker et al. 2015 (CHARMONAZE) 0.61 2.26 Not estimable Butter et al. 2022 (OMMOND) 12 39 1.6% 1.19 (0.26, 0.52) Total events <td>Pitt et al. 2015 (OPAL-HK)</td> <td>15</td> <td>27</td> <td>14</td> <td>22</td> <td>6.8%</td> <td>0.87 [0.55, 1.39]</td> <td></td>	Pitt et al. 2015 (OPAL-HK)	15	27	14	22	6.8%	0.87 [0.55, 1.39]	
Tardiff and 2022 (PRIORINZE-HF) 43 91 47 90 87.% 0.80 (0.87, 1.21) Total events 469 443 Heterogenetix, Tau" = 0.02, Ch" = 61, df = 5 ($P = 0.13$); P = 42% Test for overall effect Z = 0.46 ($P = 0.64$) 5.6.3 Any Serious Adverse Events Anker at 1.2015 (APAMEMALZE) 0 61 0 26 Not estimable Buller et al. 2022 (DMAMOND) 54 439 58 439 81% 0.33 (0.86, 1.32) Pitt et al. 2012 (APAMEMALZE) 0 61 0 26 Not estimable Buller et al. 2022 (CPAL-HK) 0 27 1 22 0.4% 0.27 (0.01, 641) Fossign et al. 2020 (AMBER) 0 63 3 69 0.4% 0.05 (0.01, 2.87) Total events 70 74 Heterogenetix, Tau" = 0.00; Ch" = 0.50; P = 0% Test for overall effect Z = 0.24 ($P = 0.55$); P = 0% Test for overall effect Z = 0.24 ($P = 0.55$); P = 0% Test for overall effect Z = 0.24 ($P = 0.57$); P = 0% Test for overall effect Z = 0.33 ($P = 0.72$); P = 0% Test for overall effect Z = 0.33 ($P = 0.72$); P = 0% Test for overall effect Z = 0.33 ($P = 0.72$); P = 0% Test for overall effect Z = 0.33 ($P = 0.72$); P = 0% Test for overall effect Z = 0.34 ($P = 0.57$); P = 0% Test for overall effect Z = 0.33 ($P = 0.72$); P = 0% Test for overall effect Z = 0.33 ($P = 0.72$); P = 0% Test for overall effect Z = 0.33 ($P = 0.72$); P = 0% Test for overall effect Z = 0.33 ($P = 0.72$); P = 0% Test for overall effect Z = 0.33 ($P = 0.72$); P = 0% Test for overall effect Z = 0.34 ($P = 0.57$); F = 0% Test for overall effect Z = 0.34 ($P = 0.72$); P = 0% Test for overall effect Z = 0.33 ($P = 0.74$) 6.6.5 Gastrointestinal Disorders Anker et al. 2015 (PAL-HK) 12 25 3 429 21% 0.34 [0.10, 1.17] Tubal events 65 46 Heterogenetix; Tau" = 1.02, Ch" = 4.34 C, df = 30 ($P = 0.72$); P = 0% Test for overall effect Z = 1.11 ($P = 0.27$) 6.6.6 Hypokalemia Anker et al. 2015 (PAL-HK) 2 27 0 22 0.5% 0.44 (0.53, 15.47] Total events 65 46 Heterogenetix; Tau" = 1.74; Ch" = 34 62, df = 5 ($P = 0.000$); P = 68% Test for overall effect Z = 1.11 ($P = 0.27$) 6.6.6 Hypokalemia Anker et al. 2015 (PAL-HK) 2 27 0 22 0.5% 0.44 (0.63, 25.59] Subtotal (9% CI) 736 695 10.0%	Rossignol et al. 2020 (AMBER)	29	63	33	69	7.9%	0.96 [0.67, 1.38]	+
Subtotal (95% C) 736 695 46.1% 1.04 [0.88, 1.23] Total events 469 443 Heterogeneity: Tau" = 0.02; ChiP = 8.61, df = 5 (P = 0.13); P = 42% Test for overall effect Z = 0.46 (P = 0.64) 6.5.3 Ary Serious Adverses Events Anker et al. 2015 (CHARMONIZE) 0 61 0 26 Not estimable Builder et al. 2022 (CMANOND) 54 439 58 439 81% 0.38 [0.36, 60] Pitt et al. 2015 (CHARMONIZE) 0 61 0 26 Not estimable Builder et al. 2022 (CMANOND) 54 439 58 439 81% 0.38 [0.52, 207] (0.16, 61] Pitt et al. 2015 (CHARMONIZE) 0 61 0 26 Not estimable Subtotal (95% C) 71 726 695 14.0% 0.38 [0.52, 207] (0.17, 1.31] Total events 70 74 Heterogeneity: Tau" = 0.00; Chi" = 3.02, df = 4 (P = 0.55); P = 0% Test for overall effect Z = 0.24 (P = 0.51) Fest for overall effect Z = 0.24 (P = 0.51) Fest for overall effect Z = 0.24 (P = 0.51) Fest for overall effect Z = 0.24 (P = 0.51) Fint et al. 2015 (CPAL-HK) 1 27 2 22 0.7% 0.44 [0.04, 4.20] Subtotal (95% C) 7.9% 0.50 [0.42, 1.0] Subtotal (95% C) 7.9% 0.50 [0.42, 1.0] Subtotal (95% C) 7.9% 0.50 [0.42, 1.0] Subtotal (95% C) 7.9% 0.50 [0.42, 1.0] Fint et al. 2015 (CPAL-HK) 1 27 2 22 0.7% 0.44 [0.04, 4.20] Subtotal (95% C) 7.9% 0.50 [0.42, 1.0] Subtotal (95% C) 7.9% 0.50 [0.43, 1.14 [0.25, 8.57] Total events 20 22 Pitt et al. 2015 (CPAL-HK) 5 27 0 22 0.5% 0.44 [0.03, 1.43 [0.33, 1.43 [0.33, 1.43 [0.24, 1.52] Total events 20 0.720; Pit e 0.43 15.5% 1.57 [0.52, 0.57] Subtotal (95% C) 7.30 0.50 1.1% 1.40 [0.53, 1.54 7] Subtotal (95% C) 7.30 0.50 0.44 0.27 [0.27, 7.28] Subtotal (95% C) 7.30 0.50 0.44 0.30 0.5% 1.148 (0.68, 255.59] Subtotal (95% C) 7.30 650 1.0.5% 1.18 [0.57, 1.44] Fit et al. 2015 (CPAL-HK) 2 27 0.22 0.5% 0.44 (0.63, 15.587] Total events 6 7.00 0.5% 1.148 (0.68, 255.59] Subtotal (95% C) 7.30 650 1.0.5% 1.18 [0.57, 1.44] Fit et al. 2015 (CPAL-HK) 7 9 0 0.005 5% 1.148 (0.68, 255.59] Subtotal (95% C) 7.90 4395 10.0.5% 1.18 [0.57, 1.44] Fit et al. 201	Tardif et al. 2022 (PRIORITIZE-HF)	43	91	47	90	8.7%	0.90 (0.67, 1.21)	
Total events $499 + 443$ Heterogeneity: Tau" = 0.02; Ch ² = 881, df = 5 (<i>P</i> = 0.13); P = 42%. Test for overall effect Z = 0.46 (<i>P</i> = 0.64) 6.6.3 Any Serious Adverse Events Anker et al. 2015 (<i>U</i> ARMON,ZE) 0 61 0 26 Not estimable Builder et al. 2022 (<i>D</i> IAMOND) 54 439 58 439 8.1% 0.33 (0.56, 1.32) Otal events 2015 (<i>U</i> ARMON,ZE) 0 63 3 69 0.4% 0.16 (0.01, 2.87) Tradi et al. 2012 (<i>C</i> PHORTIZE-HF) 14 91 10 90 4.2% 1.38 (0.52, 2.50) Total events 7 74 Heterogeneity: Tau" = 0.00; Ch" = 3.02, df = 4 (<i>P</i> = 0.55); <i>P</i> = 0% Test for overall effect Z = 0.24 (<i>P</i> = 0.55); <i>P</i> = 0% Test for overall effect Z = 0.24 (<i>P</i> = 0.55); <i>P</i> = 0% Test for overall effect Z = 0.24 (<i>P</i> = 0.55); <i>P</i> = 0% Test for overall effect Z = 0.24 (<i>P</i> = 0.55); <i>P</i> = 0% Test for overall effect Z = 0.31 6.6.4 Any AE Leading to Drug Discontinuation Anker et al. 2015 (<i>C</i> HARMON,ZE) 0 61 0 26 Not estimable Builder et al. 2022 (<i>D</i> MMOND) 12 439 11 439 3.8% 1.199 (0.49, 2.45) Total events 7 0 22 0.7% 0.41 (0.04, 4.20) Anker et al. 2015 (<i>C</i> HARMON,ZE) 0 61 0 26 Not estimable Builder et al. 2022 (<i>D</i> MMOND) 12 439 11 439 3.8% 1.09 (0.49, 1.45) Total events 2 0.02 (<i>D</i> = 0.72); <i>P</i> = 0% Test for overall effect Z = 0.33 (<i>P</i> = 0.72); <i>P</i> = 0% Test for overall effect Z = 0.33 (<i>P</i> = 0.72); <i>P</i> = 0% Test for overall effect Z = 0.33 (<i>P</i> = 0.72); <i>P</i> = 0% Test for overall effect Z = 0.34 (<i>D</i> = 0.64 5 0.65 15.5% 1.97 (0.59, 6.57) Total events 6 27 0 22 0.5% 0.04 (0.27, 1.52) Tardif et al. 2022 (<i>C</i> MANOND) 34 439 24 439 8.3% 1.42 (0.55, 6.57) Total events 6 6 6 Tast for overall effect Z = 1.11 (<i>P</i> = 0.27) 56.6 Hypokalemia Anker et al. 2015 (<i>C</i> PAL-HK) 5 27 0 22 0.5% 1.92 (0.12, 7.13) Total events 6 6 6 Heterogeneity: Tau" = 1.00; Ch" = 3.42, df = 5 (<i>P</i> = 0.045); <i>I</i> = 0% Test for overall effect Z = 1.61 (<i>P</i> = 0.05); 736 005 10.05% 1.148 (0.68, 25.59) Total events 736 005 10.05% 1.148 (0.68, 25.59) Total events 736 005 10.05% 1.148 (0.68, 25.59) Total events 730 650 10.05% 1.18 (0.69, 7.144) Tat = 1.000; Ch" = 4.72, df	Subtotal (95% CI)		736		695	46.1%	1.04 [0.88, 1.23]	•
Heterogeneiky Tau" = 0.02; Chi" = 6.81, df = 5 (ρ = 0.13); P = 42% Test for overall effect Z = 0.46 (ρ = 0.84) 65.3 Ary Serious Adverse Events Anker et al. 2015 (CHALHK) 5 4 39 58 439 81%, 0.38 [0.56, 0.39] Pill et al. 2012 (DMANDD) 5 4 439 58 439 81%, 0.38 [0.56, 0.39] Pill et al. 2012 (MAPER) 0 63 3 66 43 0.4%, 0.27 [0.01, 6.87] Fill et al. 2012 (PHORINZE) 1 4 91 0 90 4.2%, 1.38 [0.52, 2.55] Total avents 7 0 7 74 Heterogeneiky: Tau" = 0.00; Chi" = 3.02, df = 4 (ρ = 0.55); P = 0% Test for overall effect Z = 0.24 (ρ = 0.81) 6.6.4 Any AE Leading to Drug Discontinuation Anker et al. 2015 (CHALHK) 1 2 72 22 0.7%, 0.44 [10.10, 1.17] Builder tal. 2012 (CHALHK) 1 2 72 22 0.7%, 0.44 [10.10, 2.56] Anker et al. 2015 (CHALHK) 1 2 72 22 0.7%, 0.44 [10.28, 5.65] Total avents 20 22 Heterogeneiky: Tau" = 0.00; Chi" = 1.33, df = 3 (ρ = 0.72); P = 0% Test for overall effect Z = 0.34 (ρ = 0.74) 6.6.5 Gastrointestinal Disorders Anker et al. 2015 (CHALHK) 1 2 75 2 22 0.7%, 0.44 [10.10, 1.17] Subtotal (9% C) 7.51 2.72 0.720; 0.58 0.44 [0.25, 1.52] Heterogeneiky: Tau" = 0.00; Chi" = 1.33, df = 3 (ρ = 0.72); P = 0% Test for overall effect Z = 0.34 (ρ = 0.74) 6.6.5 Gastrointestinal Disorders Anker et al. 2015 (CHALHK) 5 27 0 22 0.5% 0.44 (10.53, 1.54.87] Challevents 4 20 1202 (MMOREP) 3 61 0 26 0.4% 3.92 (0.22, 70.28] Builter et al. 2020 (MMOREP) 7 63 12 69 3.5% 0.44 (10.21, 1.52] Total avents 4 5 5 46 Heterogeneiky: Tau" = 1.74; Chi" = 34.62, df = 6 (ρ = 0.00001); P = 8% Test for overall effect Z = 0.11 (ρ = 0.72) 6.6.6 Hypokalemia Anker et al. 2015 (CHALHK) 2 27 0 22 0.5% 0.44 (10.23, 1.54.87] Total avents 4 5 5 0 49 0.4% 3.28 (0.43, 9.21.162] Total events 6 5 0 49 0.4% 3.28 (0.47, 9.11] Total events 6 7 0 0.000; Chi" = 4.72, df = 5 (ρ = 0.0000); P = 8% Test for overall effect Z = 1.30 (ρ = 0.000; Fill = 0.000; F	Total events	469		443				
