Novel Potassium binders in reduction of hyperkalemia and optimization of RAAS inhibitors treatment in patients with chronic kidney disease or heart failure: a systematic review and meta-analysis

Short title: A meta-analysis of novel potassium binders in RAAS inhibitor treatment optimization

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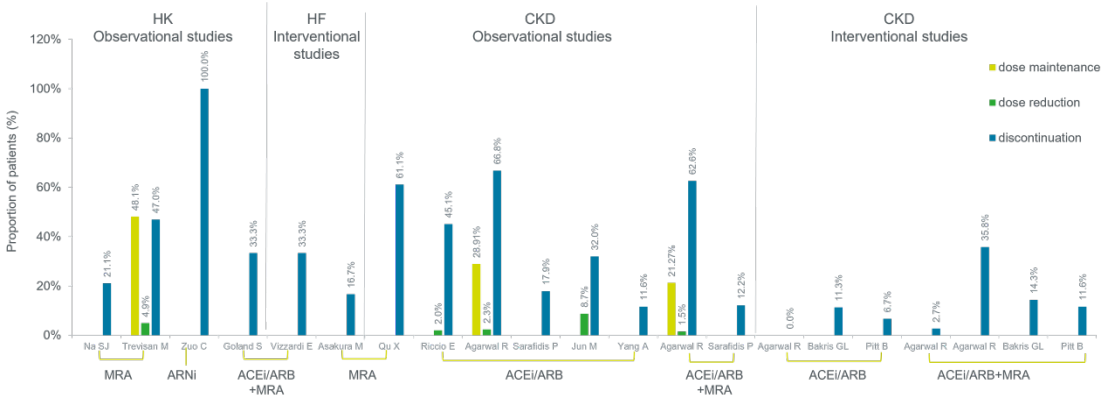
Electronic Supplementary Material

Online Resource 1 Search strings

Search	
#1	"RAASi" OR "Inhibitors of the renin-angiotensin-aldosterone system" OR "RAAS inhibitor" OR "aliskiren" OR "ACEi" OR "angiotensin-converting enzyme inhibitor" OR "captopril" OR "enalapril" OR "lisinopril" OR "benazepril" OR "fosinopril" OR "Perindopril" OR "Ramipril" OR "quinapril" OR "trandolapril" OR "ARB" OR "angiotensin receptor blocker" OR "valsartan" OR "losartan" OR "irbesartan" OR "candesartan" OR "ARNi" OR "angiotensin receptor-neprilysin inhibitor" OR "sacubitril-valsartan" OR "MRA" OR "mineralocorticoid receptor antagonist" OR "spironolactone" OR "eplerenone"
#2	"Chronic kidney disease" OR "chronic renal" OR "renal disease, chronic" OR "chronic renal disease" OR "kidney disease, chronic" OR "chronic kidney insufficiency" OR "chronic kidney insufficiencies" OR "chronic renal insufficiency" OR "renal insufficiencies, chronic" OR "chronic renal insufficiencies" OR "CKD"
#3	"HF" OR "heart failure" OR "heart failure, left sided" OR "heart failure, congestive" OR "cardiac failure" OR "heart failure, right-sided" OR "heart decompensation" OR "myocardial failure" OR "myocardial infarction" OR "heart medicine" OR "heart stroke" OR "HRmrEF" OR "heart failure with mildly reduced ejection fraction" OR "HFrEF" OR "heart failure with reduced ejection fraction" OR "LVEF" OR "left ventricular ejection fraction"
#4	"Hyperkalemia" OR "hyperpotassemia" OR "hyperkalemia" OR "high potassium disease" OR "high potassium anemia" OR "elevated blood potassium"
Combination	"#1 AND #2 AND #4" OR "#1 AND #3 AND #4" OR "#1 AND (#2 OR #3) AND #4"

Online Resource 2 Proportion of patients who adjust RAASi dosage



Online Resource 3 Risk factors of HK

Study (year)	Intervention vs. control (n)	Follow-up duration	Risk factor	Estimate (95%CI)
Observational study				
Jun HR, et al. (2021)	ACEI(n=562) vs ARB(n=2539)	6 years	Lower MDRD-eGFR values	HR=13.06; 95%CI 4.05-42.1; p < 0.001
			Creatinine increased	HR =7.31; 95%CI = 4.19-12.76; p < 0.001
Thomsen RW, et al. (2018)	CKD patients with first HK level >5.0 mmol/L(n=43397) vs Matched CKD comparison patients without HK(n=43257)	13 years	Heart failure	PR 2.3 (95% CI 2.2–2.4)
			Diabetes	PR 1.7 (95% CI 1.7–1.8)
			More ACEis	PR 1.4 (95% CI 1.4–1.5)
			More potassium supplements	PR 1.6 (95% CI 1.5–1.6)
			More spironolactone	PR 2.5 (95% CI 2.4–2.6)
Jun M, et al. (2019)	eGFR 45-59(n=9444) vs 30-44(n=7739) vs 15-29(n=2632) vs ＜15(n=369)	4.5 years	Female sex	vs. male: HR 0.76(0.67-0.86)
			Older age	per year increase: HR 0.99, 95% CI: 0.98–0.99
			Smoking status	vs. non-smoker: HR 1.38, 95% CI: 1.05–1.80
			Smoker	HR 1.38(1.05-1.80)
			Worsening eGFR level	eGFR 45–59 vs. <15ml/min/1.73m^2 :HR 3.73, 95% CI, 2.71–5.13

			Baseline serum potassium level	per 0.1 mmol/L increase: HR 1.13, 95% CI: 1.12–1.14
			Diabetes	yes vs. no: HR 1.26, 95% CI: 1.12–1.41
			Heart failure	yes vs. no: HR 1.38, 95% CI: 1.19–1.60
Yang A, et al. (2022)	Continued (n=8634) vs Discontinued (n=1766)	10 years	Discontinued-RASi	Discontinued-RASi vs. Continued-RASi HR2.55 (1.36-4.78 (Baseline uACR<3 mg/mmol）
An J, et al.（2021）	MRA+ACEI/ARB(n=1282) vs ACEI/ ARB Only(n=5484)	17 years	Short-term use of combination therapy (drug exposure days < 90 days)	OR = 1.54; 95% CI 1.01, 2.33
Hyunwoo Kim (2024）			Diabetes mellitus	HR 1.842; 95% CI, 1.046-3.243; P=0.034
			Prior history of hyperkalemia	HR, 2.288; 95% CI, 1.372-3.815; P=0.002
			Low baseline eGFR	HR, 0.973; 95% CI, 0.948-0.998; P=0.037
			Low serum Aldo/K ratio	HR, 3.654; 95% CI, 2.066-6.463; P<0.001
Interventional study				
Fried LF, et al. (2014)	Losartan+Placebo (n=724) vs Losartan+Lisinopril (n=724)	2 years	Combination therapy with an ACE inhibitor and an ARB	HR 2.8 (1.8-4.3)

Studies (year)	Intervention vs. control (n)	Follow-up duration	Risk factor	Estimate (95%CI)
Observational studies				
Trevisan M, et al. (2021)	developed hyperkalaemia (n=7366)	12 years	stop MRA (recurrent HK, potassium >5.0 mmol/L）	RR 0.80(0.76-0.83)
			stop MRA（recurrent moderate/severe HK, potassium >5.5 mmol/L）	RR 0.73(0.67-0.78)
Martens P, et al. (2021)	K+ < 5.5 mmol/L (n=292) vs. K+＞5.5 mmol/L (n=104)	7 years	Diabetes mellitus	OR 1.88(1.18-2.99), Univariate analysis
			Creatinine	OR 1.80(1.03-3.19), Multivariate analysis
				OR 2.16(1.40-3.33), Univariate analysis
				OR 2.37(1.45-3.85), Multivariate analysis
			Loop diuretic	OR 1.80(1.10-2.93)
			Beta-blocker	OR 4.99(1.16-21.42)
			MRA during follow-up	OR 1.83(1.09-3.09)
Secora AM, et al. (2020)	Never initiators spironolactone(N=13881) vs Ever initiators(n=3229)	12 years	spironolactone	sHR 1.88(1.59-2.23), unadjusted
				sHR 1.75(1.46-2.09), fully-adjusted
				sHR 1.58(1.28-1.94), IPTW
				sHR 1.69(1.35-2.10), PS-matched
Lee, KK, et al. (2013)	Spironolactone(n=521) Vs NO Spironolactone(n=1837)	2 years	Spironolactone	HR 3.46(1.97-6.06)
			eGFR	HR 3.86(1.63-9.13), ＜30(reference ≥60）
Abbas S, et al. (2015)	Sp + ACEi/ARB (1062) vs. matched controls with no HK (10620)	398 (397) days	Age	OR 8.73 [5.05-15.08], <70 years
				OR 12.32 [9.35-6.23], ≥70 years
			RAASi	OR 13.59 [11.63-15.88], Sp

				OR 11.05 [8.67-14.08], Sp OR 13.00 [9.82-17.21], Sp ST OR 9.12 [6.78-12.26], Sp LT
Michel A, et al. (2015)	Cases of HK (2176) vs. controls (4000)	3.9 (3.21) years	Diabetes	OR 1.52 [1.31-1.75], type II
			CKD	OR 1.43 [1.10-1.87], type II + eGFR ≥60 ml/min OR 6.34 [5.19-7.74], type II + eGFR <60 ml/min OR 4.34 [3.51-5.37], type II + eGFR 30-59 ml/min OR 23.22 [16.25-33.18], type II + eGFR <30 ml/min OR 3.81 [3.29-4.42], eGFR <60 ml/min OR 16.32 [12.96-20.56], eGFR <30 ml/min OR 4.57 [3.82-5.46], eGFR 30-44 ml/min OR 1.82 [1.53-2.16], eGFR 45-59 ml/min
			RAASi	OR 3.23 [2.77-3.77], Sp, current use OR 10.68 [6.61-17.26], Sp, use <30 days OR 4.99 [3.42-7.27], Sp, use 1-3 months OR 3.40 [2.62-4.43], Sp, use >3-12 months OR 2.17 [1.76-2.66], Sp, use >12 months OR 1.70 [1.41-2.04], ACEi, current use OR 5.47 [3.66-8.19], ACEi, use <30 days

