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SUPPLEMENTARY MATERIAL

Heart failure outcomes among reduced and preserved ejection fraction patients on sodium-glucose cotransporter-2 inhibitors with different dosing patterns of diuretics: a systematic review and meta-analysis

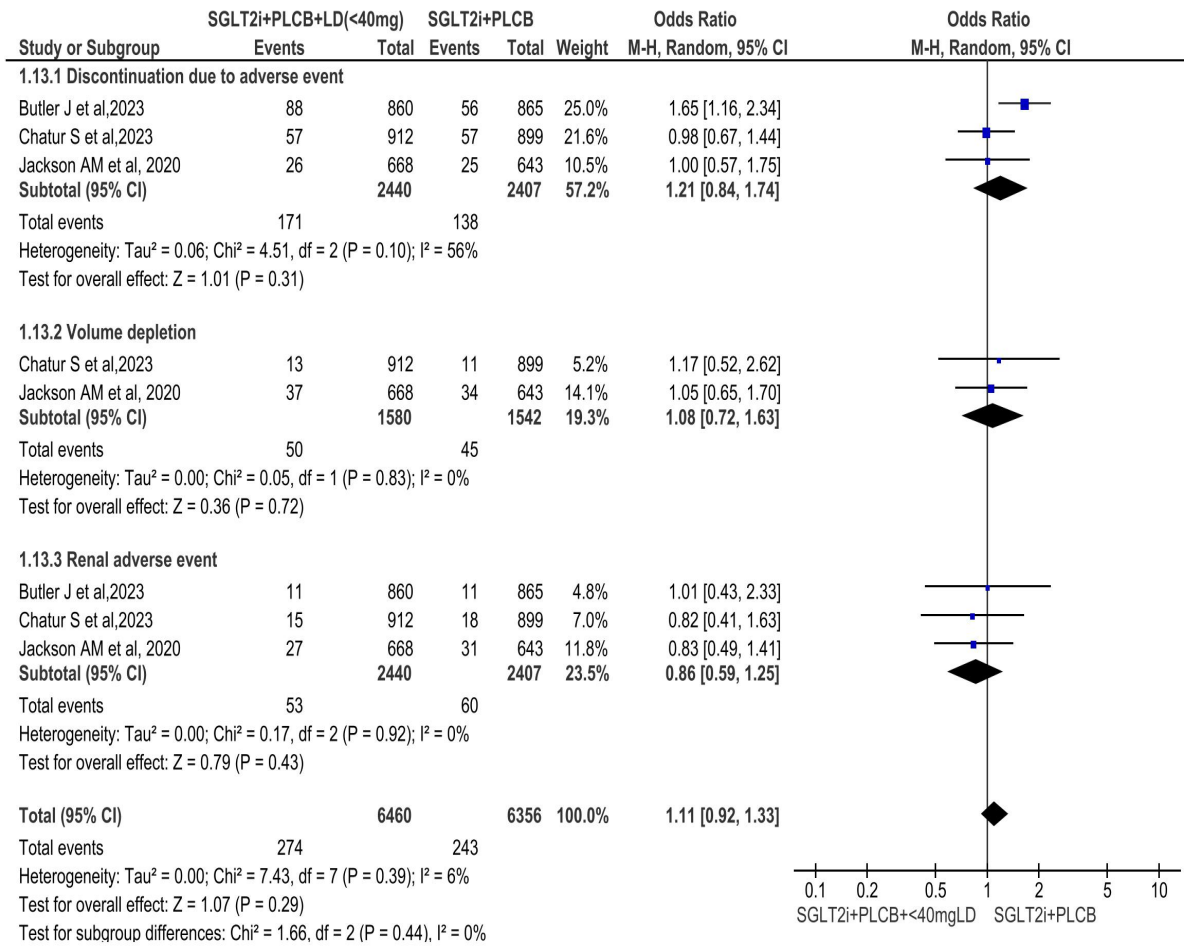
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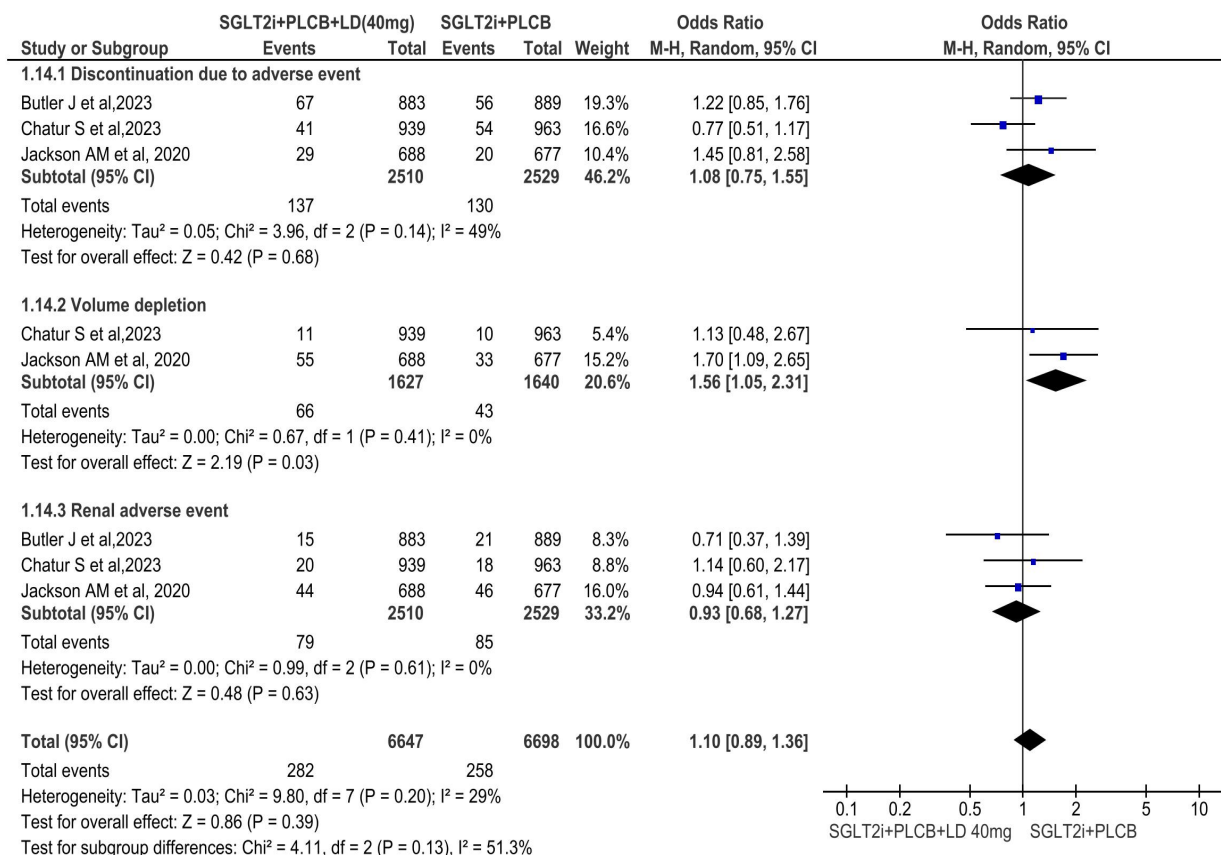
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Key words: ejection fraction, heart failure, loop diuretics, outcomes, safety and efficacy, SGLT2i.