Test for overall effect $Z = 0.46 (P = 0.84)$ 6.6.3 Any Serious Adverse Events Anker et al. 2015 (OAPAENOND) 54 439 59 439 81% 0.93 [0.68, 1.32] Pill et al. 2021 (the PEARL-HF) 2 55 2 49 10% 0.89 [0.13, 6.09] Pill et al. 2015 (OAPAENOND) 54 439 61 0 % 0.89 [0.13, 6.09] Pill et al. 2015 (OPAL-HK) 0 27 1 22 0.4% 0.93 [0.64, 11] Tradif et al. 2020 (PRIORITEZ-HF) 14 91 10 90 42% 138 [0.65, 2.59] Subtotal (95% C) 736 74 Heterogeneity: Tau" = 0.00; Chi" = 3.02, df = 4 (P = 0.55); P = 0% Test for overall effect $Z = 0.24 (P = 0.81)$ 6.6.4 Any AE Leading to Drug Discontinuation Anker et al. 2015 (HARMONIZE) 0 61 0 26 Not estimable Butter et al. 2020 (DMABER) 12 439 11 439 3.8% 1.99 [0.49, 2.45] Test for overall effect $Z = 0.24 (P = 0.81)$ 6.6.4 Any AE Leading to Drug Discontinuation Anker et al. 2015 (HARMONIZE) 0 61 0 26 Not estimable Butter et al. 2020 (DMABER) 12 439 11 439 3.8% 1.99 [0.49, 2.45] Pill et al. 2015 (OPAL-HK) 1 27 2 22 0.7% 0.41 [0.04, 2.45] Pill et al. 2015 (OPAL-HK) 1 27 2 22 0.7% 0.41 [0.04, 2.45] Total events 20 22 Heterogeneity: Tau" = 0.00; Chi" = 1.33, df = 3 (P = 0.72); P = 0% Test for overall effect $Z = 0.33 (P = 0.74)$ 6.6.5 Gastrointestimal Disorders Anker et al. 2015 (OHARMONIZE) 4 61 5 26 2.1% 0.34 [0.10, 1.17] Dutler et al. 2022 (DMAMOND) 34 439 2.44 439 6.3% 1.42 [0.85, 2.35] Total events Test for overall effect $Z = 0.33 (P = 0.74)$ 6.6.5 Gastrointestimal Disorders Anker et al. 2015 (OHARMONIZE) 4 61 5 26 2.1% 0.34 [0.10, 1.17] Dutler et al. 2022 (DMAMOND) 34 439 2.44 39 6.3 % 1.42 [0.85, 2.35] Total events 65 46 Heterogeneity, Tau" = 1.04; Char = 3.42; df = 5 (P < 0.00001); P = 86% Test for overall effect Z = 1.11 (P = 0.27) 6.6.6 Hypokalemia Anker et al. 2015 (OHARMONIZE) 4 61 0 26 0.4% 3.92 [0.27, 70.28] Subtotal (95% C1) 7.36 (095 10.0% 1.48 [0.97, 1.44] Total events 65 46 Heterogeneity, Tau" = 0.00; Chi" = 4.72, df = 6 (P = 0.45); P = 0% Test for overall effect Z = 0.30 (P = 0.45); P = 0% Test for overall effect Z = 0.30 (P = 0.000); P = 56	Heterogeneity: Tau² = 0.02: Chi² = 8.6	61. df = 5	(P = 0.1)	3): ² = 4	2%			
6.6.3 Any Serious Adverse Events Anker et al. 2015 (HARMONIZE) 0 61 0 26 Not estimable Buffer et al. 2015 (UAMANON) 54 439 58 439 8.1% 0.93 [0.66, 1.32] Pilt et al. 2015 (DAU-HK) 0 27 1 22 0.4% 0.93 [0.10, 1.297] Rossignol et al. 2020 (MBREF) 0 63 3 69 0.4% 0.18 [0.01, 2.97] Total events 70 74 10 90 4.2% 1.38 [0.65, 2.94] Subtotal [05% CI) 736 695 14.0% 0.96 [0.71, 1.31] 9 Sci Any AE Leading to Drug Discontinuation Anker et al. 2015 (DPAL-HK) 1 27 2.22 0.7% 0.41 [0.49, 2.45] Buffer et al. 2022 (DAMANON) 12 4.39 1.8% 1.09 [0.49, 2.45] 1.91 [0.25, 5.05] Pilt et al. 2015 (DPAL-HK) 1 27 2.22 0.7% 0.41 [0.04, 4.20] 0.55 [0.14, 2.10] Subtotal (95% CI) 645 605 7.9% 0.39 [0.49, 1.65] 1.42 [0.85, 2.13] 1.42 [0.85, 2.13] Total events 20 22	Test for overall effect: $Z = 0.46$ ($P = 0.$	64)	v – 0.1	0,1 - 4	2.70			
Arker et al. 2015 (HARMONIZE) 0 61 0 26 Not estimable Under et al. 2025 (DAMAND) 54 439 58 439 81% 0.39 [0.65, 1.32] Pill et al. 2015 (DAMAND) 54 439 58 439 81% 0.39 [0.65, 1.32] Pill et al. 2015 (DAMAND) 0 54 72 1 22 0.4% 0.16 [0.01, 2.97] Total events 70 74 14 10 90 42% 139 [0.55, 2.95] Subtoal (95% CI) 736 695 14.0% 0.96 [0.71, 1.31] 6.6.4 Any AE Leading to Drug Discontinuation Anker et al. 2015 (HARMOND) 12 439 11 439 3.8% 1.09 [0.48, 2.45] Pill et al. 2015 (OPAL-HK) 1 27 2 22 0.7% 0.41 [0.04, 2.26] Pill et al. 2015 (DPAL-HK) 1 27 2 22 0.7% 0.41 [0.04, 4.20] Rossignol et al. 2022 (DAMANDD) 12 439 11 439 3.8% 1.09 [0.48, 2.45] Pill et al. 2015 (DPAL-HK) 1 27 2 22 0.7% 0.41 [0.04, 4.20] Rossignol et al. 2020 (AMBER) 3 63 6 69 1.8% 0.56 [0.14, 2.10] Subtoal (95% CI) 645 605 7.9% 0.90 [0.48, 1.65] Total events 20 22 Heterogeneity: Tau ² = 0.03 (Ch ² = 1.33, df = 3 (<i>P</i> = 0.72); P = 0%. Test for overall effect Z = 0.33 (<i>P</i> = 0.72); P = 0%. Test for overall effect Z = 0.33 (<i>P</i> = 0.72); P = 0%. Test for overall effect Z = 0.33 (<i>P</i> = 0.72); P = 0%. Test for overall effect Z = 0.33 (<i>P</i> = 0.72); P = 0%. Test for overall effect Z = 0.33 (<i>P</i> = 0.72); P = 0%. Test for overall effect Z = 0.33 (<i>P</i> = 0.72); P = 0%. Test for overall effect Z = 0.33 (<i>P</i> = 0.72); P = 0%. Test for overall effect Z = 0.33 (<i>P</i> = 0.72); P = 0%. Test for overall effect Z = 0.33 (<i>P</i> = 0.72); P = 0%. Test for overall effect Z = 0.30 (<i>P</i> = 0.72); P = 0%. Test for overall effect Z = 0.30 (<i>P</i> = 0.72); P = 0%. Test for overall effect Z = 0.30 (<i>P</i> = 0.72); P = 0%. Test for overall effect Z = 0.30 (<i>P</i> = 0.72); P = 0%. Test for overall effect Z = 0.30 (<i>P</i> = 0.0001); P = 68%. Test for overall effect Z = 0.20 (<i>P</i> = 0.45); P = 0%. Test for overall effect Z = 0.30 (<i>P</i> = 0.45); P = 0%. Test for overall effect Z = 0.30 (<i>P</i> = 0.45); P = 0%. Test for overall effect Z = 0.30 (<i>P</i> = 0.45); P = 0%. Test for overall effect Z = 0.30 (<i>P</i> = 0.45); P = 0%. Test for overall effect Z = 0.30 (<i>P</i> = 0.45); P = 0%. Test f	6.6.3 Any Serious Adverse Events							
Buller et al. 2012 (DIAMOND) 54 439 58 439 81% 0.9310.66, 1.32] Pitt et al. 2016 (OPAL-HK) 0 27 1 22 0.4% 0.27 (D.0.1, 6.41) Rossignol et al. 2020 (AMBERP) 0 63 3 69 0.4% 0.16 [0.01, 2.97] Tradif et al. 2022 (PRIORITZE-HF) 14 91 10 90 4.2% 0.16 [0.01, 2.97] Total events 736 695 14.0% 0.96 [0.71, 1.31] Total events 74 Heterogeneity. Tau" = 0.00, Chi" = 3.02, dir = 4 ($P = 0.55$); $P = 0\%$ Test for overall effect Z = 0.24 ($P = 0.05$) 6.6.4 Any AE Leading to Drug Discontinuation Anker et al. 2015 (HARMONIZE) 0 61 0 26 Not estimable Butler et al. 2022 (OMBOND) 12 439 11 439 3.8% 1.09 [0.49, 2.45] Pitt et al. 2015 (HARMONIZE) 0 61 0 26 Not estimable Butler et al. 2022 (OMBER) 3 63 6 69 18% 0.55 [0.14, 2.10] Subtrati (95% CI) 645 605 7.9% 0.90 [0.49, 1.65] Total events 7.3% 0.44 [0.04, 4.20] Fit et al. 2015 (HARMONIZE) 4 61 5 26 2.1% 0.34 (0.10, 1.17] Butler et al. 2012 (OMBER) 3 63 6 69 18% 0.55 [0.14, 2.10] Subtrati (95% CI) 645 7.0% 0.90 [0.49, 1.65] Total events 645 605 7.9% 0.90 [0.49, 1.65] Total events 7.3% 0.40 (0.31, 1.42 [0.85, 2.35] Pitt et al. 2015 (HARMONIZE) 4 61 5 26 2.1% 0.34 (0.10, 1.17] Butler et al. 2012 (OMBER) 7 63 12 69 3.5% 0.64 (0.27, 1.52] Total events 65 6 ($P < 0.00001$); $P = 63\%$ Test for overall effect Z = 0.32 ($P = 0.74$) 6.6.5 Gastrointestinal Disorders Anker et al. 2015 (HARMONIZE) 4 61 0 26 0.4% 3.92 [0.22, 70.28] Butler et al. 2022 (OMMOND) 54 439 24 439 8.3% 1.42 [0.85, 2.857] Total events 65 6 ($P < 0.00001$); $P = 86\%$ Test for overall effect Z = 1.11 ($P = 0.27$) 6.6.6 Hypokalemia Anker et al. 2012 (HARENNIZE) 4 61 0 26 0.4% 3.92 [0.22, 70.28] Butler et al. 2020 (MMERP 1 63 0 ($P < 0.00001$); $P = 86\%$ Test for overall effect Z = 2.10 ($P = 0.0000$ Total events 63 46 Heterogeneik; Tau" = 0.00; Chi" = 4.72, dir = 5 ($P = 0.45$); $P = 0\%$ Total events 63 46 Heterogeneik; Tau" = 0.00; Chi" = 4.72, dir = 5 ($P = 0.45$); $P = 0\%$ Total events 736 409 10.4% 6.25 [0.31, 110.5] Total events 736 400 40.4% 6.25 [0.31, 110.5] Total events 736 400 4	Anker et al. 2015 (HARMONIZE)	0	61	0	26		Not estimable	