		OR 3.00 [2.14-4.21], ACEi, use 1-3 months OR 1.71 [1.33-2.19], ACEi, use >3-12 months OR 1.39 [1.13-1.72], ACEi, use >12 months OR 4.46 [3.47-5.74], K + -diuretics + ACEi OR 4.97 [3.87-6.39], Sp + ACEi OR 3.29 [2.41-4.50], Sp + ARB OR 2.03 [1.18-3.50], ACEi + ARB OR 6.81 [2.50-18.52], ACEi + ARB + Sp OR 7.49 [3.25-17.80], diuretic + trimethoprim OR 7.03 [3.69-13.41], ACEi + trimethoprim
	Other factors	OR 3.01 [2.61-3.48], diuretics, current use OR 9.16 [5.99-14.02], diuretics, use <30 days OR 4.74 [3.36-6.67], diuretics, use 1-3 months OR 2.98 [2.35-3.77], diuretics, use >3-12 months OR 2.16 [1.79-2.61], diuretics, use >12 months OR 2.63 [1.96-3.54], amiloride, current use OR 0.81 [0.67-0.99], loop diuretics, current use OR 0.60 [0.46-0.77], thiazides and related diuretics,current use OR 0.81 [0.69-0.96], calcium channel

				blockers, current use
Kiernan MS, et al. (2012) HEAAL	Lsr 150 mg (828) vs. Lsr 50 mg (889)		Older Age	HR 1.18 [1.06-1.32], older age, per 10 years older
			Diabetes	HR 1.77 [1.42-2.22]
			RAASi	HR 1.51 [1.21-1.89], 150 mg Lsr (vs. 50 mg)
				HR 1.76 [1.40-2.22], ARB use
				HR 2.29 [1.35-3.90], ACEi intolerance due to AE
			Bsl K+, per 1 mmol/l	HR 2.57 [2.15-3.07]
			bsl diuretic use	HR 1.41 [1.03-1.93]
			HbA1c, per 1g/dl lower	HR 1.20 [1.11-1.30]
Rossignol P, et al. (2014) HEAAL	Lsr 150 mg (828) vs. Lsr 50 mg (889)	4.7 (3.7-5.5) years	Diabetes	HR 1.361 [1.152-1.608]
			CKD	HR 1.789 [1.489-2.150], incident 20% reduction in eGFR
				HR 0.984 [0.980-0.989], bsl eGFR
			RAASi	HR 1.261 [1.065-1.493], MRA
			K+	HR 2.517 [2.217-2.858], bsl K+
			Other factors	HR 0.942 [0.892-0.996], bsl Hb
				HR 0.801 [0.674-0.952], white
				NYHA III/IV, HR 1.289 [1.088-1.529]
Vardeny O, et al. (2014)	Sp 25-50 mg qd (822) vs. placebo (841)	24 months	Age	HR 1.02 [1.0-1.03], age/1 year
			Diabetes	HR 1.47 [1.09-2.0]
			RAASi	HR 3.20 [2.26-4.47], Sp
				HR 1.04 [1.03-1.05], dose of Sp/12.5 mg/day
				HR 5.96 [1.47-24.2], bsl ACEi/ARB use

			K+	HR 1.94 [1.47-2.57], bsl K+/1 mmol/l
			Other factors	HR 1.51 [1.11-2.05], NYHA HR 0.53 [0.31-0.90], bsl BB use HR 1.09 [1.0-1.2], bsl SBP/10 mmHg
Interventional studies				
COMPARE-HF Hernandez AF, et al. (2012)	MRA at discharge (1070) vs. no MRA (4817)	3 years	RAASi	HR 5.96 [1.31-27.15]
Jering KS, et al. (2021) PARAGON-HF	Valsartan vs. Sacubitril/Valsartan	4 months	Sacubitril/Valsartan	HR 2.51 [1.45-4.34] HR 1.48 [1.20-1.84] HR 0.83(0.69-0.99), K >5.5 mmol/l（baseline no-MRA user）vs. Valsartan HR 0.67(0.47-0.96), K >6.0 mmol/l
Vardeny O, et al. (2012)	Sp 25-50 mg qd vs. placebo		Spironolactone	OR 3.7 [2.5-5.7], Baseline eGFR <60 OR 2.9 [1.85-4.6], Baseline eGFR ≥60 OR 3.1 (2.2, 4.4), No WRF OR 3.8(1.2,6.4), WRF
Rossignol P, et al. (2014EMPHASIS-HF)	Epl (1364) vs. placebo (1373)	21 months, median	Worsening of renal function	HR 2.23 [1.56-3.19]
			Baseline eGFR ≤ median (68 mL/min per 1.73 m^2)	HR 1.77 [1.36-2.30]
			RAASi	HR 1.67 [1.29-2.17]
			Hypertension	HR 1.69 [1.25-2.29]
			White ethnicity	HR 0.71 [0.50-1.00]
Desai AS, et al. (2018)	Spironolactone(n=886) vs Placebo(n=881)	60 days	Spironolactone	HR 3.21(2.46-4.20), Moderate Hyperkalemia (≥ 5.5 mmol/L) HR 3.14(1.94-5.08), Severe Hyperkalemia (≥ 6.0 mmol/L)
			Serum Potassium (meq/L)	HR 3.12(2.33-4.18)

			eGFR (per 10 mL/min/1.73m2)	HR 0.84(0.78-0.89)
			Diabetes Mellitus	HR 1.38(1.08-1.77)
			Spironolactone + ACE/ARB	HR 2.98(1.81-4.92)
Muzzarelli S, et al. (2012) TIME-CHF	ACEi + ARB, Sp, NT-BNP-guided medical vs. standard symptom-guided therapy (566)	18 months	CKD	OR 1.11 [1.04-1.19], Cr/ 10 μmol/l
			RAASi	OR 1.20 [1.00-1.42], dose of Sp per 12.5 mg
				OR 2.52 [1.45-4.35], dose change 25 mg
				OR 3.24 [1.52-6.91], dose change >25 mg
				OR 1.36 [1.14-1.63], maximum dose Sp per 12.5 mg
				OR 1.28 [1.07-1.52], maximum dose changes per 12.5 mg
				OR 1.59 [1.19-2.14], mean dose per 12.5 mg
			K+	OR 2.92 [1.75-4.89], K+ per mmol/l
			Other factors	OR 2.56 [1.22-5.38], gout
				OR 3.08 [1.37-6.95], NYHA IV

Online Resource 4 PRISMA Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Page 1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Page 3-4
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Page 3-4
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Page 4-5
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Page 4
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Online Resource 1
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Figure 1
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Page 5-6
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Page 5-6
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Page 5-6
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Page 5

Section and Topic	Item #	Checklist item	Location where item is reported
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Page 5
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Page 6
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Page 6
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Page 6
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Page 6
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Page 6
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Page 6
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Page 6
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	n/a
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Page 6-8
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Figure 1
Study characteristics	17	Cite each included study and present its characteristics.	Online Resource 5 and 6
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Page 8
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Page 6-10
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Online Resource 6

Section and Topic	Item #	Checklist item	Location where item is reported
			and 7
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Page 7-9
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Figure 1 and 2; Online Resource 7,8 and 9
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Online Resource 12
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Online Resource 10 and 11
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	n/a
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Page 10-12
	23b	Discuss any limitations of the evidence included in the review.	Page 12
	23c	Discuss any limitations of the review processes used.	n/a
	23d	Discuss implications of the results for practice, policy, and future research.	Page 12
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Page 4
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	protocol was not prepared
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	n/a
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Page 13
Competing interests	26	Declare any competing interests of review authors.	Page 13
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Data are not publicly available but are available upon request

PRISMA Checklist for Abstracts

Section and Topic	Item #	Checklist item	Reported (Yes/No)
TITLE			
Title	1	Identify the report as a systematic review.	Y
BACKGROUND			
Objectives	2	Provide an explicit statement of the main objective(s) or question(s) the review addresses.	Y
METHODS			
Eligibility criteria	3	Specify the inclusion and exclusion criteria for the review.	Y
Information sources	4	Specify the information sources (e.g. databases, registers) used to identify studies and the date when each was last searched.	Y
Risk of bias	5	Specify the methods used to assess risk of bias in the included studies.	N
Synthesis of results	6	Specify the methods used to present and synthesise results.	Y
RESULTS			
Included studies	7	Give the total number of included studies and participants and summarise relevant characteristics of studies.	Y
Synthesis of results	8	Present results for main outcomes, preferably indicating the number of included studies and participants for each. If meta-analysis was done, report the summary estimate and confidence/credible interval. If comparing groups, indicate the direction of the effect (i.e. which group is favoured).	Y
DISCUSSION			
Limitations of evidence	9	Provide a brief summary of the limitations of the evidence included in the review (e.g. study risk of bias, inconsistency and imprecision).	N
Interpretation	10	Provide a general interpretation of the results and important implications.	Y
OTHER			
Funding	11	Specify the primary source of funding for the review.	N
Registration	12	Provide the register name and registration number.	N

Online Resource 5 Baseline characteristics of the included studies for meta-analysis

Trial name (registration number)	Year	Treatment	Patients (n)	Study population	Inclusion criteria	Primary outcome	Age (±SD)	Male (%)	Baseline potassium levels (±SD)	Follow-up (weeks)	Primary outcome result
AMBER (NCT03071263)	2020	Patiromer	295	CKD with HF (n=132), CKD without HF (n=163）	➢ ≥18 years of age ➢ eGFR of 25–45 mL/min/1.73 m^2 ➢ Serum K+ of 4.3-5.1 mmol/L ➢ Resistant hypertension	Difference at week 12 in the proportion of patients on spironolactone	68.1 (11.7)	51.9	4.72 (0.37)	12	68.1% of patients receiving placebo on spironolactone, 84.1% of patients receiving patiromer (P=0.0504)
CRYSTAL	2024	SZC	86	DKD		Proportion of patients with increased RAASi dose by week 12	58.7	59.3		24	A significantly higher proportion of patients in the SZC group achieved increased dose of ACEi/ARB than control at week 12 (ITT: 55.8% vs. 27.9%, p<0.05)
DIAMOND (NCT03888066)	2022	Patiromer	1195	HF	➢ 18 years of age ➢ NYHA Class II–IV heart failure ➢ Left ventricular ejection fraction ≤40% ➢ Hyperkalemia at screening (defined as two serum potassium values of >5.0 mmol/l) while receiving RAASi therapy ➢ Normokalemic at screening but had a history of dose reduction or discontinuation of the RAASi therapy due to	Adjusted mean change in serum potassium	66.9 (9.9)	72.9	4.6 (0.3)	27	Serum potassium was +0.03 mmol/l (95% CI–0.01, 0.07) in the patiromer group and +0.13 mmol/l (95% CI 0.09, 0.16) in the placebo group, for a between-group difference of –0.10 mmol/l (95% CI –0.13, –0.07; P<0.001)

					hyperkalemia in the previous 12 months						
HARMONIZE (NCT02107092)	2015	SZC	94	HF	➢ Adults ➢ Hyperkalemia (serum potassium ≥ 5.1 mmol/L) ➢ History of HF	Mean serum potassium determined from days 8 to 29 after randomization	69.0	63.8	5.6	4	Patients on 5 g, 10 g, and 15 g ZS-9 maintained a lower potassium level (4.7 mmol/L, 4.5 mmol/L, and 4.4 mmol/L, respectively) than the placebo group (5.2 mmol/L; *P*<0.01 vs. each ZS-9 group)
OPAL-HK (NCT01810939)	2015	Patiromer	243	CKD with HF (n=102), CKD without HF (n=141)	➢ 18-80 years of age ➢ Had stage 3 or 4 CKD(eGFR of 15-60 mL/min/1.73 m^2 of body surface area) ➢ Serum K+ 5.1-6.5 mEq/L ➢ Indicative of hyperkalaemia, and had been receiving a stable dose of ≥1 RAASi for ≥28 days	Mean change in serum K+ level from baseline to week 4	64.2 (10.5)	57.6	5.5 (0.5)	4	Serum K+ from baseline to week 4 was −1.06±0.05 mEq/L (95% CI),−1.16,−0.95; P <0.001); 76% (95% CI, 69,84) achieved serum K+, 3.8-5.1 mEq/L
PEARL-HF (NCT00868439)	2011	Patiromer	104	HF	➢ ≥18 years of age ➢ History of chronic HF ➢ Indication to initiate spironolactone therapy, ➢ Serum K+ concentration of 4.3-5.1 mEq/L ➢ CKD [eGFR ＜ 60 mL/min] and were receiving one or more HF therapies(ACE-Is, ARBs, beta-blockers) ➢ A documented history of hyperkalaemia that led to discontinuation of therapy with an AA, ACE-I,ARB, or beta-blocker	Mean change of serum K+ from baseline to the end of the study	68.0 (9.9)	60.6	4.7	4	RLY5016 serum K+ levels with a difference between groups of -0.45 mEq/L (P< 0.001)