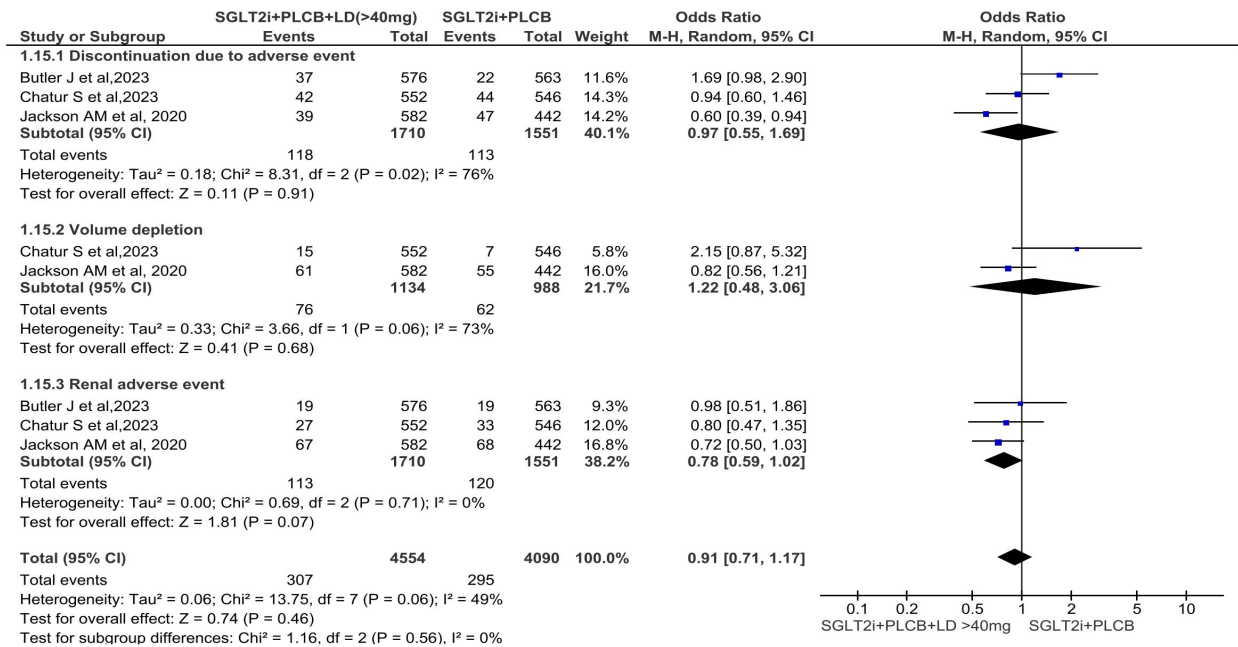
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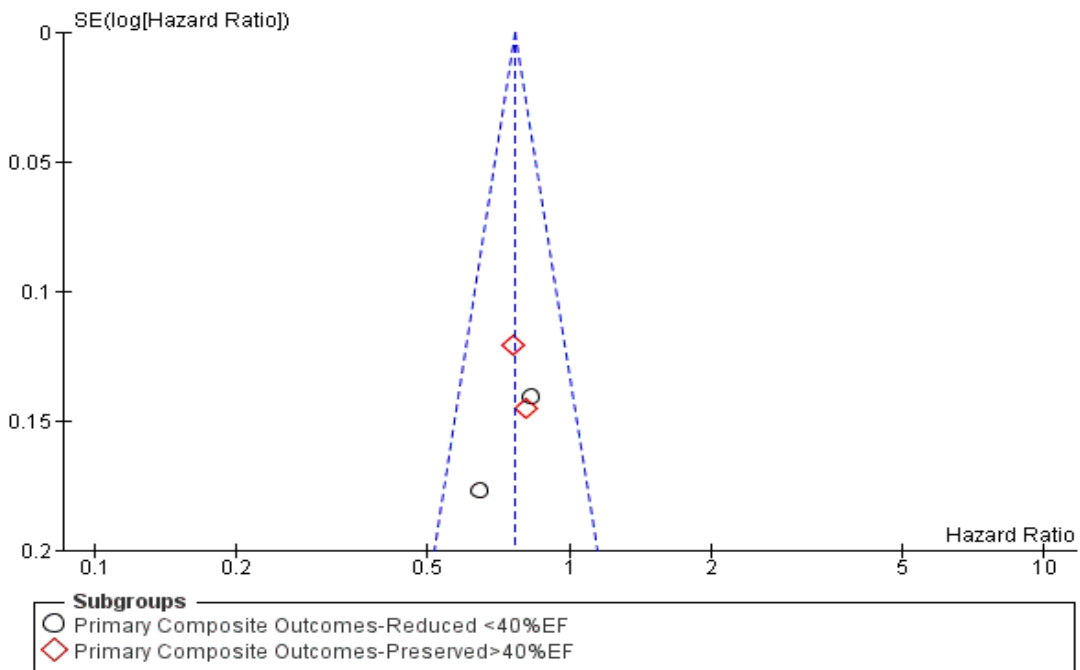
Supplementary Figure 1. The forest plot illustrates the adjusted hazard ratios for discontinuation of the drug due to adverse events, volume depletion, and renal adverse events among patients with heart failure with reduced ejection fraction and heart failure with preserved ejection fraction, stratified by treatment with sodium-glucose co-transporter 2 inhibitor (SGLT2i), placebo, and SGLT2i plus loop diuretics at doses below 40 mg.