Pite tal 2011 (the PEARL-HF) 2 55 2 49 10% 0.89 [0.15, 0.09] Pite tal 2015 (PAL-HK) 0 27 11 22 4.4% 0.27 [0.01, 6.41] Rossignol et al. 2020 (AMBER) 0 63 3 69 0.4% 0.16 [0.01, 2.97] Tardif et al. 2022 (PRIORTIZE-HF) 14 91 10 90 4.2% 1.38 [0.65, 2.95] Subtotal (95% CI) 736 695 14.0% Total events 70 74 Heterogenetic, Tar ² = 0.00; Chi ² = 3.02, df = 4 ($P = 0.55$); $P = 0\%$ Test for overall effect Z = 0.24 ($P = 0.81$) 6.6.4 Any AE Leading to Drug Discontinuation Anker et al. 2015 (HARMONID) 12 439 11 439 38% 1.09 [0.49, 2.45] Pite tal. 2022 (DIAMOND) 12 439 11 439 38% 1.09 [0.49, 2.45] Pite tal. 2022 (DIAMOND) 12 439 1.6% 1.19 [0.28, 5.05] Pite tal. 2022 (DIAMOND) 12 439 1.6% 0.55 [0.14, 2.10] Subtotal (95% CI) 645 605 7.9% Test for overall effect Z = 0.33 ($P = 0.72$); $P = 0\%$ Test for overall effect Z = 0.33 ($P = 0.72$); $P = 0\%$ Test for overall effect Z = 0.33 ($P = 0.72$); $P = 0\%$ Test for overall effect Z = 0.33 ($P = 0.72$); $P = 0\%$ Test for overall effect Z = 0.33 ($P = 0.72$); $P = 0\%$ Test for overall effect Z = 0.33 ($P = 0.72$); $P = 0\%$ Test for overall effect Z = 0.33 ($P = 0.72$); $P = 0\%$ Test for overall effect Z = 0.11 ($P = 0.27$) 6.6.6 Hypokalemia Anker et al. 2015 (HARMONIZE) 4 61 5 26 2.1% 0.34 [0.10, 1.17] Butler et al. 2022 (DIAMOND) 34 439 24 439 6.3% 1.42 [0.85, 2.35] Pit et al. 2015 (PAL-HF) 3 91 2 90 1.1% 1.48 [0.25, 6.57] Total events 65 46 Heterogenetic, Tar ² = 1.02, 2 (FRIORTIZE-HF) 3 91 2 90 1.1% 1.48 [0.25, 6.57] Total events 75 408 1.55\% 1.97 [0.59, 6.57] Total events 65 46 Heterogenetic Tar ² = 1.00; Chi ² = 4.72, df = 5 ($P = 0.45$); $P = 0\%$ Subtotal (95% CI) 736 695 10.1% 1.48 [0.86, 255.98] Differ tal. 2015 (HARMONIZE) 4 61 0 26 0.4% 3.28 [0.14, 70.11] Tardif et al. 2022 (OPAL-HF) 3 55 0 49 0.4% 6.55 (5.97] Total events 8 3 46 Heterogenetic, Tar ² = 0.00; Chi ² = 4.72, df = 5 ($P = 0.45$); $P = 0\%$ Total events 8 3 46 Heterogenetic, Tar ² = 0.00; Chi ² = 4.72, df = 5 ($P = 0.45$); $P = 0\%$ Total events 8 3 46 Heterogeneti	Butler et al. 2022 (DIAMOND)	54	439	58	439	8.1%	0.93 [0.66, 1.32]	-+
Pitt et al 2015 (OPAL-HK) 0 0 27 1 22 0.4% 027 [0.01, 6.41] Rossignol et al. 2022 (PRIORTIZE-HF) 14 91 0 90 4.2% 0.4% 0.16 [0.01, 2.97] Tradif et al 2022 (PRIORTIZE-HF) 14 91 0 90 4.2% 0.96 [0.71, 1.31] Subtotal (95% CI) 736 695 14.4% 0.96 [0.71, 1.31] Total events 70 74 Heterogeneity, Tau" = 0.00; Chi" = 3.02, dir = 4 ($P = 0.55$); $P = 0\%$ Test for overall effect Z = 0.24 ($P = 0.81$) 6.6.4 Any AE Leading to Drug Discontinuation Anker et al. 2015 (HARMONIZE) 0 61 0 26 Not estimable Butler et al. 2022 (DIAMOND) 12 439 11 439 3.8% 1.09 [0.49, 2.45] Pitt et al. 2011 (DPAL-HK) 1 27 2 22 0.7% 0.41 [0.04, 4.20] Rossignol et al. 2020 (AMBER) 3 63 6 69 18.% 0.55 [0.14, 2.10] Subtotal (95% CI) 645 605 7.9% 0.90 [0.49, 1.65] Total events 20 0.22 Heterogeneity, Tau" = 0.00; Chi" = 1.33, df = 3 ($P = 0.72$); $P = 0\%$ Test for overall effect Z = 0.33 ($P = 0.74$) 6.6.5 Gastrointestinal Disorders Anker et al. 2015 (HARMONIZE) 4 61 5 26 2.1% 0.34 [0.10, 1.17] Butler et al. 2015 (HARMONIZE) 4 61 5 26 2.1% 0.34 [0.10, 1.17] Butler et al. 2015 (HARMONIZE) 4 61 5 26 3.3% 1.42 [0.85, 2.35] Pitt et al. 2015 (HARMONIZE) 4 61 5 26 0.3% 0.64 [0.53, 154.97] Rossignio et al. 2020 (AMBER) 7 63 12 29 0 1.1% 1.48 [0.25, 8.67] Tardif et al. 2022 (PRIORTIZE-HF) 12 65 3 4439 2.1% 3.139 [3.30, 10.06 AI Pitt et al. 2015 (HARMONIZE) 4 61 0 26 0.4% 3.29 [0.12, 70.28] Butler et al. 2015 (HARMONIZE) 4 61 0 26 0.4% 3.29 [0.22, 70.28] Butler et al. 2022 (PRIORTIZE-HF) 3 91 2 90 1.1% 1.48 [0.25, 8.67] Tardif et al. 2022 (PRIORTIZE-HF) 3 65 0 49 0.4% 3.29 [0.14, 70.11] Tardif et al. 2022 (PRIORTIZE-HF) 7 91 0.90 0.5% 1.4.84 [0.86, 255.99] Subtotal (95% CI) 736 695 10.1% 1.57 [1.12, 2.21] Total events 83 46 Heterogeneity, Tau" = 0.0C, Chi" = 4.72, df = 5 ($P = 0.45$); $P = 0\%$ Test for overall effect Z = 2.80 ($P = 0.003$) Total (95% CI) 736 (95 10.0\%) 1.18 [0.97, 1.44] Total events 83 46 Heterogeneity, Tau" = 0.00; Chi" = 6.74, 0.0005; PI = 0\% Test for overall effect Z = 2.80 ($P = 0.003$); $P = 56\%$	Pitt et al. 2011 (the PEARL-HF)	2	55	2	49	1.0%	0.89 (0.13, 6,09)	
Ressignol et al. 2020 (AMBER) 0 63 3 68 0.4% 0.16 [0.01, 2.97] Tardif et al. 2022 (PRIORTIZE-HF) 1 91 0.96 [0.71, 1.31] 1.36 [0.65, 2.95] Total events 70 74 Febrogeneity. Tar" = 0.00; Chi" = 3.02, dfr = 4 (P = 0.55); P = 0% Test for overall effect Z = 0.24 (P = 0.81) 6.6.4 Any AE Leading to Drug Discontinuation Anker et al. 2015 (HARMONIZE) 0 61 0 26 Not estimable Butler et al. 2022 (DIAMOND) 12 439 1.6% 1.19 [0.28, 6.05] 1.19 [0.24, 6.05] 1.19 [0.24, 6.05] Pitt et al. 2022 (DIAMOND) 12 27 2 2.07% 0.44 [10.04, 4.20] 0.50 [0.44, 2.10] Rossignoil et al. 2020 (AMBER) 3 63 6 69 1.8% 0.55 [0.14, 2.10] Subtotal (95% CI) 0 645 6.0% 1.42 [0.85, 2.35] 1.42 [0.85, 2.35] Pitt et al. 2016 (PAL-HF) 3 91 2 0.5% 0.34 [0.10, 1.17] Butler et al. 2022 (DIAMOND) 34 439 24 439 6.3% 1.42 [0.85, 2.35] Pitt et al. 2016 (PAL-HF) 5 2 <t< td=""><td>Pitt et al. 2015 (OPAL-HK)</td><td>ñ</td><td>27</td><td>- 1</td><td>22</td><td>0.4%</td><td>0.27 [0.01 6 41]</td><td></td></t<>	Pitt et al. 2015 (OPAL-HK)	ñ	27	- 1	22	0.4%	0.27 [0.01 6 41]	
$\begin{array}{c} \text{Laborgino 11 and 2022} (CPRIORITIZE-HP) & 14 & 91 & 10 & 90 & 4.2\% \\ \text{Subtotal (95\% CI)} & 736 & 695 & 14.0\% & 0.96 [0.71, 1.31] \\ \text{Subtotal (95\% CI)} & 736 & 695 & 14.0\% & 0.96 [0.71, 1.31] \\ \text{Total events} & 736 & 695 & 14.0\% & 0.96 [0.71, 1.31] \\ \text{Total events} & 736 & 695 & 14.0\% & 0.96 [0.71, 1.31] \\ \text{Total events} & 736 & 695 & 10.0\% & 1.38 [0.52, 2.55] \\ \text{Subtotal (95\% CI)} & 736 & 695 & 14.0\% & 0.96 [0.71, 1.31] \\ \text{Total events} & 730 & 74 \\ \text{Heterogeneily}; Tau2 = 0.00; Ch2 = 3.02, df = 4 (P = 0.55); P = 0\% \\ \text{Test for overall effect Z = 0.24 (P = 0.81) \\ \text{Solution} & 1.220 (OMAOND) & 12 & 438 & 11 & 439 & 3.8\% & 1.09 [0.49, 2.45] \\ \text{Subtotal (95\% CI)} & 0 & 61 & 0 & 26 \\ \text{Not estimable} & 1.09 [0.49, 2.45] \\ \text{Subtotal (95\% CI)} & 645 & 605 & 7.9\% & 0.90 [0.49, 1.65] \\ \text{Total events} & 20 & 22 \\ \text{Heterogeneily}; Tau2 = 0.00; Ch2 = 1.33, df = 3 (P = 0.72); P = 0\% \\ \text{Test for overall effect Z = 0.33 (P = 0.74) \\ \text{6.5. Gastrointestinal Disorders } \\ \text{Anker et al. 2015 (HARMONIZE)} & 4 & 61 & 5 & 26 & 2.1\% & 0.34 [0.10, 1.17] \\ \text{Subtotal (95\% CI)} & 736 & 1085 & 15.5\% & 1.97 [0.59, 6.57] \\ \text{Total events} & 1.2020 (AMBER) & 7 & 63 & 12 & 69 & 3.5\% & 0.44 [0.53, 154.97] \\ \text{Total events} & 1.2020 (AMBER) & 7 & 63 & 12 & 69 & 3.5\% & 0.44 [0.53, 154.97] \\ \text{Total events} & 36.5 & 0.44 & 0.26 & 0.4\% & 3.28 [0.12, 70.28] \\ \text{Butter et al. 2015 (HARMONIZE)} & 4 & 61 & 0 & 26 & 0.4\% & 3.28 [0.22, 70.28] \\ \text{Butter et al. 2015 (HARMONIZE)} & 4 & 61 & 0 & 26 & 0.4\% & 3.28 [0.22, 70.28] \\ \text{Butter et al. 2015 (HARMONIZE)} & 4 & 61 & 0 & 26 & 0.4\% & 3.28 [0.12, 70.18] \\ \text{Total events} & 3.5 & 0.44 (0.36, 25.5.98] \\ \text{Subtotal (95\% CI)} & 736 & 695 & 10.1\% & 1.37 [0.12, 2.04] \\ \text{Fit et al. 2011 (The PEARL-HF)} & 3 & 55 & 0 & 49 & 0.4\% & 6.25 [0.33, 118.05] \\ \text{Fit et al. 2012 (PNIOND)} & 66 & 439 & 439 & 0.0\% & 1.48 (0.36, 25.5.98] \\ \text{Subtotal (95\% CI)} & 736 & 695 & 10.1\% & 1.57 [1.12, 2.21] \\ \text{Fit et al. 2020 (MMEER)} & 1 & 63 & 0.6\% & 0.4\% & 3.28 [0.14, 79.11] \\ Total eve$	Rossignol et al. 2020 (AMRER)	0	62	2	60	0.4%	0.16 (0.01, 0.41)	