					within 6 months prior to the baseline visit						
PRIORITIZE-HF (NCT03532009)	2023	SZC	182	HF	➢ Adult women or men ➢ Had a documented diagnosis of symptomatic HFrEF(NYHA) functional Class II to IV ➢ LVEF≤40% ➢ Treatment with RAAS inhibitors and a beta-blocker had to be stable for at least four weeks before randomization. ➢ Patients needed to be treated with an ACEi, ARB or ARNI ➢ Participants could either be taking a low dose of spironolactone or eplerenone (less than or equal to 12.5 mg once daily or 25 mg every other day) or not receiving an MRA ➢ Mild hyperkalaemia or be at risk of developing hyperkalaemia defined as follows: ✧ eGFR 20-44 mL/min/1.73 m^2 and K+ 4.0-5.5 mmol/L, ✧ Or eGFR 45-59 mL/min/1.73 m^2 and K+5.1-5.5 mmol/L, ✧ Or eGFR 45-59 mL/min/1.73 m^2 and K+4.0 and 5.0 mmol/L, and prior documented K+ concentration ＞5.0 mmol/L（used a RAAS inhibitor）	Proportion of patients at 12 weeks in the following categories: (i) any of ACEi, ARB,or ARNI at less than target dose (including no treatment), and no MRA; (ii) any of ACEi, ARB, or ARNI at target dose and no MRA; (iii) MRA at less than target dose; and (4) MRA at target dose	72. 0 (8. 5)	59. 3	4.9 (0.3)	12	The proportion of patients at target MRA dose was numerically higher in the SZC group (56.4%) compared with the placebo group (47.0%)
REALIZE-K (NCT046	2024	SZC	365	HF	➢ ≥18 years of age ➢ Cohort 1 (hyperkalemic): sK+ 5.1-	Proportion of patients achieving	70. 1	75. 9	4.8 (0.5)	24	Percentage With Optimal Treatment

76646)					5.9 mEq/L and eGFR ≥30 mL/min/1.73 m2 ➢ Cohort 2 (normokalemic): sK+ 3.5-5.0 mEq/L and "at risk" of developing HK defined as any of the following: ✧ history of HK (sK+ >5.0 mEq/L) within previous 36 months and eGFR ≥30 mL/min/1.73 m2 ✧ sK+ 4.5-5.0 mEq/L and eGFR 30-60 mL/min/1.73 m2 ✧ sK+ 4.5-5.0 mEq/L and age >75 y ➢ Symptomatic HFrEF (NYHA functional class II-IV) ≥3 months ➢ LVEF <40% ➢ Previous/concomitant therapy: ✧ Receiving ACEI, ARB, or ARNI ✧ Receiving beta-blocker, unless contraindicated	an optimal treatment response					Response was higher in SZC group (71.2%) compared with the placebo group (35.7%)

Online Resource 6 Risk of Bias assessment

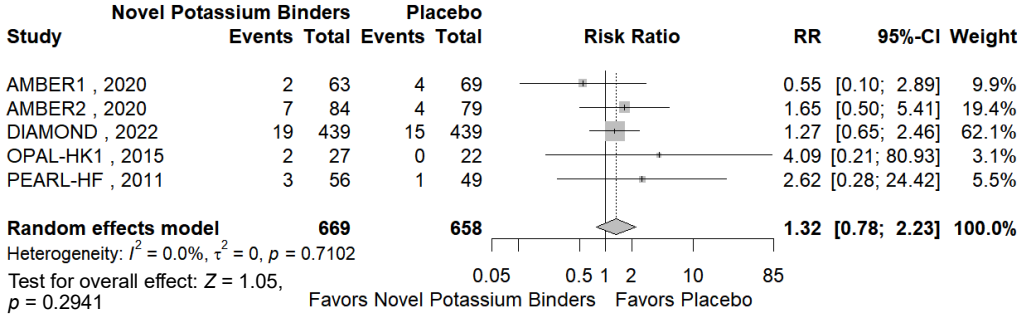
	D1	D2	D3	D4	D5	Overall
AMBER, 2020	+	+	+	+	+	+
CRYSTAL, 2024	+	!	+	!	+	!
DIAMOND, 2022	+	+	+	+	+	+
HARMONIZE, 2015	+	+	+	+	+	+
OPAL-HK, 2015	+	!	+	!	+	!
PEARL-HF, 2011	+	+	+	+	+	+
PRIORITIZE-HF, 2023	+	+	+	+	+	+
REALIZE-K, 2024	+	+	+	+	+	+

Note: + low risk; ! Some concerns; - High risk.

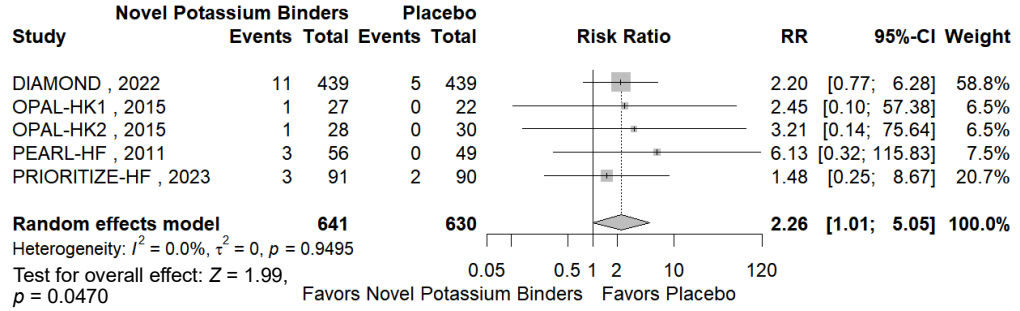
D1, Randomisation process; D2, Deviations from the intended interventions; D3, Missing outcome data; D4, Measurement of the outcome; D5, Selection of the reported result.

Online Resource 7 Forest plots for diarrhea, constipation, nausea or vomiting, hypomagnesemia, edema, Serious AE, any AE leading to discontinuation