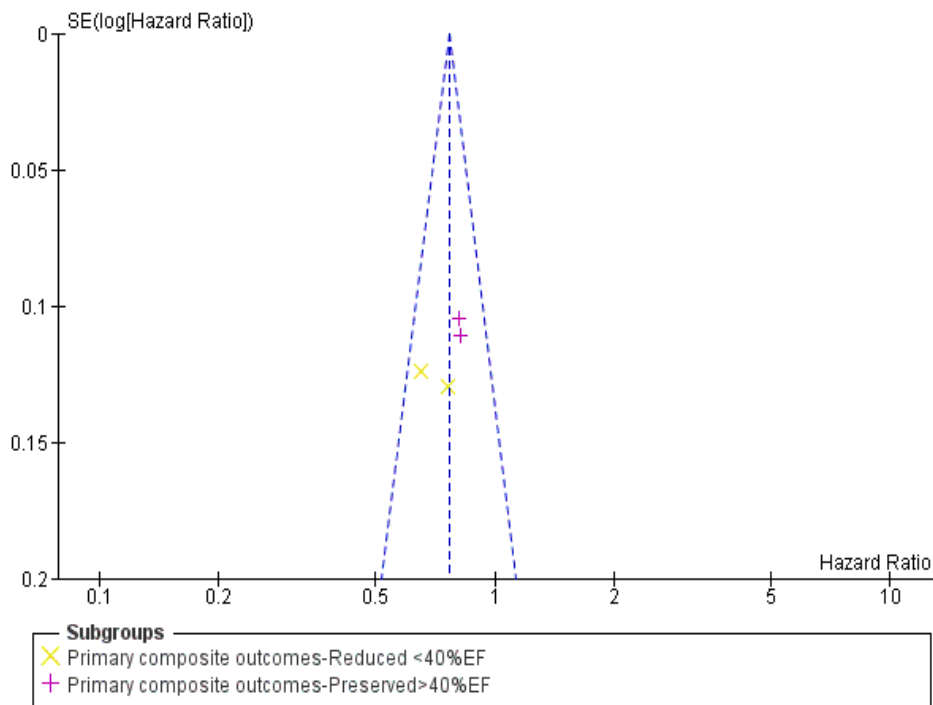
Supplementary Figure 2. The forest plot illustrates the adjusted hazard ratios for discontinuation of the drug due to adverse events, volume depletion, and renal adverse events among patients with heart failure with reduced ejection fraction and heart failure with preserved ejection fraction, stratified by treatment with sodium-glucose co-transporter 2 inhibitor (SGLT2i), placebo, and SGLT2i plus loop diuretics at doses equal to 40 mg.