$ \begin{array}{c} \text{ration} \text{ call } 2022 (PRIONILE=PT) & 14 & 39 & 10 & 90 & 94.2 & 9 & 1.3 & 10 & 90.5 & 2.3 \\ \hline 736 & 695 & 14.0\% & 0.96 [0.71, 1.31] \\ \hline 736 & 695 & 14.0\% & 0.96 [0.71, 1.31] \\ \hline 736 & 695 & 14.0\% & 0.96 [0.71, 1.31] \\ \hline 736 & 695 & 14.0\% & 0.96 [0.71, 1.31] \\ \hline 736 & 695 & 14.0\% & 0.96 [0.71, 1.31] \\ \hline 736 & 695 & 14.0\% & 0.96 [0.71, 1.31] \\ \hline 736 & 695 & 14.0\% & 0.96 [0.71, 1.31] \\ \hline 736 & 695 & 14.0\% & 0.96 [0.71, 1.31] \\ \hline 736 & 695 & 14.0\% & 0.96 [0.71, 1.31] \\ \hline 736 & 695 & 14.0\% & 0.96 [0.71, 1.31] \\ \hline 6.6.4 \text{ Any AE Leading to Drug Discontinuation} \\ \hline 8.6.4 \text{ Any AE Leading to Drug Discontinuation} \\ \hline 8.6.4 \text{ Any AE Leading to Drug Discontinuation} \\ \hline 8.6.4 \text{ Any AE Leading to Drug Discontinuation} \\ \hline 8.6.4 \text{ Any AE Leading to Drug Oiscontinuation} \\ \hline 8.6.6 \text{ CPAL-HK}) & 1 & 27 & 22 & 0.7\% & 0.41 [0.04, 4.20] \\ \hline \text{Pitt et al. 2015 (PARL-HK) & 1 & 27 & 22 & 0.7\% & 0.41 [0.04, 4.20] \\ \hline \text{Pitt et al. 2015 (PARL-HK) & 1 & 27 & 22 & 0.7\% & 0.41 [0.04, 4.20] \\ \hline \text{Sotiponel effect } Z & 0.32 & (p = 0.72); p = 0\% \\ \hline \text{Test or overall effect } Z & -0.33 & (p = 0.72); p = 0\% \\ \hline \text{Test or overall effect } Z & -0.32 & (p = 0.72); p = 0\% \\ \hline \text{Test or overall effect } Z & -0.32 & (p = 0.72); p = 0\% \\ \hline \text{Test or overall effect } Z & -0.32 & (p = 0.72); p = 0\% \\ \hline \text{Test or overall effect } Z & -0.32 & (p = 0.72); p = 0\% \\ \hline \text{Test or overall effect } Z & -1.33 & (f = 3 & (p = 0.72); p = 0\% \\ \hline \text{Test or overall effect } Z & -1.11 & (p = 0.27) \\ \hline \text{6.6.6 Hypokalemia} \\ \hline \text{Anker et al. 2015 (PARL-HK) & 2 & 27 & 0 & 22 & 0.4\% & 4.11 & 0.27, 8.13 \\ \hline \text{Tardif et al. 2022 (PMIONDE}) & 6 & 61 & 0 & 26 & 0.4\% & 3.28 [0.14, 79, 11] \\ \hline \text{Test or overall effect } Z & -1.11 & (p = 0.27) \\ \hline \text{6.6.6 Hypokalemia} \\ \hline \text{Anker et al. 2022 (PMIONDE}) & 6 & 61 & 0 & 26 & 0.4\% & 3.28 [0.27, 7.28] \\ \hline \text{Pitt et al. 2021 (DMADKDD) & 66 & 39 & 46 & 4.39 & 3.0\% & 1.48 [0.36, 255.99] \\ \hline \text{Total events} & 83 & 46 \\ \hline Heterogenely; Tau2 = 0.00; Ch2 = 4.72, df = 5 & (p = 0.45); p^2 = 0\% \\ \hline \text{Test or over$	Tardif at al. 2020 (AMDER)	1.4	03	10	00	1 20/	1 20 10 66 2 051	
$\begin{aligned} & \text{Latternet}, & \text{CLAS}, & $	Subtotal (95% CI)	14	736	10	605	4.2%	1.38 [0.65, 2.95]	▲
$ \begin{array}{c} 10 \text{ all events}\\ 10 \text{ all events}\\ 12 \text{ Test for overall effect: } Z = 0.24 \ (P = 0.55); P = 0\%\\ 12 \text{ for overall effect: } Z = 0.24 \ (P = 0.81)\\ \hline \\ 6.6.4 \text{ Any AE Leading to Drug Discontinuation}\\ Anker et al. 2015 \ (HARMONIZE) 0 & 61 0 26 \\ \text{Nutler et al. 2012 \ (DAMAGN) 1 2 439 11 439 3.8\% 1.09 \ (0.49, 2.45)\\ \text{Pitt et al. 2015 \ (CPAL-HF) 4 55 3 49 1.6\% 1.19 \ (0.24, 5.05)\\ \text{Pitt et al. 2015 \ (CPAL-HF) 1 4 55 3 49 1.6\% 0.55 \ (0.14, 2.10)\\ \text{Rossignol et al. 2020 \ (AMBER) 3 63 6 69 1.8\% 0.55 \ (0.14, 2.10)\\ \text{Subtotal (95% C) 645 605 7.9\% 0.90 \ (0.49, 1.65)\\ \text{Total events} 20 22 \\ \text{Heterogeneily: Tau" = 0.00; Chi" = 1.33, df = 3 \ (P = 0.72); P = 0\%\\ \text{Test for overall effect: } Z = 0.33 \ (f = 3.16 + 0.72); P = 0\%\\ \text{Test for overall effect: } Z = 0.33 \ (f = 3.16 + 0.72); P = 0\%\\ \text{Test for overall effect: } Z = 0.33 \ (f = 3.16 + 0.72); P = 0\%\\ \text{Test for overall effect: } Z = 0.33 \ (f = 3.16 + 0.72); P = 0\%\\ \text{Test for overall effect: } Z = 0.33 \ (f = 3.16 + 0.72); P = 0\%\\ \text{Test for overall effect: } Z = 0.33 \ (f = 3.16 + 0.72); P = 0\%\\ \text{Test for overall effect: } Z = 0.33 \ (f = 3.16 + 0.72); P = 0\%\\ \text{Test for overall effect: } Z = 0.22 \ (CFMONIZE) 4 61 5 26 2.1\% \ 0.34 \ (0.07, 1.52)\\ \text{Tardif et al. 2020 \ (MMBER) 7 63 12 69 3.5\% \ 0.44 \ (0.27, 1.52)\\ \text{Tardif et al. 2020 \ (PMEEN) 7 63 12 69 3.5\% \ 0.48 \ (0.27, 1.52)\\ \text{Tardif et al. 2020 \ (PMEEN) 7 63 12 69 3.5\% \ 0.48 \ (0.27, 1.52)\\ \text{Total events} 65 \ 46 \\ \text{Heterogeneily}, Tau" = 1.74 \ (Chi" = 34.62, \ df = 5 \ (F < 0.00001); P = 86\%\\ \text{Test for overall effect: } Z = 1.11 \ (P = 0.27)\\ \text{Cossignol et al. 2020 \ (MMEER) 1 63 0 68 0.4\% \ 3.28 \ (0.14, 73.11)\\ \text{Tardif et al. 2020 \ (MMEER) 1 63 0 68 0 0.4\% \ 3.28 \ (0.14, 73.11)\\ \text{Tardif et al. 2020 \ (MMEER) 1 63 0 68 0 0.4\% \ 3.28 \ (0.14, 73.11)\\ \text{Tardif et al. 2020 \ (MMEER) 1 63 0 68 0 0.4\% \ 3.28 \ (0.14, 73.11)\\ \text{Tardif events} 83 \ 46 \\ \text{Heterogeneily}, Tau" = 0.00; Chi" = 4.72, df = 5 \ (P = 0.45); P = 0\%\\ \text{Total (95\% CI) } \ 736 \ 605 \ 10.1\% \$		70	150	74	035	14.0 /0	0.50 [0.71, 1.51]	▼
Heterogeneity: Tau" = 0.00; Ch ² = 3.02, df = 4 ($r = 0.55$); r = 0% Test for overall effect. Z = 0.24 ($r = 0.61$) 6.6.4 Any AE Leading to Drug Discontinuation Anker et al. 2015 (HARMONIZE) 0 61 0 26 Not estimable Builter et al. 2022 (DIAMOND) 12 439 11 439 3.8% 1.09 [0.49, 245] Pitt et al. 2014 (Dn PEARL-HF) 4 55 3 49 1.6% 1.19 [0.28, 5.05] Pitt et al. 2012 (DAMBER) 3 63 6 69 1.6% 0.55 [0.14, 2.10] Subtoal (95% CI) 645 605 7.9% 0.90 [0.49, 1.65] Total events 20 22 Heterogeneity: Tau" = 0.00; Ch ² = 1.33, df = 3 ($r = 0.72$); P = 0% Test for overall effect. Z = 0.33 ($r = 0.74$) 6.6.5 Gastrointestinal Disorders Anker et al. 2015 (HARMONIZE) 4 61 5 26 2.1% 0.34 [0.10, 1.17] Builter et al. 2022 (PIMORNIZE) 4 61 5 27 0 22 0.5% 9.044 [0.53, 154.97] Rossignol et al. 2022 (PIMORNIZE) 7 63 12 69 3.5% 0.64 [0.27, 1.52] Total events 65 46 Heterogeneity: Tau" = 1.74; Ch ² = 34.62, df = 5 ($r < 0.00001$); P = 86% Test for overall effect. Z = 1.11 ($r = 0.27$) 6.6.6 Hypokalemia Anker et al. 2015 (HARMONIZE) 4 61 0 26 0.4% 3.92 [0.22, 70.28] Builter et al. 2022 (DIAMONIZE) 4 61 0 26 0.4% 3.92 [0.22, 70.28] Builter et al. 2015 (HARMONIZE) 4 61 0 26 0.4% 3.92 [0.22, 70.28] Builter et al. 2015 (HARMONIZE) 4 61 0 26 0.4% 3.92 [0.22, 70.28] Builter et al. 2015 (HARMONIZE) 4 61 0 26 0.4% 3.92 [0.22, 70.28] Builter et al. 2015 (HARMONIZE) 4 61 0 26 0.4% 3.92 [0.22, 70.28] Builter et al. 2015 (HARMONIZE) 4 61 0 26 0.4% 3.92 [0.22, 70.28] Builter et al. 2015 (HARMONIZE) 4 61 0 26 0.4% 3.92 [0.22, 70.28] Builter et al. 2015 (HARMONIZE) 4 61 0 26 0.4% 3.92 [0.22, 70.28] Builter et al. 2015 (HARMONIZE) 4 61 0 26 0.4% 3.92 [0.22, 70.28] Builter et al. 2015 (HARMONIZE) 4 61 0 26 0.4% 3.92 [0.22, 70.28] Builter et al. 2015 (HARMONIZE) 4 61 0 26 0.4% 3.92 [0.24, 70.18] Total events 42 2015 (HARMONIZE) 4 61 0 26 0.4% 3.92 [0.14, 70.11] Tardif et al. 2022 (DIAMONE) 1 63 0 69 0.4% 3.28 [0.14, 70.11] Tardif et al. 2022 (DAMOER) 1 63 0 69 0.4% 3.28 [0.14, 70.11] Tardif et al. 2020 (CPAL-HF) 7 73 6 695 10.0	Total events	10		74	~			
6.6.4 Any AE Leading to Drug Discontinuation Anker et al. 2015 (HARMONIZE) 0 61 0 26 Not estimable Buller et al. 2022 (DIAMOND) 12 433 11 439 3.8% 1.09 [0.49, 245] Pitt et al. 2015 (OPAL-HK) 1 27 2 22 0.7% 0.41 [0.04, 4.20] Rossignol et al. 2020 (AMBER) 3 63 6 69 7.3% 0.90 [0.49, 1.65] Total events 20 22 22 7.3% 0.34 [0.10, 1.17] Resignol et al. 2002 (AMBER) 3 63 6.93 1.42 [0.85, 2.35] Total events 20 22 0.5% 0.34 [0.10, 1.17] Butler et al. 2015 (HARMONIZE) 4 61 5 26 2.1% 31.93 [9.30, 109.64] Pitt et al. 2015 (PAR-HK) 12 290 1.1% 1.42 [0.85, 2.35] 1.42 [0.85, 2.35] Pitt et al. 2012 (DIAMOND) 34 439 2.4 31.93 [9.30, 109.64] 1.42 [0.25, 8.67] Subtotal (95% CI) 7.36 1085 1.55% 1.97 [0.59, 6.57] 1.48 [0.25, 8.67] Subtotal (95% CI) 7.36	Heterogeneity: Tau* = 0.00; Cni* = 3.0 Test for overall effect: Z = 0.24 (P = 0.	J2, ατ = 4 : 81)	(P = 0.5	5); I* = U	%			