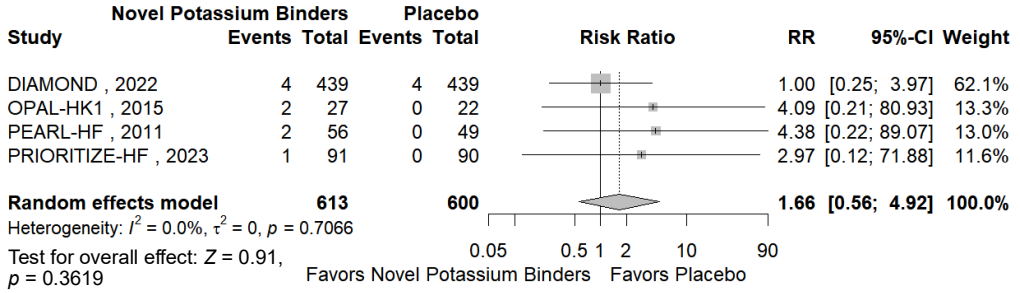
A Diarrhea



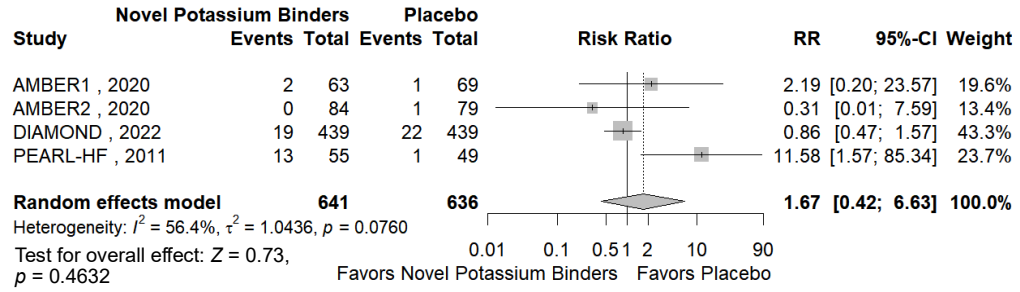
B Constipation



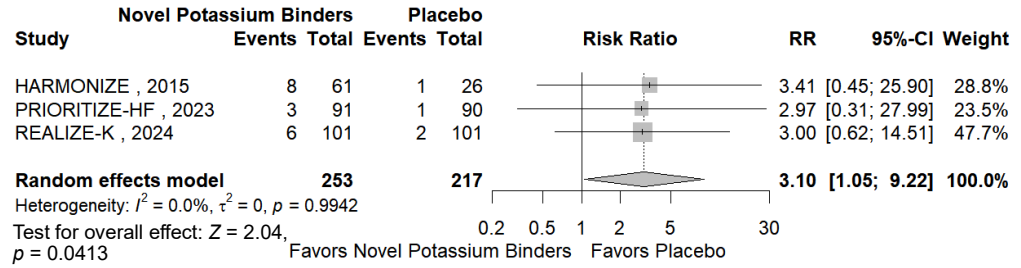
C Nausea or vomiting



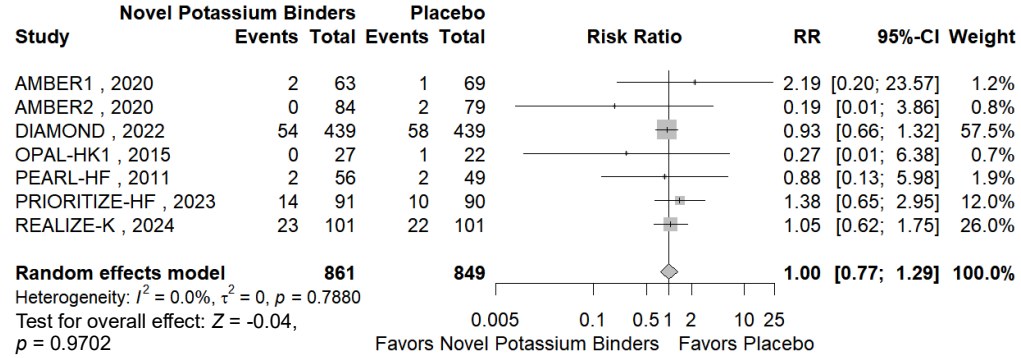
D Hypomagnesemia



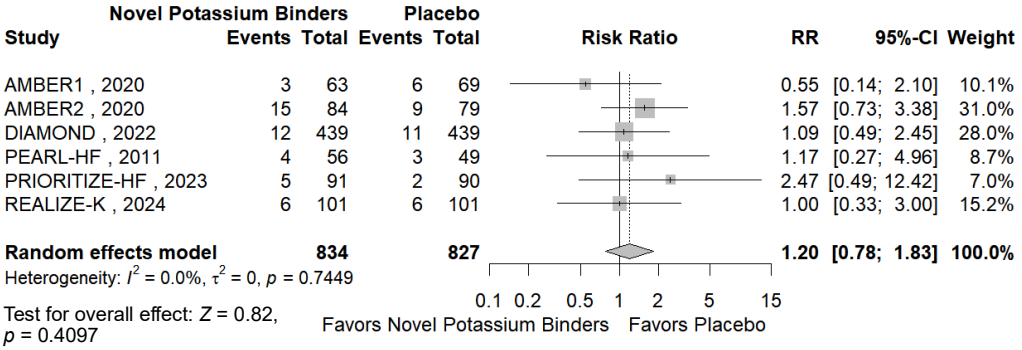
E Edema



F Serious AE

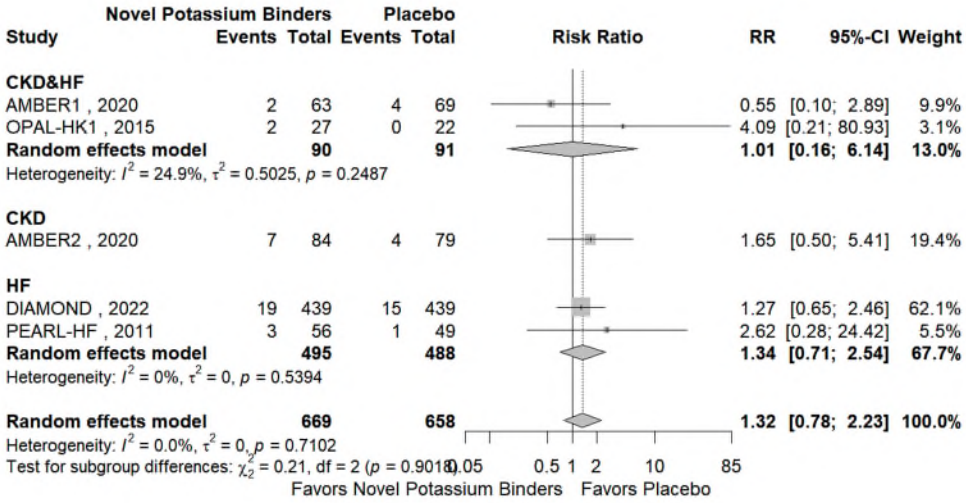


G Any AE leading to discontinuation

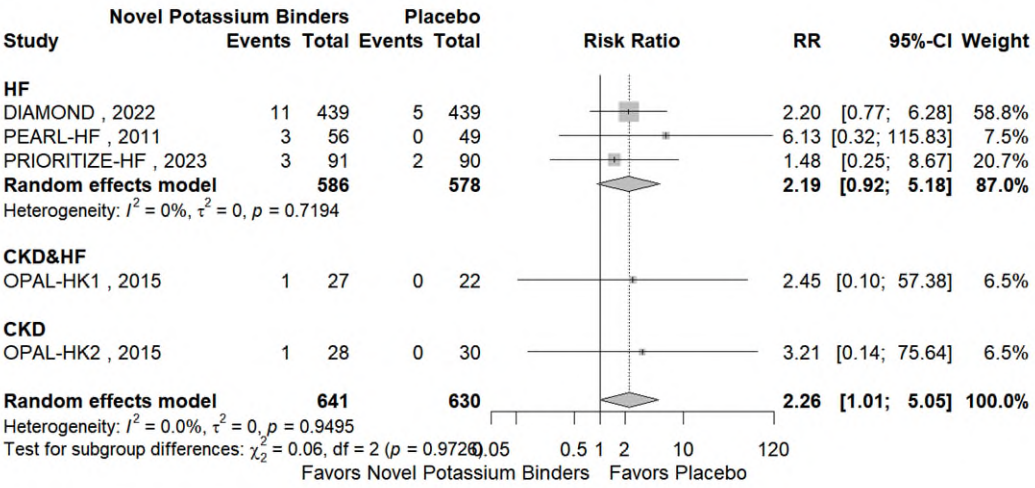


Online Resource 8 Subgroup analysis according to the patient population on diarrhea, constipation, nausea or vomiting, hypomagnesemia, edema, Serious AE, any AE leading to discontinuation

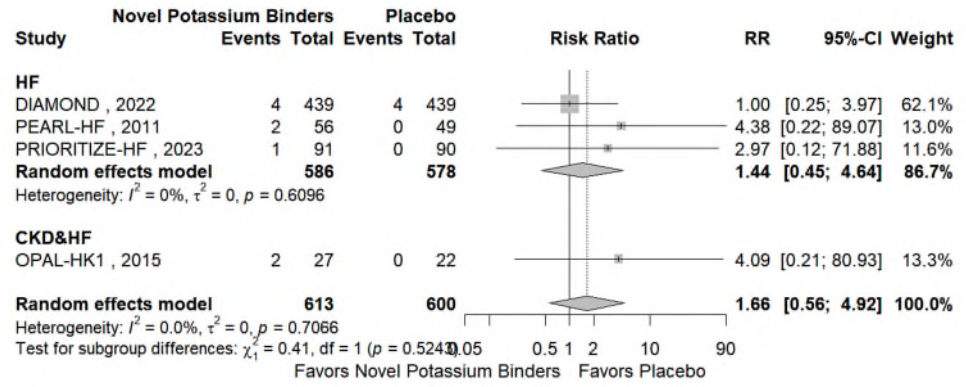
A Diarrhea (subgroup analysis according to the population)



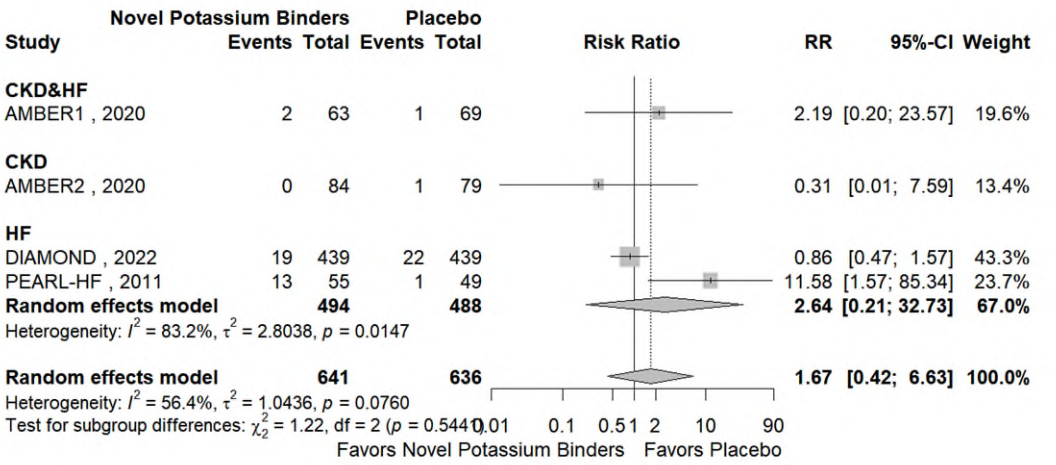
B Constipation (subgroup analysis according to the population)



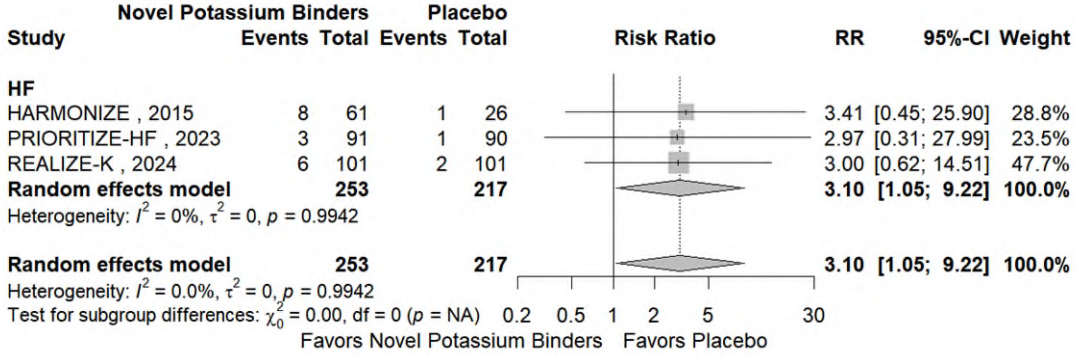
C Nausea or vomiting (subgroup analysis according to the population)



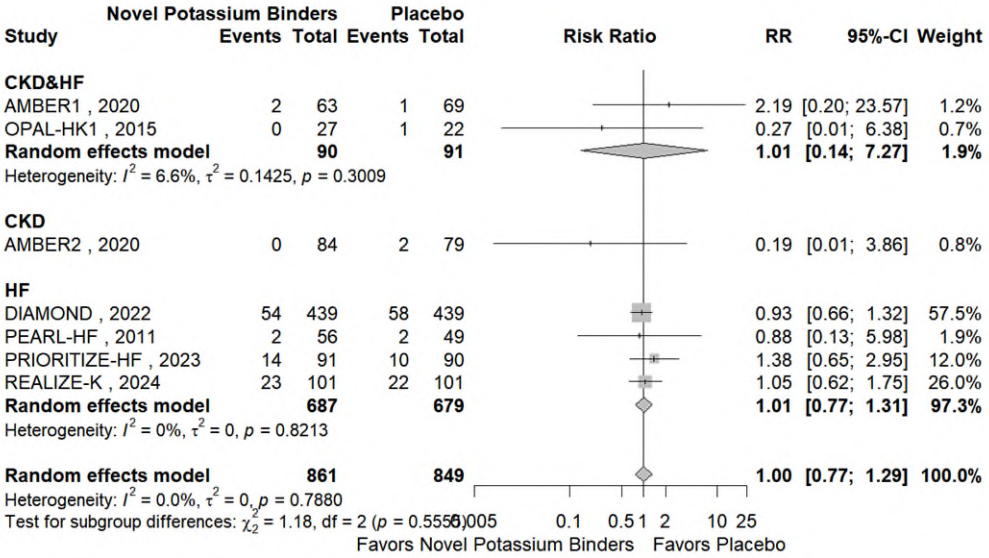
D Hypomagnesemia (subgroup analysis according to the population)



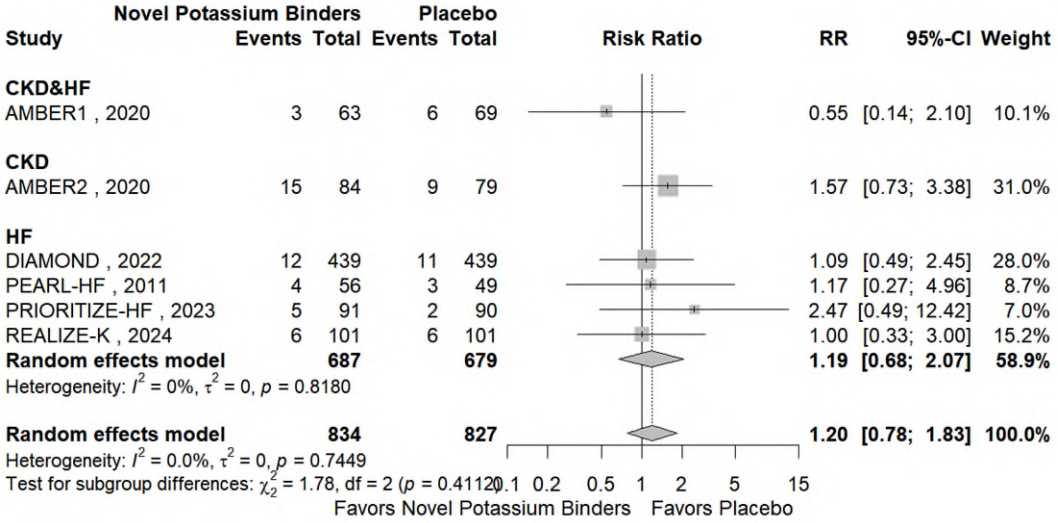
E Edema (subgroup analysis according to the population)