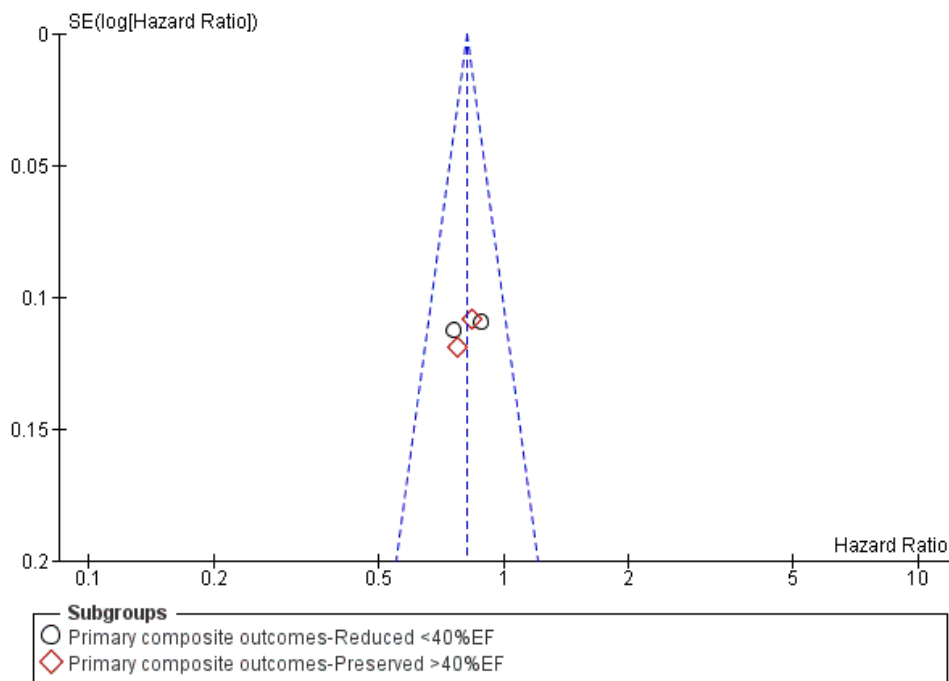
Supplementary Figure 3. The forest plot illustrates the adjusted hazard ratios for discontinuation of the drug due to adverse events, volume depletion, and renal adverse events among patients with heart failure with reduced ejection fraction and heart failure with preserved ejection fraction, stratified by treatment with sodium-glucose co-transporter 2 inhibitor (SGLT2i), placebo, and SGLT2i plus loop diuretics at doses above 40 mg.



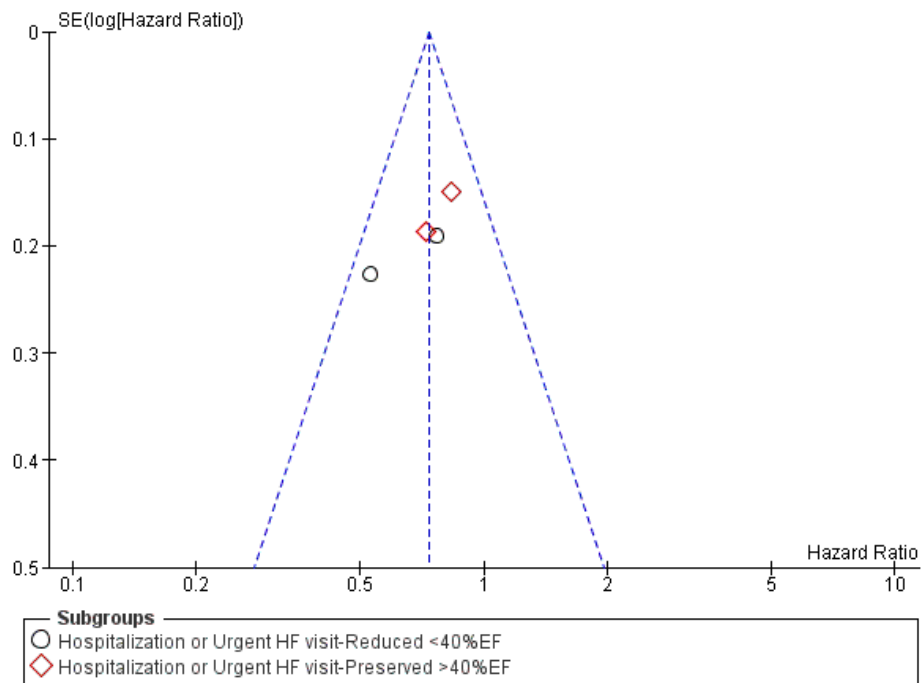
Supplementary Figure 4. A funnel plot comparing the primary composite outcome in patients with heart failure with reduced ejection fraction and heart failure with preserved ejection fraction, those treated with sodium-glucose co-transporter 2 inhibitor (SGLT2i) and placebo vs. SGLT2i, placebo, and loop diuretics at doses below 40 mg.