$ \begin{array}{c} \text{Act} \text{Ark} \text{ret} 1.2015 (HARMONIZE) & 0 & 61 & 0 & 26 & \text{Not estimable} \\ \text{Butter et al. 2022 (DIAMOND) & 12 & 439 & 11 & 439 & 3.8\% & 1.09 [0.49, 2.45] \\ \text{Pitt et al. 2015 (OPAL-HK) & 1 & 27 & 2 & 22 & 0.7\% & 0.41 [0.04, 4.20] \\ \text{Rossignol et al. 2020 (AMBER) & 3 & 63 & 6 & 69 & 1.8\% & 0.55 [0.14, 2.10] \\ \text{Subtotal (95% C)} & 645 & 605 & 7.9\% & 0.90 [0.49, 1.65] \\ \text{Test for overall effect Z = 0.33 (P = 0.72); P = 0\% \\ \text{Test for overall effect Z = 0.33 (P = 0.72); P = 0\% \\ \text{Test for overall effect Z = 0.33 (P = 0.72); P = 0\% \\ \text{Test for overall effect Z = 0.33 (P = 0.72); P = 0\% \\ \text{Test for overall effect Z = 0.33 (P = 0.72); P = 0\% \\ \text{Test for overall effect Z = 0.33 (P = 0.72); P = 0\% \\ \text{Test for overall effect Z = 0.33 (P = 0.72); P = 0\% \\ \text{Test for overall effect Z = 0.33 (P = 0.72); P = 0\% \\ \text{Test for overall effect Z = 0.33 (P = 0.72); P = 0\% \\ \text{Test for overall effect Z = 0.33 (P = 0.72); P = 0\% \\ \text{Test for overall effect Z = 0.13 (P = 0.72); P = 0\% \\ \text{Test for overall effect Z = 0.13 (P = 0.00001); P = 56\% \\ \text{Test for overall effect Z = 1.11 (P = 0.27) \\ 6.6.6 \text{ Hypokalemia} \\ \text{Anker et al. 2022 (PRIORITIZE-HF) } 3 & 91 & 2 & 90 & 1.1\% & 1.48 [0.25, 6.67] \\ \text{Total events } 65 & 46 \\ \text{Heterogeneib; Tau" = 1.74; Chi" = 34.62, df = 5 (P < 0.00001); P = 86\% \\ \text{Test for overall effect Z = 1.11 (P = 0.27) \\ 6.6.6 \text{ Hypokalemia} \\ \text{Anker et al. 2022 (PRIORITIZE-HF) } 3 & 64 & 0.4\% & 3.28 [0.14, 7.2.04] \\ \text{Pitt et al. 2015 (HARMONIZE) } 4 & 61 & 0 & 26 & 0.4\% & 3.28 [0.14, 7.8.13] \\ \text{Test for overall effect Z = 2.60 (P = 0.009) \\ \text{Total events } 83 & 46 \\ \text{Heterogeneib; Tau" = 0.00; Chi" = 4.72, df = 5 (P = 0.4; 6.1; P = 0\% \\ \text{Total events } 730 & 60 \\ Total events$	6.6.4 Any AE Loading to Drug Discor	ntinuation						
Anker et al. 2015 (HARMONIZE) 0 61 0 26 Not estimate builter et al. 2022 (DIAMOND) 12 439 11 439 3.8% 1.09 [0.49, 2.45] Pitt et al. 2011 (the PEARL-HF) 4 55 3 49 1.6% 1.19 [0.29, 6.05] Pitt et al. 2015 (DPAL-HK) 1 27 2 22 0.7% 0.41 [0.04, 4.20] Rossignol et al. 2020 (AMBER) 3 63 6 68 1.8% 0.55 [0.14, 2.10] Subtotal (95% CI) 645 605 7.9% 0.90 [0.49, 1.65] Total events 20 22 Heterogeneity: Tau ² = 0.00; Chi ² = 1.33, df = 3 ($P = 0.72$); $P = 0$ % Test for overall effect: Z = 0.33 ($P = 0.72$); $P = 0$ % Test for overall effect: Z = 0.33 ($P = 0.72$); $P = 0$ % Test for overall effect: Z = 0.33 ($P = 0.72$); $P = 0$ % Test for overall effect: Z = 0.33 ($P = 0.72$); $P = 0$ % Test for overall effect: Z = 0.33 ($P = 0.72$); $P = 0$ % Test for overall effect: Z = 0.33 ($P = 0.72$); $P = 0$ % Total events 65 46 Heterogeneity: Tau ⁴ = 1.74; Chi ² = 34.62, df = 5 ($P < 0.00001$); $P = 86\%$ Test for overall effect: Z = 1.11 ($P = 0.27$) 6.6.6 Hypokalemia Anker et al. 2015 (DARL-HK) 2 27 0 22 0.4% 4.11 [0.21, 81.33] Rossignol et al. 2022 (QIAMOND) 66 439 46 439 8.0% 1.43 [1.01, 2.14] Pitt et al. 2015 (DARL-HK) 2 27 0 22 0.4% 4.11 [0.21, 81.33] Rossignol et al. 2022 (QIAMOND) 66 439 46 439 8.0% 1.43 [1.01, 2.14] Pitt et al. 2015 (DARL-HK) 2 27 0 22 0.4% 4.11 [0.21, 81.33] Rossignol et al. 2022 (QIAMOND) 66 439 46 439 8.0% 1.43 [1.01, 2.14] Pitt et al. 2015 (DARL-HK) 2 27 0 22 0.4% 4.11 [0.21, 81.33] Rossignol et al. 2022 (QIAMOND) 7.76 0.95 10.0% 1.48 [0.86, 255.99] Subtotal (95% CI) 736 0.95 10.1% 1.57 [1.12, 2.21] Pitt et al. 2011 (D = PEARL-HF) 3 83 46 Heterogeneity: Tau ² = 0.00; Chi ² = 4.72, df = 5 ($P = 0.45$); $P = 0$ % Test for overall effect: Z = 2.60 ($P = 0.009$) Total events 8 36 Heterogeneity: Tau ² = 0.09; Chi ² = 88.14, df = 30 ($P = 0.0001$; $P = 56\%$	0.0.4 Any AE Leading to Drug Discor	runuauon					Net e eller elle	
Buller et al. 2022 (DIAMOND) 12 4 39 11 439 3.8% 1.09 [0.49, 2.45] Pitt et al. 2015 (OPAL-HF) 4 55 3 49 1.8% 1.19 [0.28, 5.05] Pitt et al. 2015 (OPAL-HK) 1 27 2 22 0.7% 0.41 [0.04, 4.20] Rossignol et al. 2020 (AMBER) 3 63 6 69 1.8% 0.55 [0.14, 2.10] Subtotal (95% CI) 645 605 7.9% 0.90 [0.49, 1.65] Total events 20 22 Heterogeneity: Tau ² = 0.00; Chi ² = 1.33, df = 3 ($P = 0.72$); $P = 0\%$ Test for overall effect $Z = 0.33$ ($P = 0.74$) 6.6.5 Gastrointestinal Disorders Anker et al. 2015 (HARMONIZE) 4 61 5 26 2.1% 0.34 [0.10, 1.17] Butler et al. 2022 (DIAMOND) 34 439 24 439 6.3% 1.42 [0.85, 2.36] Pitt et al. 2015 (OPAL-HF) 12 55 3 439 2.1% 31.93 [9.30, 109.64] Pitt et al. 2015 (OPAL-HF) 12 55 3 439 2.1% 31.93 [9.30, 109.64] Pitt et al. 2012 (QMMOER) 7 63 12 89 3.5% 0.64 [0.27, 1.52] Total events 65 46 Heterogeneity: Tau ² = 1.74; Chi ² = 34.62; df = 5 ($P < 0.00001$); $P = 86\%$ Test for overall effect $Z = 1.11$ ($P = 0.27$) 6.6.6 Hypokalemia Anker et al. 2015 (HARMONIZE) 4 61 0 26 0.4% 3.92 [0.22, 70.28] Butler et al. 2015 (HARMONIZE) 4 61 0 26 0.4% 3.92 [0.22, 70.28] Butler et al. 2015 (HARMONIZE) 4 61 0 26 0.4% 3.92 [0.23, 118.05] Pitt et al. 2015 (HARMONIZE) 4 61 0 26 0.4% 3.92 [0.23, 118.05] Pitt et al. 2015 (HARMONIZE) 4 61 0 26 0.4% 3.92 [0.24, 70.28] Butler et al. 2015 (HARMONIZE) 4 61 0 26 0.4% 3.92 [0.24, 70.28] Butler et al. 2015 (HARMONIZE) 4 61 0 26 0.4% 3.92 [0.24, 70.28] Butler et al. 2015 (HARMONIZE) 4 61 0 26 0.4% 3.28 [0.14, 79.11] Total events 83 45 Heterogeneity: Tau ² = 0.00; Chi ² = 4.72, df = 5 ($P = 0.45$); $P = 0\%$ Test for overall effect $Z = 2.60$ ($P = 0.009$) Total [95% CI) 736 695 10.1% 1.57 [1.12, 2.21] Total events 83 45 Heterogeneity: Tau ² = 0.09; Chi ² = 68.4, df = 30 ($P < 0.0001$); $P = 56\%$	Anker et al. 2015 (HARMUNIZE)	0	61	U	26		Not estimable	
Pitt et al. 2015 (PARL-HF) 4 65 3 49 1.6% 1.19 [0.28, 5.05] Pitt et al. 2015 (PARL-HK) 1 27 2 22 0.7% 0.41 [0.04, 4.20] Rossignol et al. 2020 (AMBER) 3 63 6 69 1.8% 0.55 [0.14, 2.10] Subtotal (95% CI) 645 605 7.9% 0.90 [0.49, 1.65] Total events 20 22 Heterogeneity: Tau ² = 0.00; Chi ² = 1.33, df = 3 ($P = 0.72$); P = 0% Test for overall effect: Z = 0.33 ($P = 0.74$) 6.6.5 Gastrointestinal Disorders Anker et al. 2015 (HARMONIZE) 4 61 5 26 2.1% 0.34 [0.10, 1.17] Buttler et al. 2022 (DIAMOND) 34 439 24 439 6.3% 1.42 [0.85, 2.35] Pitt et al. 2015 (HARMONIZE) 4 61 5 27 0 22 0.5% 9.04 [0.53, 154.97] Rossignol et al. 2020 (PMBER) 7 63 12 69 3.5% 0.64 [0.27, 1.52] Total events 65 46 Heterogeneity: Tau ² = 1.74; Chi ² = 34.62, df = 5 ($P = 0.00001$); P = 86% Test for overall effect: Z = 1.11 ($P = 0.27$) 6.6.6 Hypokalemia Anker et al. 2015 (HARMONIZE) 4 61 0 26 0.4% 3.92 [0.22, 70.28] Buttler et al. 2022 (PRIORTIZE-HF) 3 91 2 90 1.1% 1.48 [0.25, 8.67] Total events 65 46 Heterogeneity: Tau ² = 1.74; Chi ² = 34.62, df = 5 ($P = 0.00001$); P = 86% Test for overall effect Z = 1.11 ($P = 0.27$) 6.6.6 Hypokalemia Anker et al. 2015 (HARMONIZE) 4 61 0 26 0.4% 3.92 [0.22, 70.28] Buttler et al. 2022 (PRIORTIZE-HF) 7 91 0 90 0.5% 14.481 (0.86, 256.93] Subtotal (95% CI) 736 695 10.1% 1.57 [1.12, 2.21] Total events 83 46 Heterogeneity: Tau ² = 0.00; Chi ² = 4.72, df = 5 ($P = 0.45$); P = 0% Test for overall effect Z = 2.50 ($P = 0.009$) Total events 730 650 Total events 730 750 730 Total events 7	Butler et al. 2022 (DIAMOND)	12	439	11	439	3.8%	1.09 [0.49, 2.45]	
Pitt et al. 2015 (OPAL-HK) 1 27 2 22 0.7% 0.41 (0.04, 4.20) Rossignol et al. 2020 (AMBER) 3 63 6 63 1.8% 0.55 [0.14, 2.10] Total events 20 22 Heterogeneity: Tau" = 0.00; Chi"= 1.33, df = 3 ($P = 0.72$); $P = 0\%$ Test for overall effect. Z = 0.30; $P = 0.74$) 6.6.5 Gastrointestinal Disorders Anker et al. 2015 (HARMONIZE) 4 61 5 26 2.1% 0.34 [0.10, 1.17] Butler et al. 2022 (DIAMOND) 34 439 244 439 6.3% 1.42 [0.05, 2.35] Pitt et al. 2015 (OPAL-HK) 5 27 0 22 0.5% 9.04 [0.53, 154.97] Rossignol et al. 2022 (QIAMOER) 7 63 12 69 3.5% 0.64 [0.27, 1.52] Tardif et al. 2022 (QIAMOER) 7 63 12 69 3.5% 0.64 [0.27, 1.52] Tardif et al. 2022 (QIAMOER) 7 63 12 69 3.5% 0.64 [0.27, 1.52] Tardif et al. 2022 (QIAMOER) 7 65 46 Heterogeneity: Tau" = 1.74; Chi" = 34.62, df = 5 ($P < 0.00001$); $P = 86\%$ Test for overall effect. Z = 1.11 ($P = 0.27$) 6.6.6 Hypokalemia Anker et al. 2015 ($OPAL-HK$) 2 27 0 22 0.4% 3.143 [1.01, 2.04] Pitt et al. 2015 ($OPAL-HK$) 3 50 49 0.4% 6.25 [0.33, 118.05] Pitt et al. 2015 ($OPAL-HK$) 2 27 0 22 0.4% 4.11 [0.1, 2.04] Pitt et al. 2015 ($OPAL-HK$) 3 55 0 49 0.4% 6.25 [0.33, 118.05] Pitt et al. 2015 ($OPAL-HK$) 2 27 0 22 0.4% 4.11 [0.1, 8.1.33] Rossignol et al. 2022 (QIAMOER) 1 63 0 68 0.4% 3.28 [0.14, 78.11] Tardif et al. 2022 (PRIORITIZE-HF) 7 91 0 90 0.5% 14.84 [0.86, 255.99] Subtotal (95% CI) 736 695 10.1% 1.57 [1.12, 2.21] Total events 8 3 46 Heterogeneity: Tau" = 0.00; Chi" = 4.72, df = 5 ($P = 0.45$); $P = 0\%$ Test for overall effect Z = 2.60 ($P = 0.009$) Total events 730 650 Heterogeneity: Tau" = 0.00; Chi" = 4.72, df = 5 ($P = 0.45$); $P = 0\%$ Total events 730 650 Heterogeneity: Tau" = 0.00; Chi" = 4.72, df = 5 ($P = 0.40$); $P = 56\%$	Pitt et al. 2011 (the PEARL-HF)	4	55	3	49	1.6%	1.19 [0.28, 5.05]	