F Serious AE (subgroup analysis according to the population)

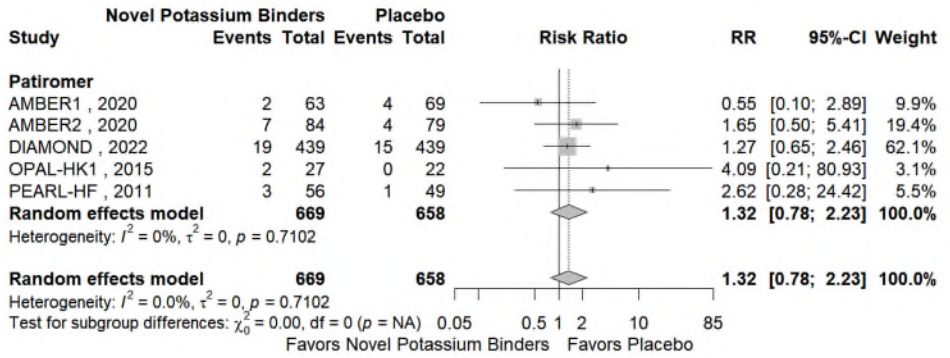


G Any AE leading to discontinuation (subgroup analysis according to the population)

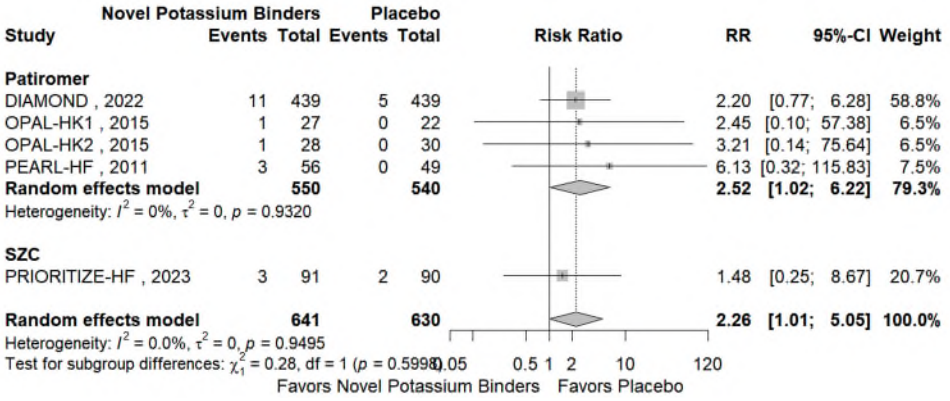

Novel Potassium Binders
Placebo
Study
Events Total Events Total
Risk Ratio
RR 95%-CI Weight
CKD&HF
AMBER1 , 2020 3 63 6 69 0.55 [0.14; 2.10] 10.1%
CKD
AMBER2 , 2020 15 84 9 79 1.57 [0.73; 3.38] 31.0%
HF
DIAMOND , 2022 12 439 11 439 1.09 [0.49; 2.45] 28.0%
PEARL-HF , 2011 4 56 3 49 1.17 [0.27; 4.96] 8.7%
PRIORITIZE-HF , 2023 5 91 2 90 2.47 [0.49; 12.42] 7.0%
REALIZE-K , 2024 6 101 6 101 1.00 [0.33; 3.00] 15.2%
Random effects model 687 679 1.19 [0.68; 2.07] 58.9%
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.8180
Random effects model 834 827 1.20 [0.78; 1.83] 100.0%
Heterogeneity: I^2 = 0.0%, τ^2 = 0, p = 0.7449
Test for subgroup differences: χ^2_2 = 1.78, df = 2 (p = 0.4112)
0.1 0.2 0.5 1 2 5 15
Favors Novel Potassium Binders
Favors Placebo

Online Resource 9 Subgroup analysis according to the type of NPBs on diarrhea, constipation, nausea or vomiting, hypomagnesemia, edema, Serious AE, any AE leading to discontinuation

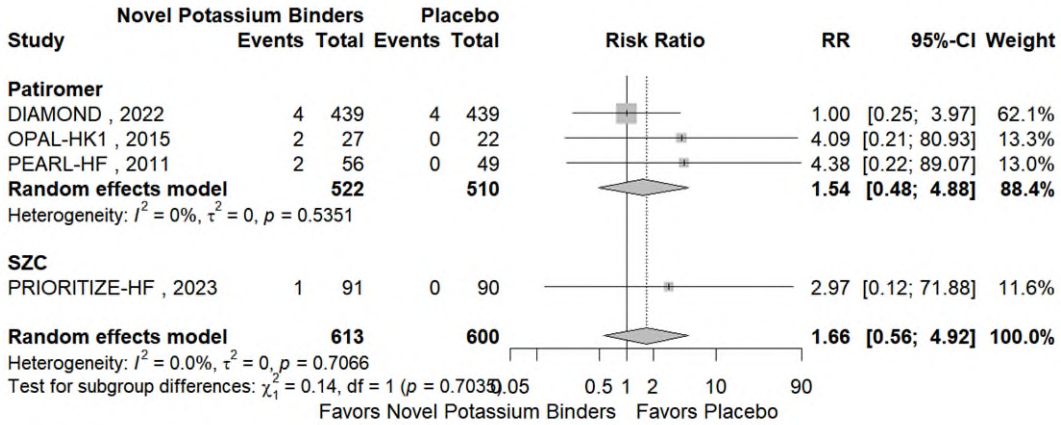
A Diarrhea (subgroup analysis according to the type of NPBs)



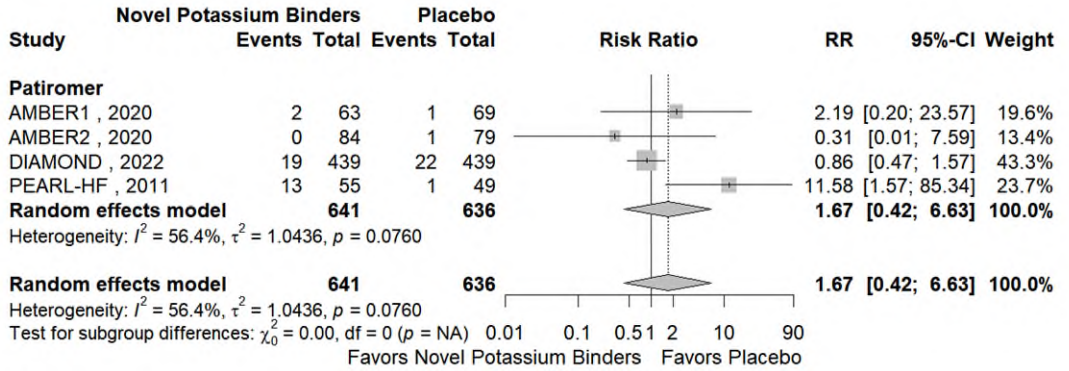
B Constipation (subgroup analysis according to the type of NPBs)



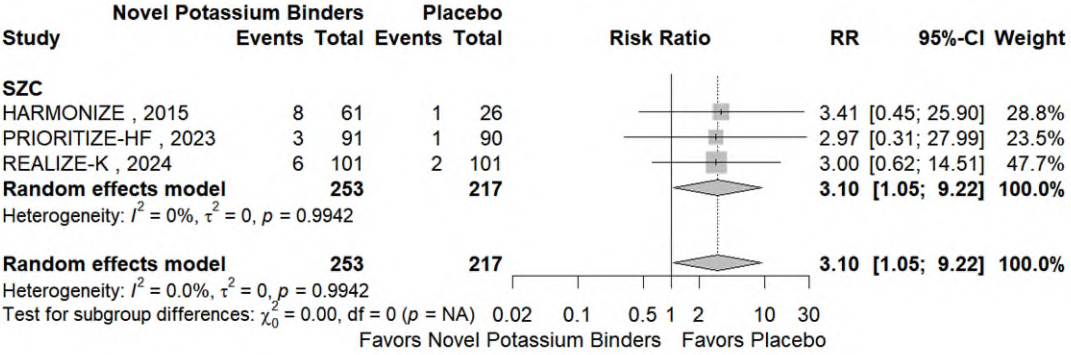
C Nausea or vomiting (subgroup analysis according to the type of NPBs)



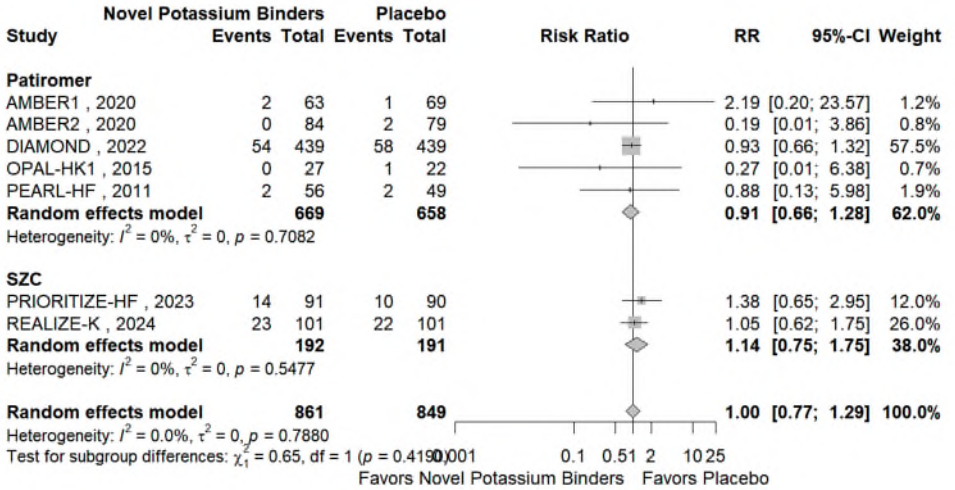
D Hypomagnesemia (subgroup analysis according to the type of NPBs)



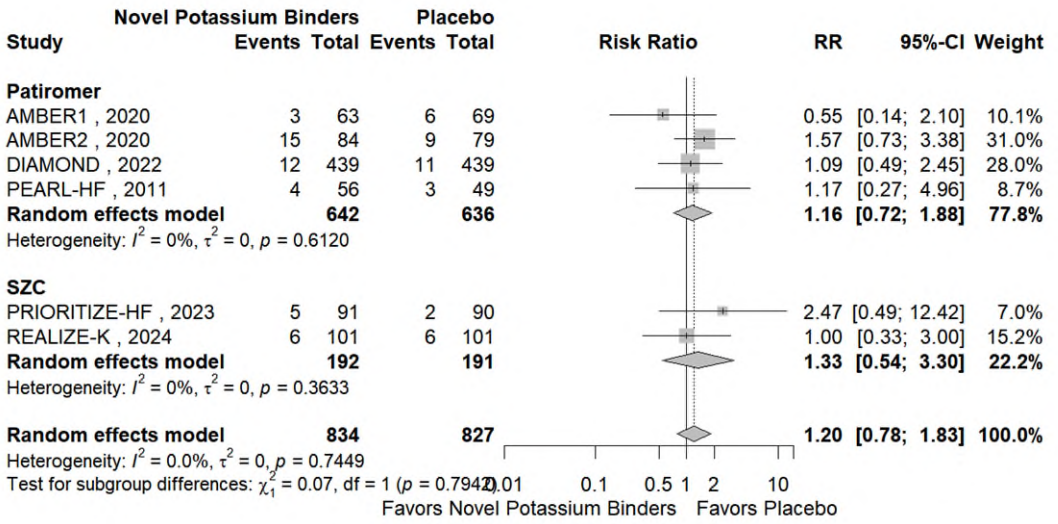
E Edema (subgroup analysis according to the type of NPBs)