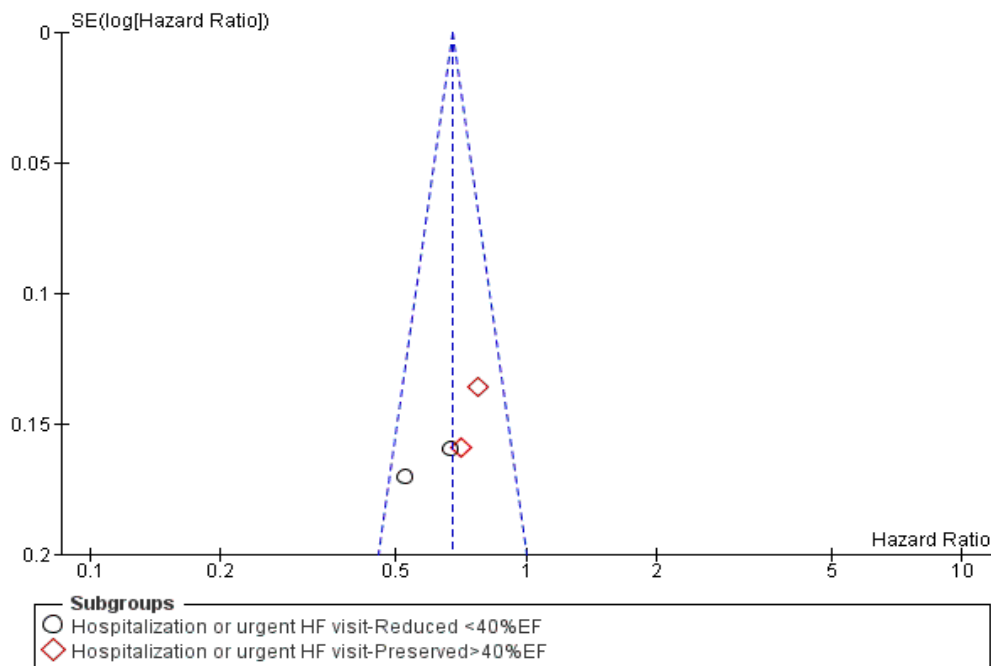
Supplementary Figure 5. A funnel plot comparing the primary composite outcome in patients with heart failure with reduced ejection fraction and heart failure with preserved ejection fraction, those treated with sodium-glucose co-transporter 2 inhibitor (SGLT2i) and placebo vs. SGLT2i, placebo, and loop diuretics at doses equal to 40 mg.



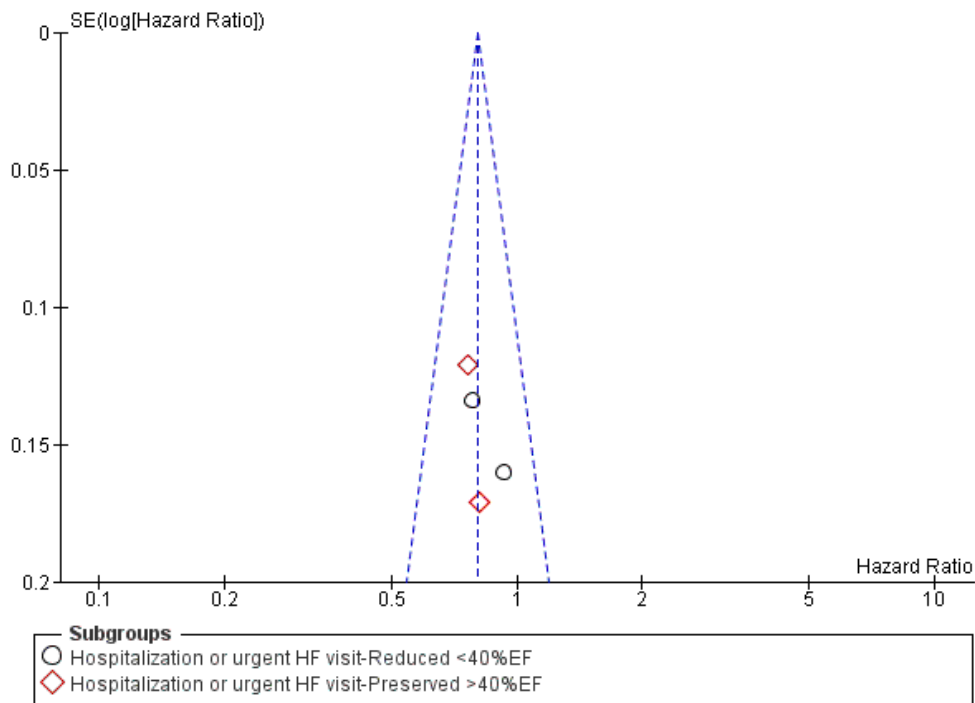
Supplementary Figure 6. A funnel plot comparing the primary composite outcome in patients with heart failure with reduced ejection fraction and heart failure with preserved ejection fraction, those treated with sodium-glucose co-transporter 2 inhibitor (SGLT2i) and placebo vs. SGLT2i, placebo, and loop diuretics at doses above 40 mg.