Ressignol et al. 2020 (AMBER) 3 63 6 69 1.8% 0.55 [0.14, 2.10] Subtotal (95% CI) 645 605 7.9% 0.90 [0.49, 1.65] Total events 20 22 Heterogeneity: Tau ² = 0.00; Chi ² = 1.33, df = 3 ($P = 0.72$); $P = 0$ % Test for overall effect: $Z = 0.33$ ($P = 0.74$) 6.6.5 Gastrointestinal Disorders Anker et al. 2015 (HARMONIZE) 4 61 5 26 2.1% 0.34 [0.10, 1.17] Butter et al. 2022 (DIAMOND) 34 439 24 439 6.3% 1.42 [0.85, 2.35] Pitt et al. 2015 (HARMONIZE) 5 27 0 22 0.5% 9.04 [0.53, 154.97] Rossignol et al. 2022 (QIAMER) 7 63 12 69 3.5% 0.64 [0.27, 1.52] Tardif et al. 2022 (QIAMER) 7 63 12 69 3.5% 1.97 [0.59, 6.57] Total events 65 46 Heterogeneity: Tau ² = 1.74; Chi ² = 34.62, df = 5 ($P < 0.00001$); $P = 86\%$ Test for overall effect: $Z = 1.11$ ($P = 0.27$) 6.6.6 Hypokalemia Anker et al. 2022 (DIAMOND) 66 439 4.6 439 8.0% 1.43 [1.01, 2.04] Pitt et al. 2022 (QIAMER) 7 63 0 69 0.4% 3.28 [0.14, 73.11] Tardif et al. 2022 (QIAMER) 1 63 0 69 0.4% 3.28 [0.14, 73.11] Tardif et al. 2022 (CIAMOND) 66 439 4.6 Heterogeneity: Tau ² = 0.00; Chi ² = 4.72, df = 5 ($P = 0.45$); $P = 0$ % Test for overall effect: $Z = 1.11$ ($P = 0.27$) 6.6.6 Hypokalemia Anker et al. 2015 (HARMONIZE) 4 61 0 26 0.4% 3.29 [0.22, 70.28] Butter et al. 2022 (DIAMOND) 66 439 4.6 439 8.0% 1.43 [1.01, 2.04] Pitt et al. 2022 (DIAMOND) 66 439 4.6 439 8.0% 1.43 [1.01, 2.04] Pitt et al. 2022 (DIAMOND) 68 4.39 4.6 4.39 8.0% 1.43 [1.01, 2.04] Pitt et al. 2022 (DIAMOND) 68 4.39 4.6 4.39 8.0% 1.43 [1.02, 1, 81.33] Rossignol et al. 2020 (AMBER) 1 63 0 69 0.4% 3.28 [0.14, 79.11] Tardif et al. 2022 (CIAMER) 7 6 ($P = 0.045$); $P = 0$ % Test for overall effect: $Z = 2.60$ ($P = 0.05$) Total events 730 650 Heterogeneity: Tau ² = 0.00; Chi ² = 4.72, df = 5 ($P = 0.45$); $P = 0$ % Test for overall effect: $Z = 2.60$ ($P = 0.009$) Total events 730 650 Heterogeneity: Tau ² = 0.00; Chi ² = 6.72, df = 5 ($P = 0.000$) Total events 730 650	Pitt et al. 2015 (OPAL-HK)	1	27	2	22	0.7%	0.41 [0.04, 4.20]	
Subtotal (95% CI) 645 605 7.9% 0.90 [0.49, 1.65] Total events 20 22 Heterogeneity: Tau ² = 0.00; Chi ² = 1.33, df = 3 ($P = 0.72$); $P = 0\%$ Test for overall effect $Z = 0.33$ ($P = 0.74$) 6.6.5 Gastrointestinal Disorders Anker et al. 2015 (HARMONIZE) 4 61 5 26 2.1% 0.34 [0.10, 1.17] Butler et al. 2015 (HARMONIZE) 4 61 5 26 3.439 2.1% 31.93 [0.30, 109.64] Pitt et al. 2011 (the PEARL-HF) 12 55 3 439 2.1% 31.93 [0.30, 109.64] Pitt et al. 2013 (OPAL-HK) 5 27 0 22 0.5% 0.64 [0.27, 1.52] Tardif et al. 2022 (CPRIORITIZE-HF) 3 91 2 90 1.1% 1.48 [0.25, 8.67] Subtotal (95% CI) 736 1085 15.5% 1.97 [0.59, 6.57] Total events 65 46 Heterogeneity: Tau ² = 1.74; Chi ² = 34.62, df = 5 ($P < 0.00001$); $P = 86\%$ Test for overall effect $Z = 1.11$ ($P = 0.27$) 6.6.6 Hypokalemia Anker et al. 2015 (HARMONIZE) 4 61 0 26 0.4% 3.92 [0.22, 70.28] Butler et al. 2015 (HARMONIZE) 4 61 0 26 0.4% 3.92 [0.22, 70.28] Butler et al. 2015 (HARMONIZE) 4 61 0 26 0.4% 3.92 [0.12, 70.28] Butler et al. 2015 (OPAL-HK) 2 27 0 22 0.4% 4.11 [0.21, 81.33] Rossignol et al. 2022 (ORMORD) 66 439 4.6 439 8.0% 1.43 [1.01, 2.04] Pitt et al. 2015 (OPAL-HK) 2 27 0 22 0.4% 4.11 [0.21, 81.33] Rossignol et al. 2020 (AMBER) 1 63 0 69 0.4% 3.28 [0.14, 73.11] Tardif et al. 2022 (PIRIORITIZE-HF) 7 91 0 90 0.5% 14.84 [0.86, 255.99] Subtotal (95% CI) 736 695 10.1% 1.57 [1.12, 2.21] Total events 8 3 46 Heterogeneity: Tau ² = 0.00; Chi ² = 4.72, df = 5 ($P = 0.45$); $P = 0\%$ Test for overall effect: $Z = 2.60$ ($P = 0.009$) Total (95% CI) 4209 4395 100.0% 1.18 [0.97, 1.44] Total events 730 650 Heterogeneity: Tau ² = 0.09; Chi ² = 68, 41, df = 30 ($P < 0.0001$); $P = 56\%$	Rossignol et al. 2020 (AMBER)	3	63	6	69	1.8%	0.55 [0.14, 2.10]	
Total events 20 22 Heterogeneity: Tau ² = 0.00; Ch ² = 1.33, df = 3 ($P = 0.72$); $P = 0\%$ Test for overall effect: Z = 0.33 ($P = 0.74$) 6.6.5 Gastrointestinal Disorders Anker et al. 2015 (HARMONIZE) 4 61 5 26 2.1% 0.34 [0.10, 1.17] Butler et al. 2022 (DIAMOND) 34 439 24 439 6.3% 1.42 [0.85, 2.35] Pitt et al. 2011 (the PEARL-HF) 12 55 3 439 2.1% 31.93 [9.30, 109.64] Pitt et al. 2015 (OPAL-HK) 5 2.7 0 22 0.5% 9.04 [0.53, 154.97] Rossignol et al. 2020 (AMBER) 7 63 12 69 3.5% 0.64 [0.27, 1.52] Tardif et al. 2022 (PIORTIZE-HF) 3 91 2 90 1.1% 1.48 [0.25, 8.67] Total events 65 46 Heterogeneity: Tau ² = 1.74; Chi ² = 34.62, df = 5 ($P < 0.00001$); $P = 86\%$ Test for overall effect: Z = 1.11 ($P = 0.27$) 6.6.6 Hypokalemia Anker et al. 2015 (HARMONIZE) 4 61 0 26 0.4% 3.92 [0.22, 70.28] Butler et al. 2015 (HARMONIZE) 4 61 0 28 0.4% 6.25 [0.33, 118.05] Pitt et al. 2015 (HARMONIZE) 4 61 0 28 0.4% 4.11 [0.21, 81.33] Rossignol et al. 2022 (DIAMOND) 66 439 46 439 8.0% 1.43 [1.01, 2.04] Pitt et al. 2015 (OPAL-HK) 2 2.7 0 22 0.4% 4.11 [0.21, 81.33] Rossignol et al. 2022 (PIORTIZE-HF) 7 91 0 90 0.5% 14.84 [0.86, 255.99] Subtotal (95% Cl) 736 695 10.1% 1.57 [1.12, 2.21] Total events 83 46 Heterogeneity: Tau ² = 0.00; Chi ² = 4.72, df = 5 ($P = 0.45$); $P = 0\%$ Test for overall effect Z = 2.60 ($P = 0.009$) Total (95% Cl) 4209 4395 100.0% 1.18 [0.97, 1.44] Total events 730 650	Subtotal (95% CI)		645		605	7.9%	0.90 [0.49, 1.65]	•
Heterogeneity: Tau ² = 0.00; Chi ² = 1.33, df = 3 ($P = 0.72$); $P = 0\%$ Test for overall effect: Z = 0.33 ($P = 0.74$) 6.6.5 Gastrointestinal Disorders Anker et al. 2015 (HARMONIZE) 4 61 5 26 2.1% 0.34 [0.10, 1.17] Butler et al. 2022 (DIAMOND) 34 439 24 439 6.3% 1.42 [0.85, 2.35] Pitt et al. 2012 (DIAMOND) 34 439 24 439 6.3% 1.42 [0.85, 2.35] Pitt et al. 2012 (DIAMOND) 34 439 24 439 6.3% 1.42 [0.85, 2.35] Pitt et al. 2015 (OPAL-HF) 12 55 3 439 2.1% 31.93 [9.30, 109.64] Pitt et al. 2015 (OPAL-HK) 5 2.7 0 2.2 0.5% 9.04 [0.53, 154.97] Rossignol et al. 2020 (AMBER) 7 63 12 69 3.5% 0.64 [0.27, 1.52] Tardif et al. 2022 (PRIORITIZE-HF) 3 91 2 90 1.1% 1.48 [0.25, 8.67] Subtotal (95% CI) 736 1085 15.5% 1.97 [0.59, 6.57] Total events 65 46 Heterogeneity: Tau ² = 1.74; Chi ² = 34.62, df = 5 ($P < 0.00001$); $P = 86\%$ Test for overall effect: Z = 1.11 ($P = 0.27$) 6.6.6 Hypokalemia Anker et al. 2015 (HARMONIZE) 4 61 0 26 0.4% 3.92 [0.22, 70.28] Butler et al. 2022 (AMBORD) 66 439 46 439 8.0% 1.43 [1.01, 2.04] Pitt et al. 2015 (OPAL-HF) 3 55 0 49 0.4% 6.25 [0.33, 118.05] Pitt et al. 2015 (OPAL-HF) 7 91 0 90 0.5% 14.84 [0.88, 255.99] Subtotal (95% CI) 736 695 10.1% 1.57 [1.12, 2.21] Total events 83 46 Heterogeneity: Tau ² = 0.00; Chi ² = 4.72, df = 5 ($P = 0.45$); $P = 0\%$ Test for overall effect: Z = 2.60 ($P = 0.009$) Total (95% CI) 4209 4395 100.0% 1.18 [0.97, 1.44] Total events 730 650 Heterogeneity: Tau ² = 0.09; Chi ² = 68.14, df = 30 ($P < 0.0001$); $P = 56\%$	Total events	20		22				
6.6.5 Gastrointestinal Disorders Anker et al. 2015 (HARMONIZE) 4 61 5 26 2.1% 0.34 [0.10, 1.17] Butler et al. 2022 (DIAMOND) 34 439 24 439 6.3% 1.42 [0.85, 2.35] Pitt et al. 2011 (the PEARL-HF) 12 55 3 439 2.1% 31.93 [9.30, 109.64] Pitt et al. 2015 (OPAL-HK) 5 27 0 22 0.5% 0.04 [0.27, 1.52] Tardif et al. 2022 (PRIORITIZE-HF) 3 91 2 90 1.1% 1.48 [0.25, 8.67] Subtotal (95% CI) 736 1085 1.55% 1.97 [0.59, 6.57] Total events 65 46 Heterogeneity: Tau ² = 1.74; Chi ² = 34.62, df = 5 (P < 0.00001); P = 86%	Heterogeneity: Tau ² = 0.00; Chi ² = 1.3 Test for overall effect: Z = 0.33 (P = 0.	33, df = 3 74)	(P = 0.7	2); I ² = 0	%			
Anker et al. 2015 (HARMONIZE) 4 61 5 26 2.1% 0.34 [0.10, 1.17] Butler et al. 2012 (DIAMOND) 34 439 24 439 6.3% 1.42 [0.85, 2.35] Pitt et al. 2011 (the PEARL-HF) 12 55 3 439 2.1% 31.93 [9.30, 109.64] Pitt et al. 2012 (DIAMOND) 34 439 24 439 6.3% 1.42 [0.85, 2.35] Pitt et al. 2013 (OPAL-HK) 5 27 0 22 0.5% 0.04 [0.53, 154.97] Rossignol et al. 2022 (AMBER) 7 63 12 69 3.5% 0.64 [0.27, 1.52] Total events 65 46 Heterogeneity: Tau ² = 1.74; Chi ² = 34.62, df = 5 (P < 0.00001); P = 86%	6 6 5 Gastrointestinal Disorders							