F Serious AE (subgroup analysis according to the type of NPBs)

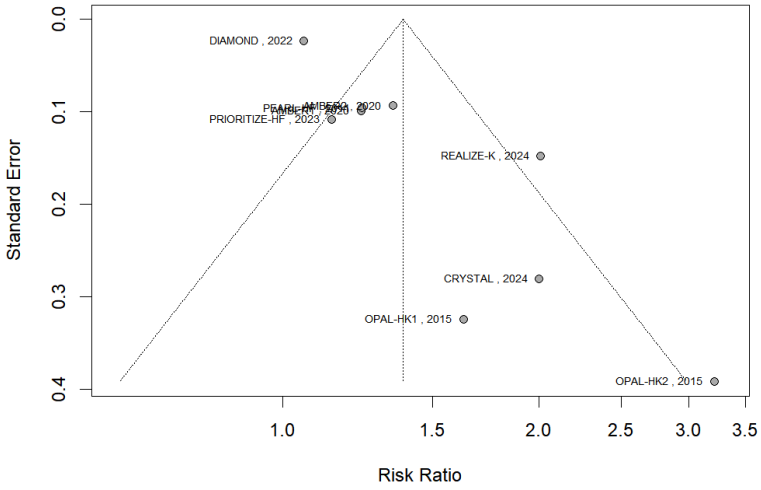


G Any AE leading to discontinuation (subgroup analysis according to the type of NPBs)

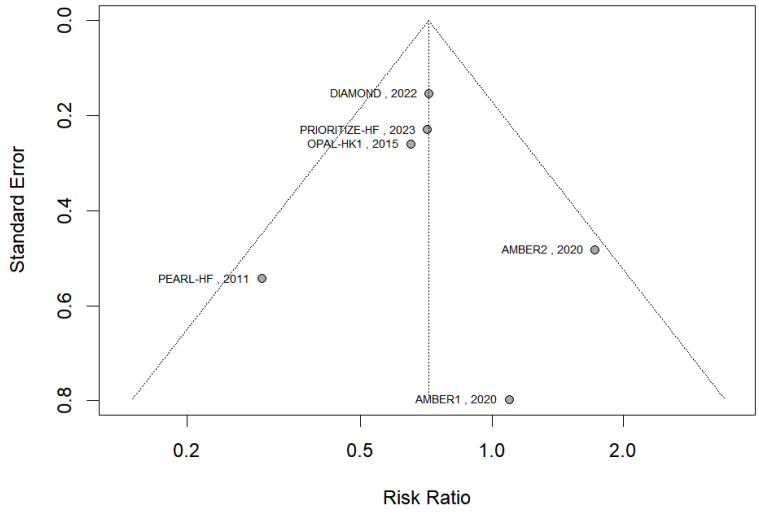

Novel Potassium Binders
Placebo
Study
Events Total Events Total
Risk Ratio
RR 95%-CI Weight
Patiromer
AMBER1 , 2020 3 63 6 69 0.55 [0.14; 2.10] 10.1%
AMBER2 , 2020 15 84 9 79 1.57 [0.73; 3.38] 31.0%
DIAMOND , 2022 12 439 11 439 1.09 [0.49; 2.45] 28.0%
PEARL-HF , 2011 4 56 3 49 1.17 [0.27; 4.96] 8.7%
Random effects model 642 636 1.16 [0.72; 1.88] 77.8%
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.6120
SZC
PRIORITIZE-HF , 2023 5 91 2 90 2.47 [0.49; 12.42] 7.0%
REALIZE-K , 2024 6 101 6 101 1.00 [0.33; 3.00] 15.2%
Random effects model 192 191 1.33 [0.54; 3.30] 22.2%
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.3633
Random effects model 834 827 1.20 [0.78; 1.83] 100.0%
Heterogeneity: I^2 = 0.0%, τ^2 = 0, p = 0.7449
Test for subgroup differences: χ^2_1 = 0.07, df = 1 (p = 0.7942)
0.01 0.1 0.5 1 2 10
Favors Novel Potassium Binders
Favors Placebo