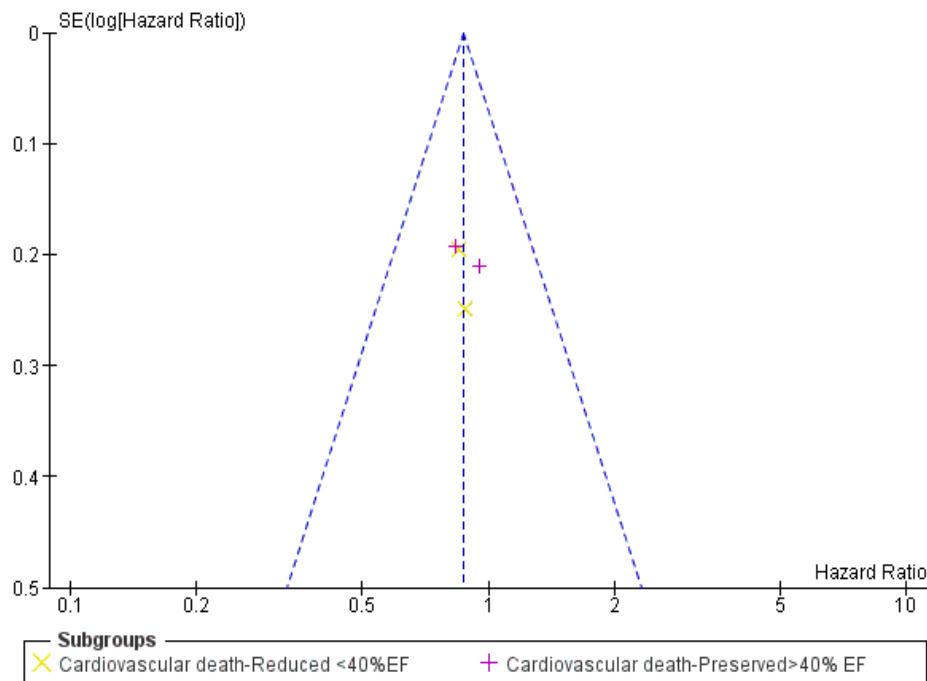
Supplementary Figure 7. A funnel plot comparing the hospitalization or urgent HF visit in patients with heart failure with reduced ejection fraction and heart failure with preserved ejection fraction, those treated with sodium-glucose co-transporter 2 inhibitor (SGLT2i) and placebo vs. SGLT2i, placebo, and loop diuretics at doses below 40 mg.



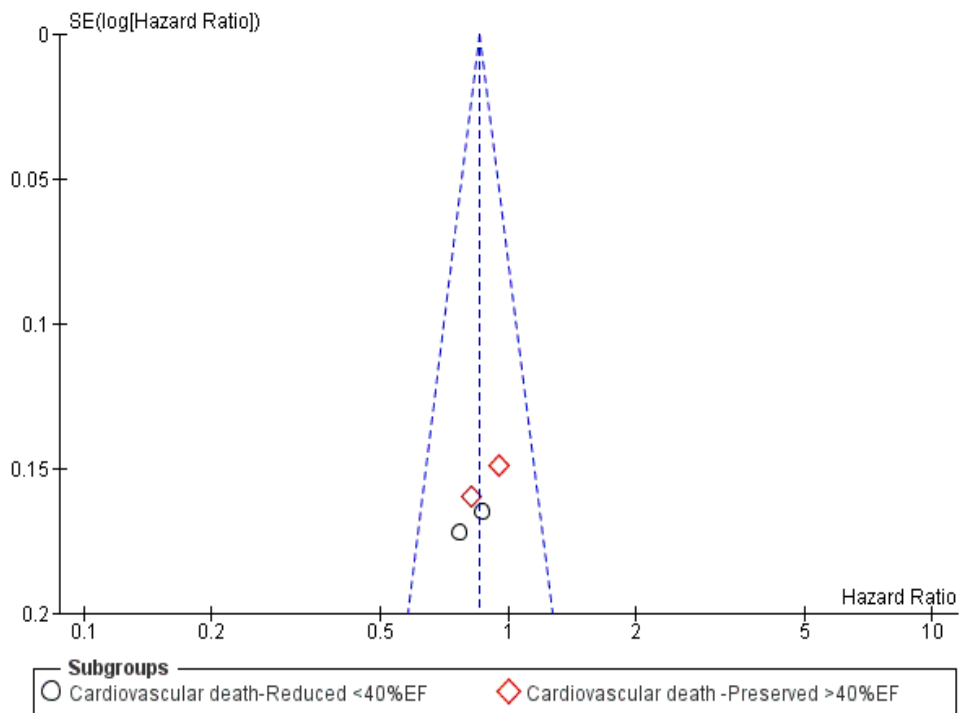
Supplementary Figure 8. A funnel plot comparing the hospitalization or urgent HF visit in patients with heart failure with reduced ejection fraction and heart failure with preserved ejection fraction, those treated with sodium-glucose co-transporter 2 inhibitor (SGLT2i) and placebo vs. LT2i, placebo, and loop diuretics at doses equal to 40 mg.