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Butter et al. 2022 (DIAMOND) 34 439 24 439 6.3% 1.42 [0.85, 2.35] Pitt et al. 2011 (the PEARL-HF) 12 55 3 439 2.1% 31.93 [9.30, 109.64] Pitt et al. 2015 (OPAL-HK) 5 27 0 22 0.5% 9.04 [0.53, 154.97] Rossignol et al. 2020 (AMBER) 7 63 12 69 3.5% 0.64 [0.27, 1.52] Tardif et al. 2022 (PRIORITIZE-HF) 3 91 2 90 1.1% 1.48 [0.25, 8.67] Subtotal (95% CI) 736 1085 15.5% 1.97 [0.59, 6.57] Total events 65 46 Heterogeneity: Tau ² = 1.74; Chi ² = 34.62, df = 5 ($P < 0.00001$); $P = 86\%$ Test for overall effect: $Z = 1.11$ ($P = 0.27$) 6.6.6 Hypokalemia Anker et al. 2015 (HARMONIZE) 4 61 0 26 0.4% 3.92 [0.22, 70.28] Butler et al. 2012 (DIAMOND) 66 439 46 439 8.0% 1.43 [1.01, 2.04] Pitt et al. 2011 (the PEARL-HF) 3 55 0 49 0.4% 6.25 [0.33, 118.05] Pitt et al. 2012 (OPAL-HK) 2 27 0 22 0.4% 4.11 [0.21, 81.33] Rossignol et al. 2020 (AMBER) 1 63 0 69 0.4% 3.28 [0.14, 79.11] Tardif et al. 2022 (PRIORITIZE-HF) 7 91 0 90 0.5% 14.84 [0.86, 255.99] Subtotal (95% CI) 736 695 10.1% 1.57 [1.12, 2.21] Total events 83 46 Heterogeneity: Tau ² = 0.00; Chi ² = 4.72, df = 5 ($P = 0.45$); $P = 0\%$ Test for overall effect: $Z = 2.60$ ($P = 0.009$) Total (95% CI) 4209 4395 100.0% 1.18 [0.97, 1.44] Total events 730 650 Heterogeneity: Tau ² = 0.09; Chi ² = 68.14, df = 30 ($P < 0.0001$); $P = 56\%$	Ariker et al. 2015 (HARMONIZE)	4	61	5	26	2.1%	0.34 [0.10, 1.17]	
Prit et al. 2011 (the PEARL-HF) 12 55 3 439 2.1% 31.93 [9.30, 109.64] Prit et al. 2015 (OPAL-HK) 5 27 0 22 0.5% 9.04 [0.53, 154.97] Rossignol et al. 2020 (AMBER) 7 63 12 69 3.5% 0.64 [0.27, 1.52] Tardif et al. 2022 (PRIORITIZE-HF) 3 91 2 90 1.1% 1.48 [0.25, 8.67] Subtotal (95% CI) 736 1085 15.5% 1.97 [0.59, 6.57] Total events 65 46 Heterogeneity: Tau ² = 1.74; Chi ² = 34.62, df = 5 ($P < 0.00001$); $ P = 86\%$ Test for overall effect: $Z = 1.11$ ($P = 0.27$) 6.6.6 Hypokalemia Anker et al. 2015 (HARMONIZE) 4 61 0 26 0.4% 3.92 [0.22, 70.28] Butter et al. 2022 (DIAMOND) 66 439 46 439 8.0% 1.43 [1.01, 2.04] Prit et al. 2015 (OPAL-HK) 2 27 0 22 0.4% 4.11 [0.21, 81.33] Rossignol et al. 2020 (AMBER) 1 63 0 69 0.4% 3.28 [0.14, 79.11] Tardif et al. 2022 (PIORITIZE-HF) 7 91 0 90 0.5% 14.84 [0.86, 255.99] Subtotal (95% CI) 736 695 10.1% 1.57 [1.12, 2.21] Total events 83 46 Heterogeneity: Tau ² = 0.00; Chi ² = 4.72, df = 5 ($P = 0.45$); $P = 0\%$ Total (95% CI) 4209 4395 100.0% 1.18 [0.97, 1.44] Total events 730 650 Heterogeneity: Tau ² = 0.09; Chi ² = 68.14, df = 30 ($P < 0.0001$); $P = 56\%$	Butier et al. 2022 (DIAMOND)	34	439	24	439	6.3%	1.42 [0.85, 2.35]	1
Pitt et al. 2015 (OPAL-HK) 5 27 0 22 0.5% 9.04 [0.53, 154.97] Rossignol et al. 2020 (AMBER) 7 63 12 69 3.5% 0.64 [0.27, 1.52] Tardif et al. 2022 (PRIORITIZE-HF) 3 91 2 90 1.1% 1.48 [0.25, 8.67] Subtotal (95% CI) 736 1085 15.5% 1.97 [0.59, 6.57] Total events 65 46 Heterogeneity: Tau ² = 1.74; Chi ² = 34.62, df = 5 ($P < 0.00001$); $ P = 86\%$ Test for overall effect: $Z = 1.11$ ($P = 0.27$) 6.6.6 Hypokalemia Anker et al. 2015 (HARMONIZE) 4 61 0 26 0.4% 3.92 [0.22, 70.28] Butter et al. 2022 (DIAMOND) 66 439 46 439 8.0% 1.43 [1.01, 2.04] Pitt et al. 2015 (OPAL-HK) 2 27 0 22 0.4% 4.11 [0.21, 81.33] Rossignol et al. 2020 (AMBER) 1 63 0 69 0.4% 3.28 [0.14, 79.11] Tardif et al. 2022 (PRIORITIZE-HF) 7 91 0 90 0.5% 14.84 [0.86, 255.99] Subtotal (95% CI) 736 695 10.1% 1.57 [1.12, 2.21] Total events 83 46 Heterogeneity: Tau ² = 0.00; Chi ² = 4.72, df = 5 ($P = 0.45$); $P = 0\%$ Total events 730 650 Heterogeneity: Tau ² = 0.09; Chi ² = 68.14, df = 30 ($P < 0.0001$); $ P = 56\%$	Pitt et al. 2011 (the PEARL-HF)	12	55	3	439	2.1%	31.93 [9.30, 109.64]	
Rossignol et al. 2020 (AMBER) 7 63 12 69 3.5% $0.64 [0.27, 1.52]$ Tardif et al. 2022 (PRIORITIZE-HF) 3 91 2 90 1.1% $1.48 [0.25, 8.67]$ Subtotal (95% CI) 736 1085 15.5% $1.97 [0.59, 6.57]$ Total events 65 46 Heterogeneity: Tau ² = 1.74; Chi ² = 34.62, df = 5 (P < 0.00001); i ² = 86% Test for overall effect: $Z = 1.11 (P = 0.27)$ 6.6.6 Hypokalemia Anker et al. 2015 (HARMONIZE) 4 61 0 26 0.4% $3.92 [0.22, 70.28]$ Butler et al. 2015 (OPARL-HF) 3 55 0 49 0.4% $6.25 [0.33, 118.05]$ Pitt et al. 2011 (the PEARL-HF) 3 55 0 49 0.4% $6.25 [0.33, 118.05]$ Pitt et al. 2012 (AMBER) 1 63 0 69 0.4% $3.28 [0.14, 79.11]$ Tardif et al. 2022 (PRIORITIZE-HF) 7 91 0 90 0.5% $14.84 [0.86, 255.99]$ Subtotal (95% CI) 736 695 10.1% $1.57 [1.12, 2.21]$ \bullet Total events	Pitt et al. 2015 (OPAL-HK)	5	27	0	22	0.5%	9.04 [0.53, 154.97]	
Tardif et al. 2022 (PRIORITIZE-HF) 3 91 2 90 1.1% 1.48 [0.25, 8.67] Subtotal (95% Cl) 736 1085 15.5% 1.97 [0.59, 6.57] Total events 65 46 Heterogeneity: Tau ² = 1.74; Chi ² = 34.62, df = 5 ($P < 0.00001$); $P = 86\%$ Test for overall effect: $Z = 1.11$ ($P = 0.27$) 6.6.6 Hypokalemia Anker et al. 2015 (HARMONIZE) 4 61 0 26 0.4% 3.92 [0.22, 70.28] Butler et al. 2022 (DIAMOND) 66 439 46 439 8.0% 1.43 [1.01, 2.04] Pitt et al. 2012 (DIAMOND) 66 439 46 439 8.0% 1.43 [1.01, 2.04] Pitt et al. 2015 (OPAL-HK) 2 27 0 22 0.4% 4.11 [0.21, 81.33] Rossignol et al. 2020 (AMBER) 1 63 0 69 0.4% 3.28 [0.14, 79.11] Tardif et al. 2022 (PRIORITIZE-HF) 7 91 0 90 0.5% 14.84 [0.86, 255.99] Subtotal (95% Cl) 736 695 10.1% 1.57 [1.12, 2.21] Total events 83 46 Heterogeneity: Tau ² = 0.00; Chi ² = 4.72, df = 5 ($P = 0.45$); $P = 0\%$ Total (95% Cl) 4209 4395 100.0% 1.18 [0.97, 1.44] Total events 730 650 Heterogeneity: Tau ² = 0.09; Chi ² = 68.14, df = 30 ($P < 0.0001$); $P = 56\%$	Rossignol et al. 2020 (AMBER)	7	63	12	69	3.5%	0.64 [0.27, 1.52]	
Subtotal (95% Cl) 736 1085 15.5% 1.97 [0.59, 6.57] Total events 65 46 Heterogeneity: Tau ² = 1.74; Chi ² = 34.62, df = 5 ($P < 0.00001$); $P = 86\%$ Test for overall effect: $Z = 1.11$ ($P = 0.27$) 6.6.6 Hypokalemia Anker et al. 2015 (HARMONIZE) 4 61 0 26 0.4% 3.92 [0.22, 70.28] Butler et al. 2022 (DIAMOND) 66 439 46 439 8.0% 1.43 [1.01, 2.04] Pitt et al. 2015 (OPAL-HK) 2 27 0 22 0.4% 4.11 [0.21, 81.33] Rossignol et al. 2020 (AMBER) 1 63 0 695 10.1% 1.57 [1.12, 2.21] Total events 83 46 Heterogeneity: Tau ² = 0.00; Chi ² = 4.72, df = 5 ($P = 0.45$); $P = 0\%$ Test for overall effect: $Z = 2.60$ ($P = 0.009$) 1.18 [0.97, 1.44] Total events 730 650 Heterogeneity: Tau ² = 0.09; Chi ² = 68.14, df = 30 ($P < 0.0001$); $P = 56\%$ 0.4 0.4	Tardif et al. 2022 (PRIORITIZE-HF)	3	91	2	90	1.1%	1.48 [0.25, 8.67]	
Total events 65 46 Heterogeneity: Tau ² = 1.74; Chi ² = 34.62, df = 5 ($P < 0.00001$); $ P = 86\%$ Test for overall effect: $Z = 1.11$ ($P = 0.27$) 6.6.6 Hypokalemia Anker et al. 2015 (HARMONIZE) 4 61 0 26 0.4% 3.92 [0.22, 70.28] Butter et al. 2022 (DIAMOND) 66 439 46 439 8.0% 1.43 [1.01, 2.04] Pitt et al. 2012 (DIAMOND) 66 439 46 439 8.0% 1.43 [1.01, 2.04] Pitt et al. 2012 (DIAMOND) 66 439 46 439 8.0% 1.43 [1.01, 2.04] Pitt et al. 2015 (OPAL-HK) 2 27 0 22 0.4% 4.11 [0.21, 81.33] Rossignol et al. 2020 (AMBER) 1 63 0 69 0.4% 3.28 [0.14, 79.11] Tardif et al. 2022 (PRIORITIZE-HF) 7 91 0 90 0.5% 14.84 [0.86, 255.99] Subtoal (95% CI) 736 695 10.1% 1.57 [1.12, 2.21] Total events 83 46 Heterogeneity: Tau ² = 0.00; Chi ² = 4.72, df = 5 ($P = 0.45$); $P = 0\%$ Total (95% CI) 4209 4395 100.0% 1.18 [0.97, 1.44] Total events 730 650 Heterogeneity: Tau ² = 0.09; Chi ² = 68.14, df = 30 ($P < 0.0001$); $P = 56\%$	Subtotal (95% CI)		736		1085	15.5%	1.97 [0.59, 6.57]	
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Heterogeneny, rau= 0.09; Chr= 68.14, dt= 30 (P < 0.0001); r= 56%	Total events	11 16 1	0.00	650	12 - 504	v		
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Figure 5 Trial sequential analysis (TSA). (A) Mineralocorticoid receptor antagonist optimization and (B) hyperkalaemia (potassium >5.5 mEq/L). NPB, new potassium binder.