Online Resource 10 Funnel plots of all outcomes

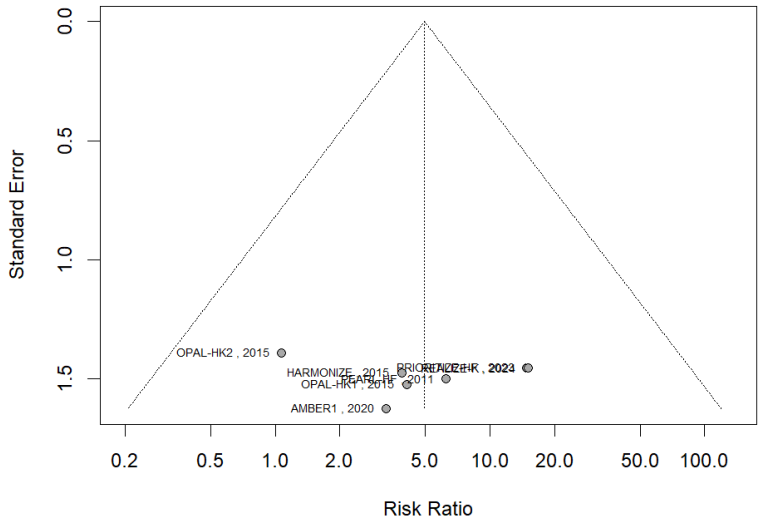
A Optimization of RAASi therapy



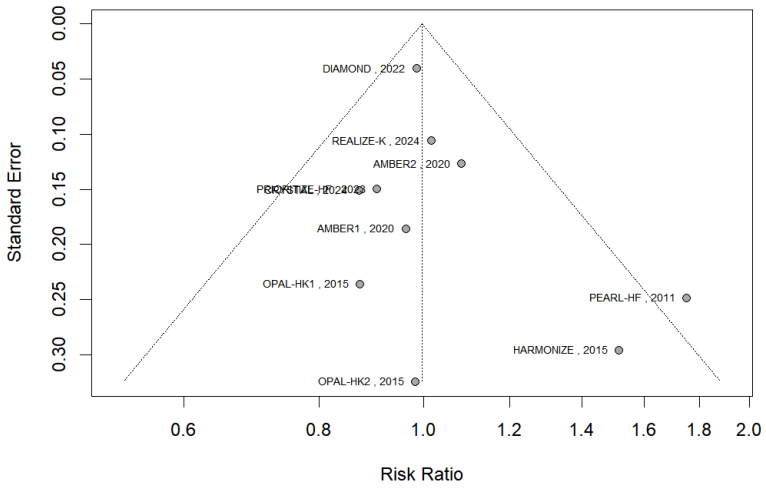
B HK events



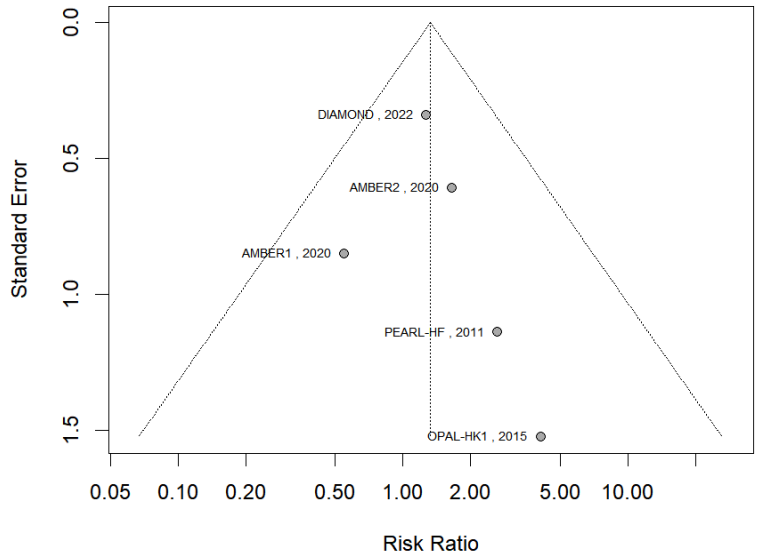
C Hypokalemia events



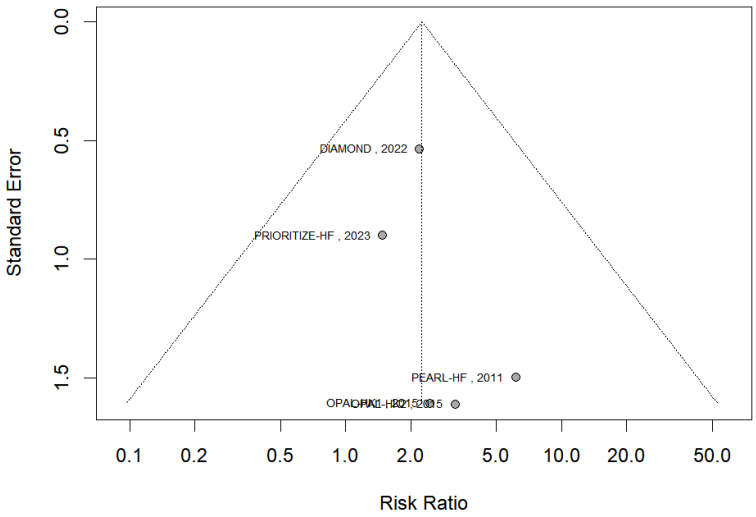
D Any adverse events



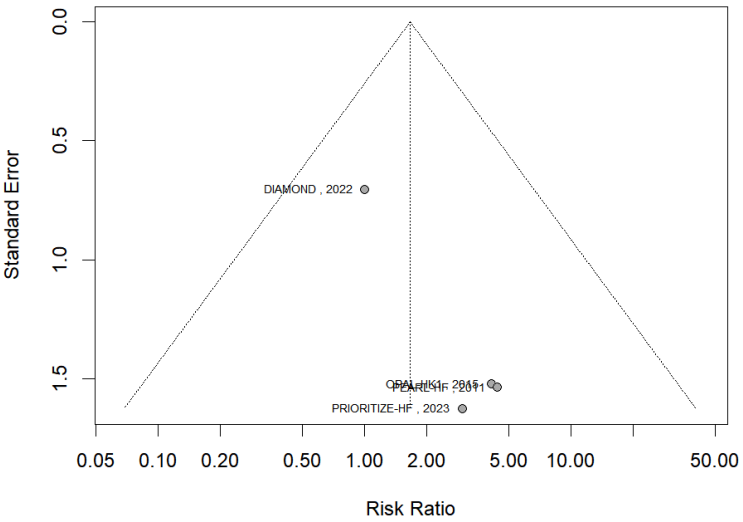
E Diarrhea



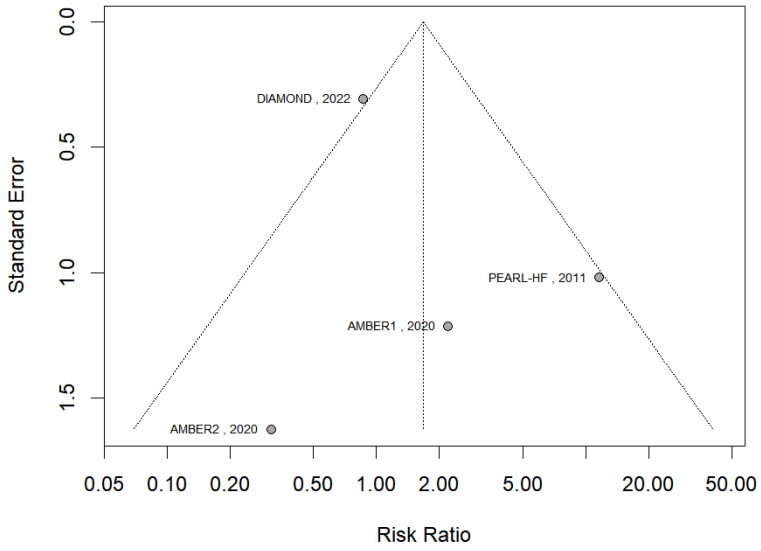
F Constipation



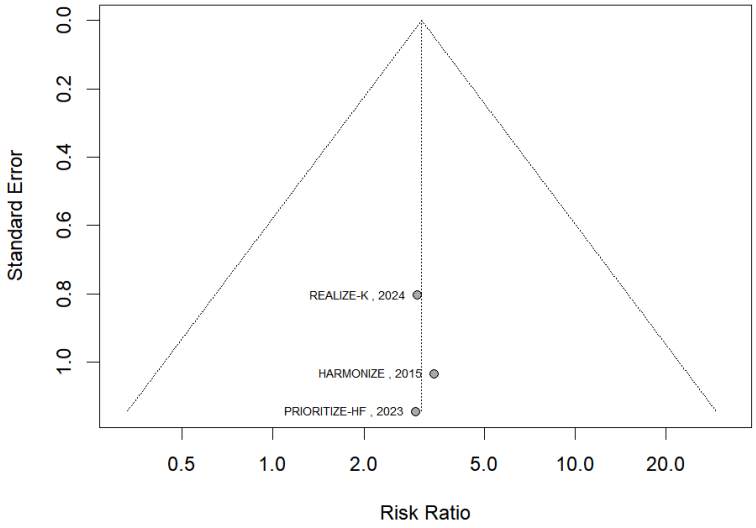
G Nausea or vomiting



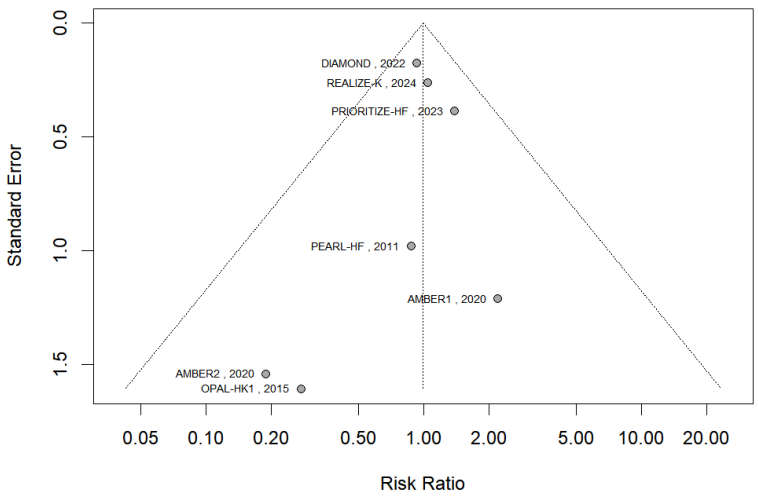
H Hypomagnesemia



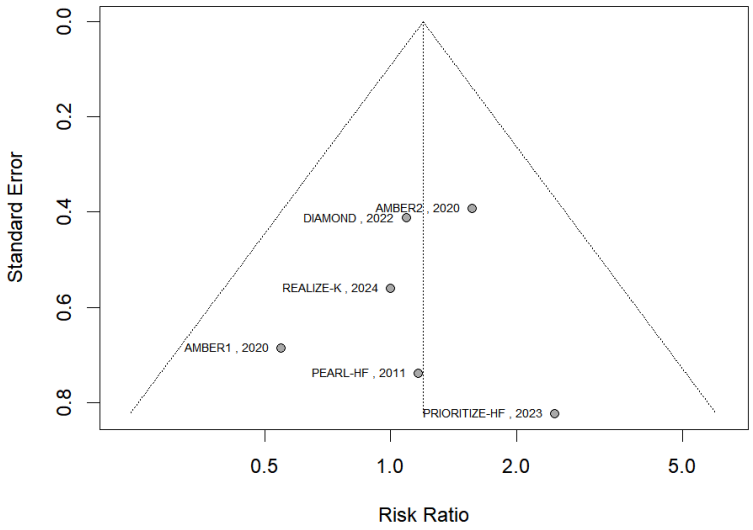
I Edema



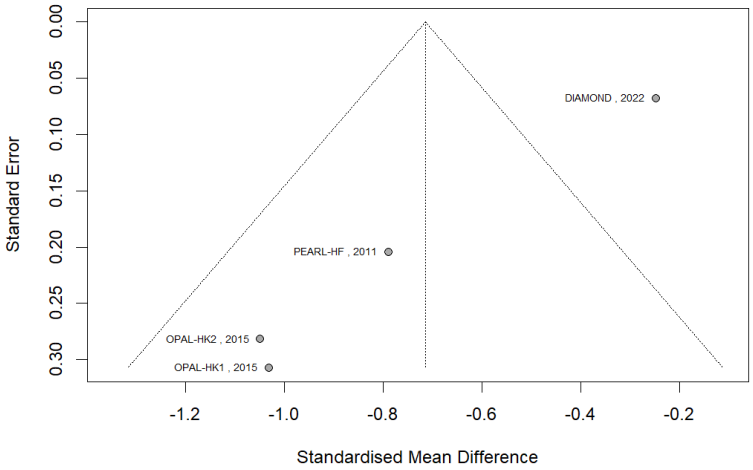
J Serious AE



K Any AE leading to discontinuation



L Potassium level reduction

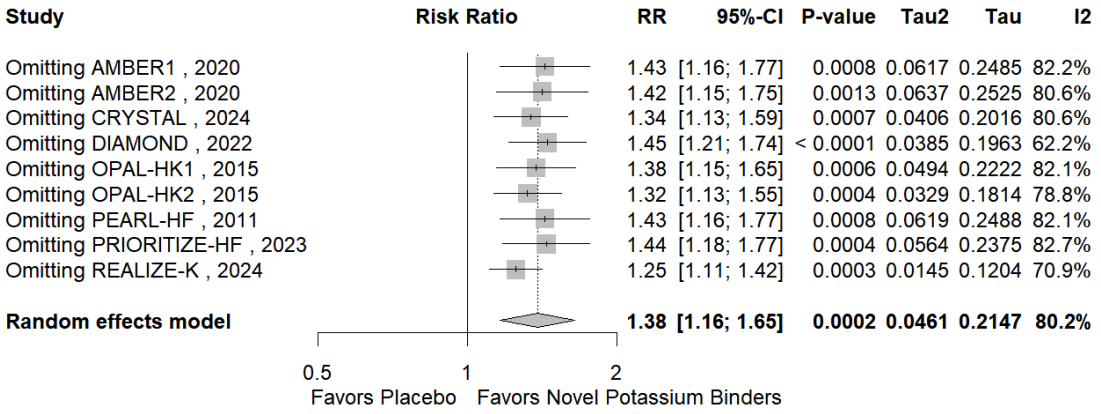


Online Resource 11 Egger's test p-value for outcomes

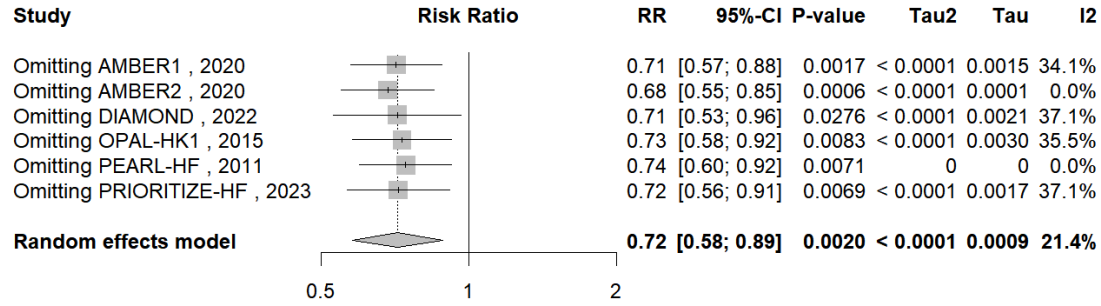
Outcomes	Egger's test p-value
Optimization of RAASi therapy	**0.0013**
Hyperkalemia events	0.8235
Hypokalemia events	0.8100
Any adverse events	0.3693
Diarrhea	0.5819
Constipation	0.3900
Nausea or vomiting	**0.0243**
Hypomagnesemia	0.5375
Edema	0.8079
Serious AE	0.6171
Any AE leading to discontinuation	0.7988
Potassium level reduction	**0.0037**