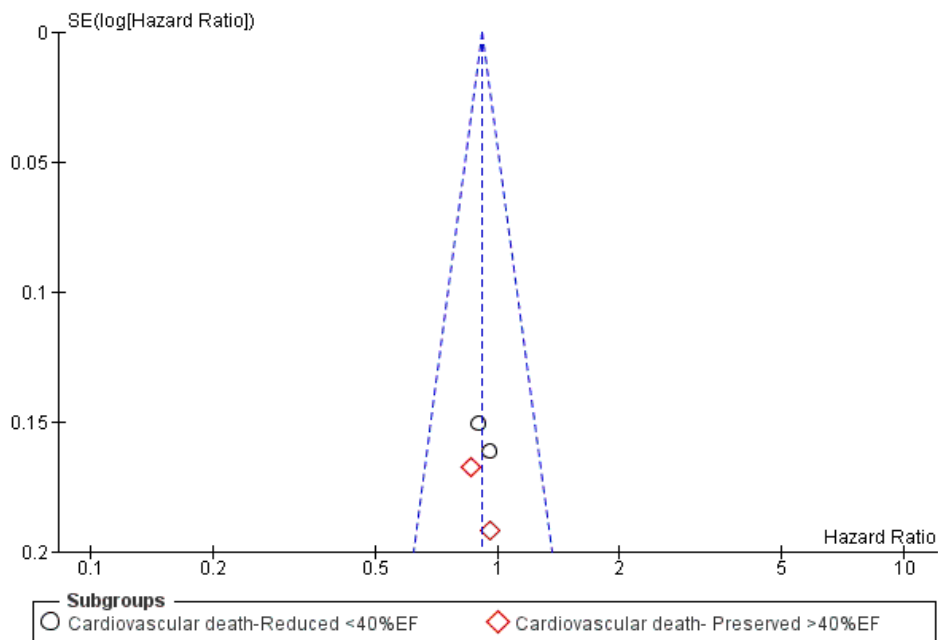
Supplementary Figure 9. A funnel plot comparing the hospitalization or urgent HF visit in patients with heart failure with reduced ejection fraction and heart failure with preserved ejection fraction, those treated with sodium-glucose co-transporter 2 inhibitor (SGLT2i) and placebo vs. SGLT2i, placebo, and loop diuretics at doses above 40 mg.



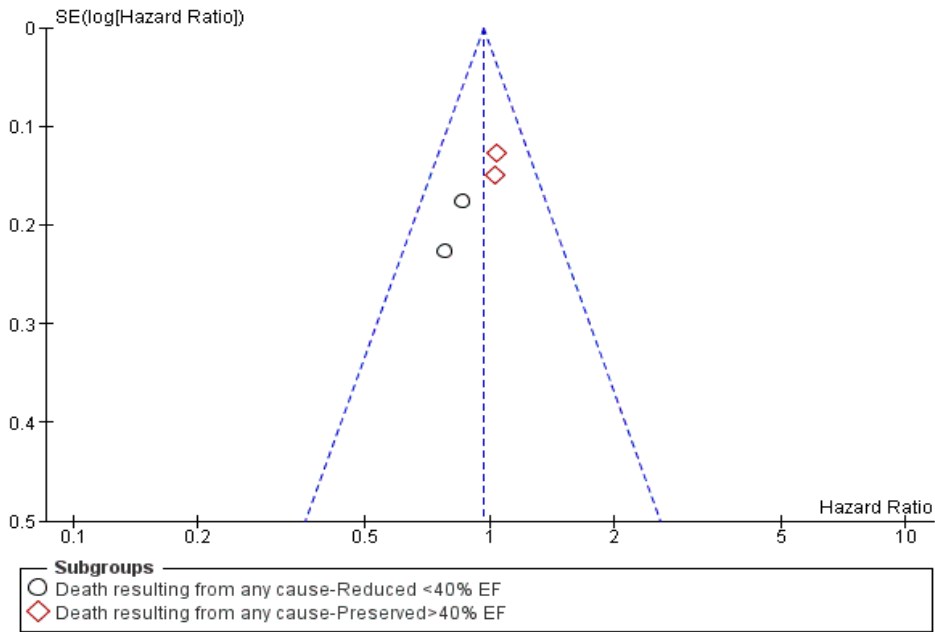
Supplementary Figure 10. A funnel plot comparing the cardiovascular death in patients with heart failure with reduced ejection fraction and heart failure with preserved ejection fraction, those treated with sodium-glucose co-transporter 2 inhibitor (SGLT2i) and placebo vs. SGLT2i, placebo, and loop diuretics at doses below 40 mg.



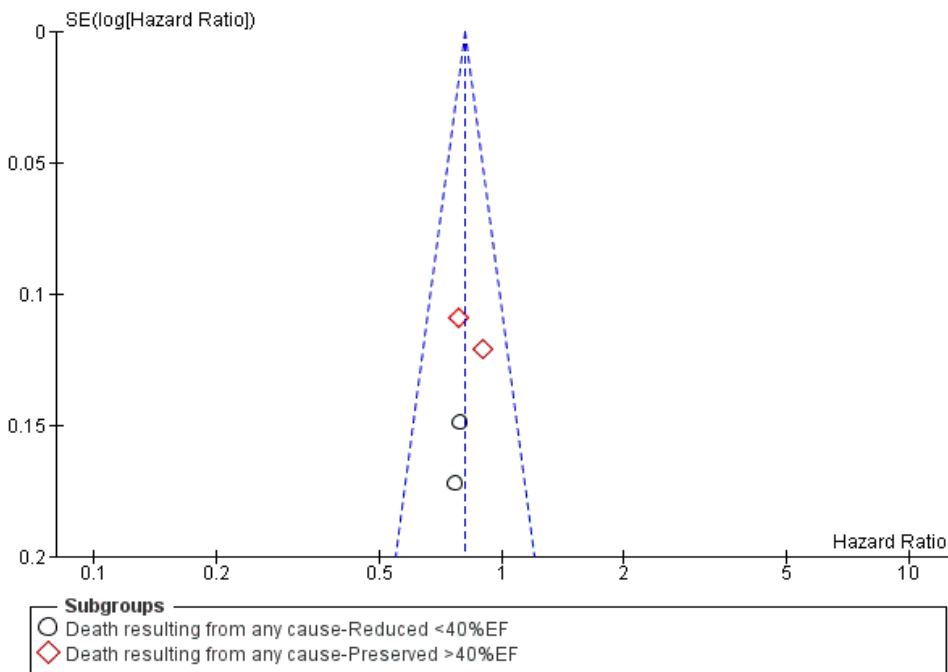
Supplementary Figure 11. A funnel plot comparing the cardiovascular death in patients with heart failure with reduced ejection fraction and heart failure with preserved ejection fraction, those treated with sodium-glucose co-transporter 2 inhibitor (SGLT2i) and placebo vs. SGLT2i, placebo, and loop diuretics at doses equal to 40 mg.