ESC Heart Failure 2024; **11**: 28–43 DOI: 10.1002/ehf2.14588 body of evidence by investigating ACEi/ARB/ANRi optimization and the thorough assessment of certainty of evidence and TSA.

Limitations

There are a few limitations in our study. First, the follow-up periods of the included studies ranged from 4 to 27 weeks, which may be relatively short for analysing hard cardiovascular endpoints, and the lack of significant results could be attributed to insufficient statistical power, especially in the serum potassium change, which included only three RCTs with a different point of assessment. Second, included trials excluded patients with severe hyperkalaemia, potassiumrelated electrocardiographic changes, and acute cardiovascular events, which restricts the generalizability of our findings to the entire population of HF patients at risk for hyperkalaemia. Third, the analysis in our study involved the examination of two NPBs with varying doses across the included studies. However, we considered these two drugs to be sufficiently similar in terms of their mechanism of action, consistent safety profile, and effectiveness across different studies. Fourth, it is important to note that adverse outcomes are infrequent events, and the lack of significant differences between the groups may be attributed to the limited statistical power of our analysis, and there is lack of direct comparisons between the two NPBs. Fifth, the DIAMOND trial⁹ was prematurely halted due to the impact of the COVID-19 pandemic, and as a result, the study experienced a reduction in the number of participants and a higher rate of premature discontinuation of treatment. Sixth, the renal function can significantly affect our findings and we could not provide a meta-regression analysis based on creatinine clearance due to the lack of data. Finally, all our meta-regression models included data from <10 studies; thus, their findings are not reliable and should be interpreted with caution.

Implications for future practice and research

The emergence of NPB has improved the outcomes of patients on HF treatment by tackling the adverse effects of hyperkalaemia. NPBs allow patients to maximize the benefits of GDMT usage, especially MRA. Guidelines recommending the addition of NPB to HF management are in line with our analysis.^{18–20} However, regular monitoring of serum potassium levels and appropriate adjustment of NPB doses can be instrumental in preventing hypokalaemia.⁴ For future research, we suggest further investigating the optimization of ACEi/ARB/ANRi, conducting head-to-head studies comparing NPB, and investigating the effect of adjuvant administration of NPB with other cardiovascular drugs especially diuretics.

Conclusion

NPBs (patiromer and SZC) can successfully improve GDMT outcomes by enhancing MRA optimization and decreasing hyperkalaemic episodes, with an increased incidence of hypokalaemia, requiring regular monitoring of serum potassium levels. However, data regarding the NPB effect on ACEi/ARB/ANRi optimization remain scarce. Therefore, future RCTs should further investigate ACEi/ARB/ANRi optimization and conduct a head-to-head comparison of NPB.

Conflict of interest

None declared.

Funding

We received no funding for this study.

Supporting information

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

Table S1: Search strategy.

Table S2: Sensitivity Analysis.

Table S3: Meta-regression analysis.

Figure S1: meta-regression analysis model for hyperkalemia based on LVEF.

Figure S2: meta-regression analysis model for hyperkalemia based on GFR.

Figure S3: meta-regression analysis model for hyperkalemia based on baseline potassium level.

Figure S4: meta-regression analysis model for hyperkalemia based on mean age.

Figure S5: meta-regression analysis model for serum potassium change based on baseline potassium level.

Figure S6: meta-regression analysis model for serum potassium change based mean age.

Figure S7: meta-regression analysis model for hypokalemia based on LVEF.

Figure S8: meta-regression analysis model for hypokalemia based on GFR.

Figure S9: meta-regression analysis model for hypokalemia based on baseline potassium level.

Figure S10: meta-regression analysis model for hypokalemia based on mean age.

Figure S11: meta-regression analysis model for MRA optimization based on LVEF. **Figure S12:** meta-regression analysis model for MRA optimization based on GFR.

Figure S13: meta-regression analysis model for MRA optimization based on baseline potassium level.

Figure S14: meta-regression analysis model for MRA optimization based on mean age.

Figure S15: meta-regression analysis model for All-Cause Mortality based on LVEF.

Figure S16: meta-regression analysis model for All-Cause Mortality based on GFR.

Figure S17: meta-regression analysis model for All-Cause Mortality based on baseline potassium level.

Figure S18: meta-regression analysis model for All-Cause Mortality based on mean age.

Figure S19: meta-regression analysis model for hyperkalemia based on LVEF.

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