Online Resource 12 Leave-one-out sensitivity analyses of endpoints

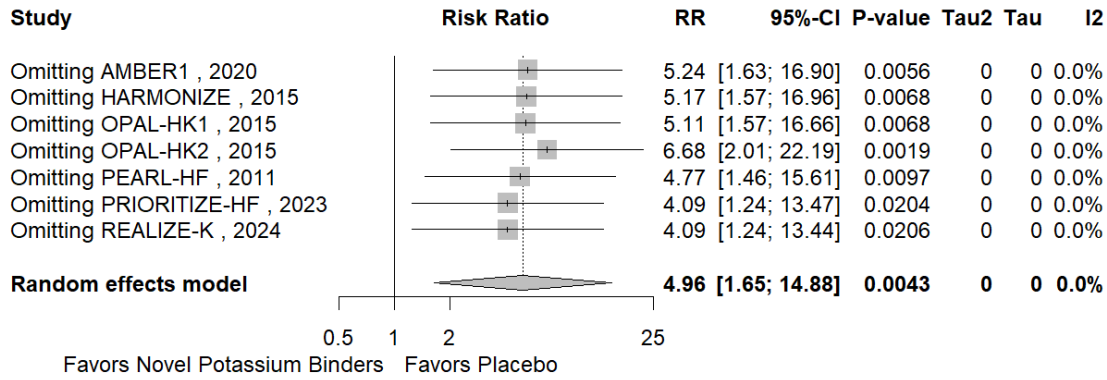
A Optimization of RAASi therapy



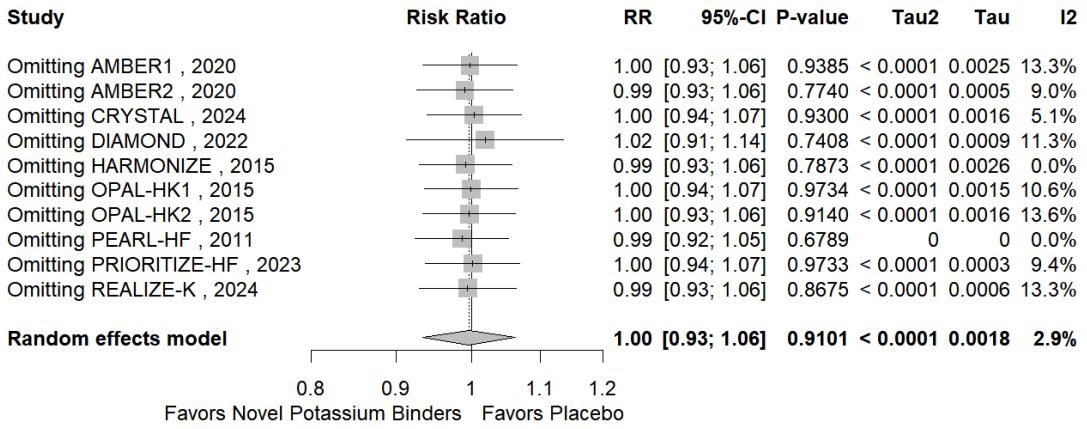
B HK events



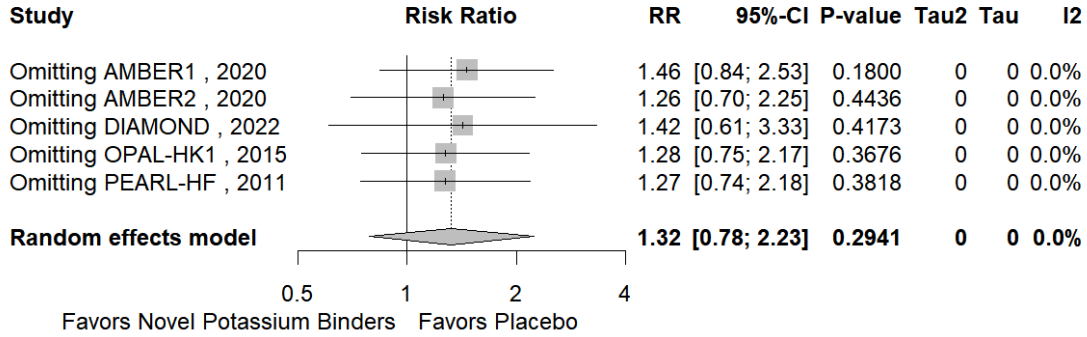
C Hypokalemia events



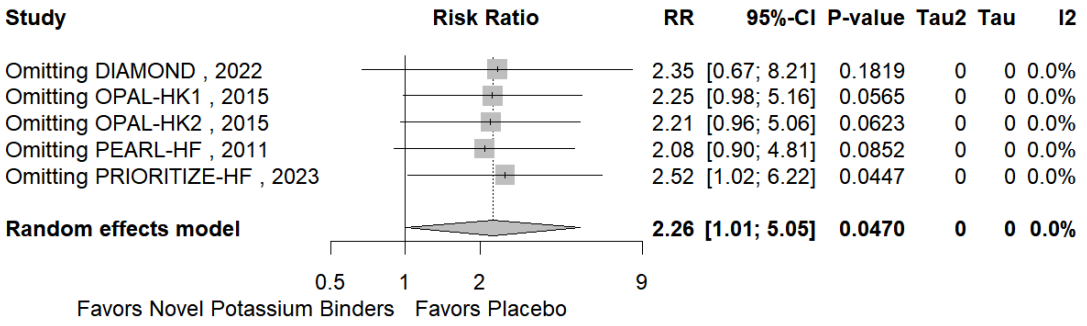
D Any adverse events



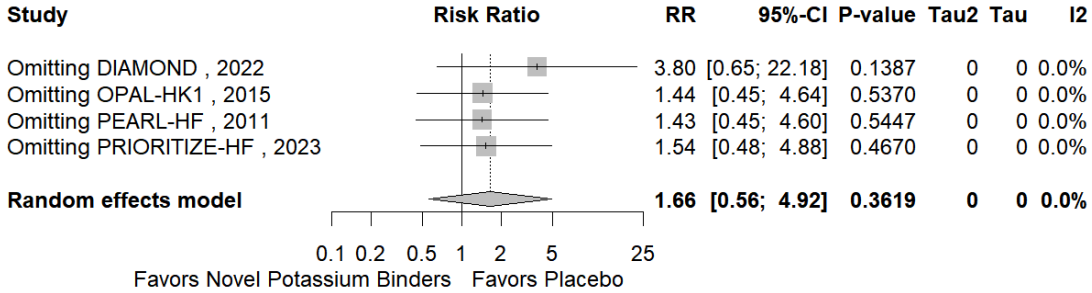
E Diarrhea



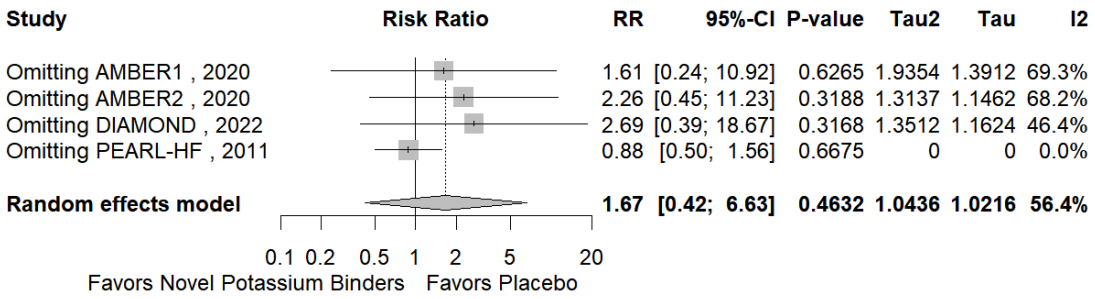
F Constipation



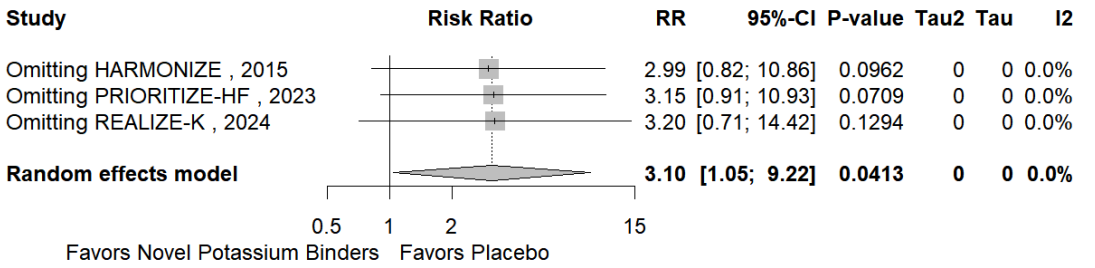
G Nausea or vomiting



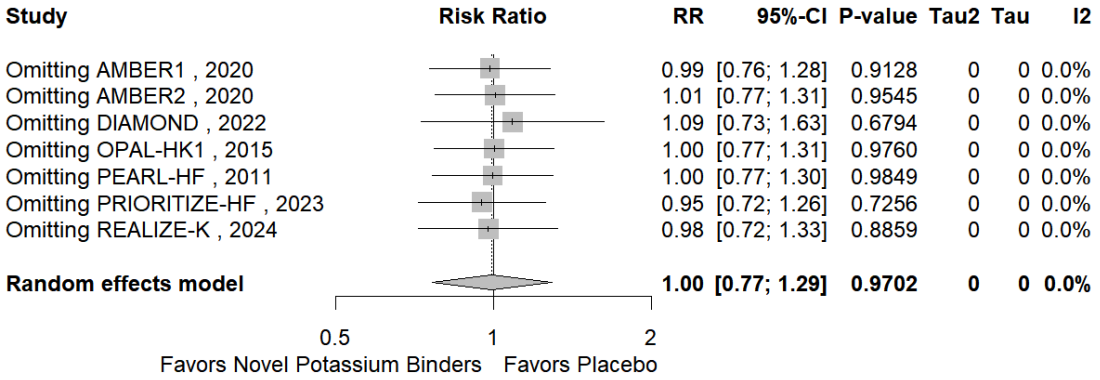
H Hypomagnesemia



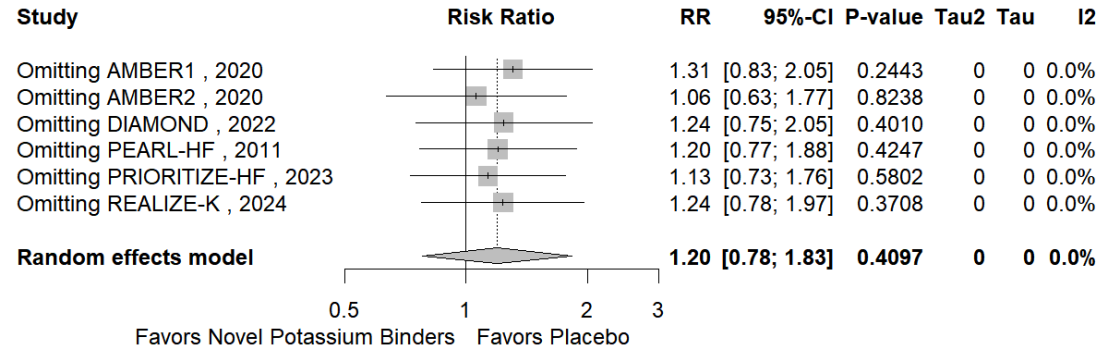
I Edema



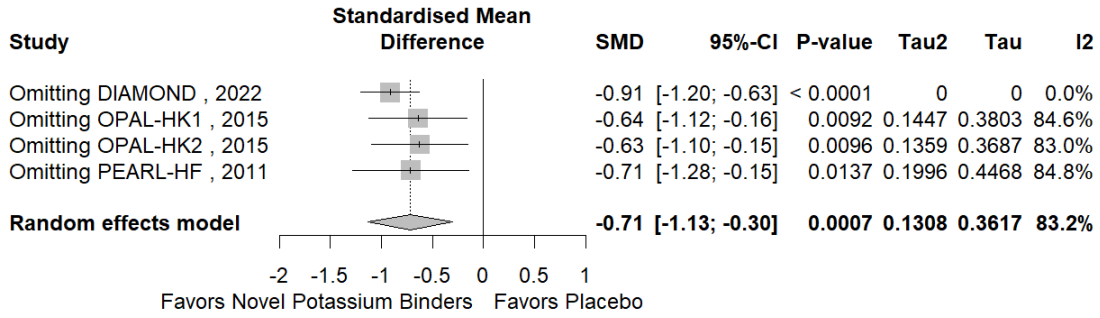
J Serious AE



K Any AE leading to discontinuation



L Potassium level reduction


Standardised Mean Difference
Study
SMD
95%-CI
P-value
Tau2
Tau
I2
Omitting DIAMOND , 2022 -0.91 [-1.20; -0.63] < 0.0001 0 0 0.0%
Omitting OPAL-HK1 , 2015 -0.64 [-1.12; -0.16] 0.0092 0.1447 0.3803 84.6%
Omitting OPAL-HK2 , 2015 -0.63 [-1.10; -0.15] 0.0096 0.1359 0.3687 83.0%
Omitting PEARL-HF , 2011 -0.71 [-1.28; -0.15] 0.0137 0.1996 0.4468 84.8%
Random effects model -0.71 [-1.13; -0.30] 0.0007 0.1308 0.3617 83.2%
-2 -1.5 -1 -0.5 0 0.5 1
Favors Novel Potassium Binders
Favors Placebo