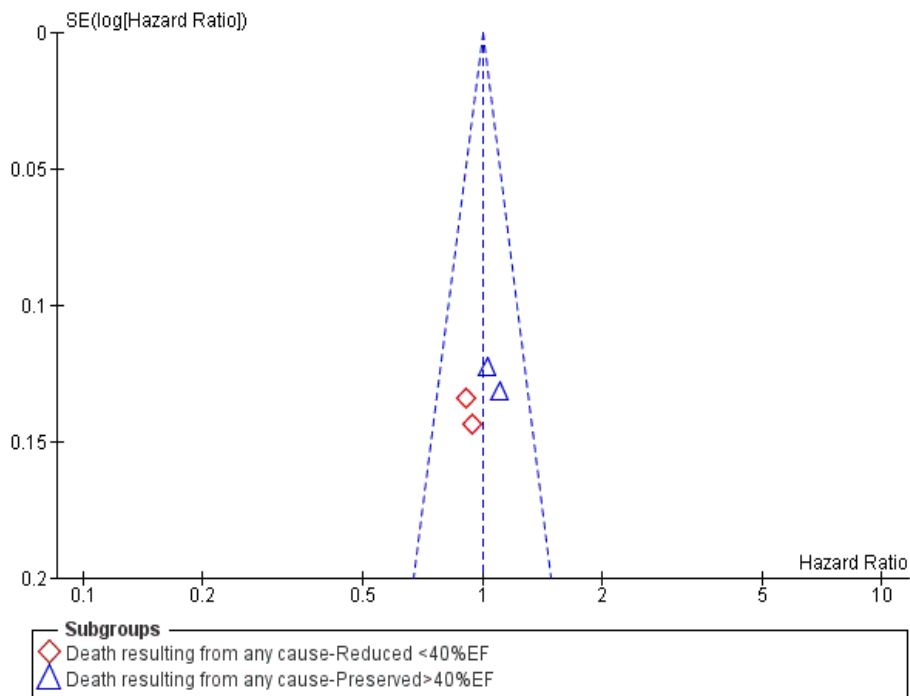
Supplementary Figure 12. A funnel plot comparing the cardiovascular death in patients with heart failure with reduced ejection fraction and heart failure with preserved ejection fraction, those treated with sodium-glucose co-transporter 2 inhibitor (SGLT2i) and placebo vs. SGLT2i, placebo, and loop diuretics at doses above 40 mg.



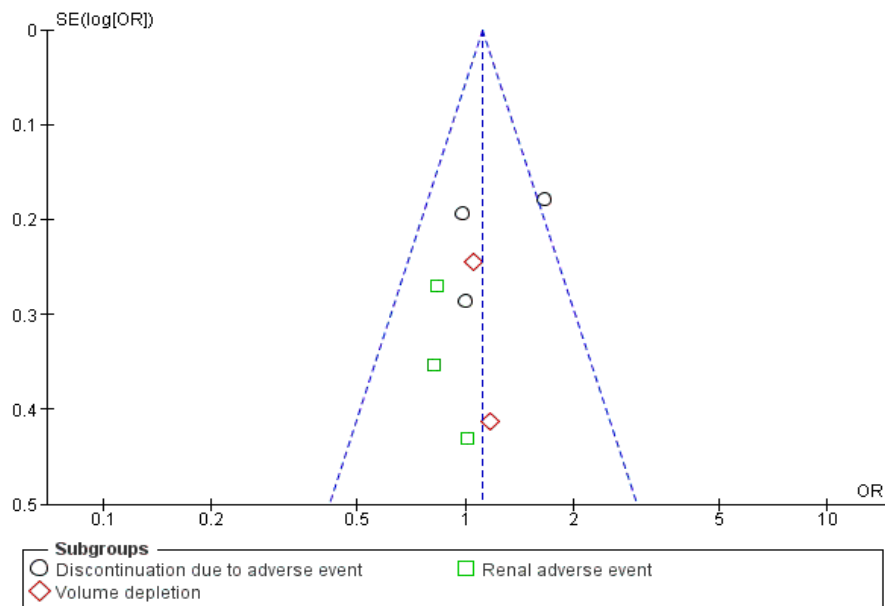
Supplementary Figure 13. A funnel plot comparing the death resulting from any cause in patients with heart failure with reduced ejection fraction and heart failure with preserved ejection fraction, those treated with sodium-glucose co-transporter 2 inhibitor (SGLT2i) and placebo vs. SGLT2i, placebo, and loop diuretics at doses below 40 mg.



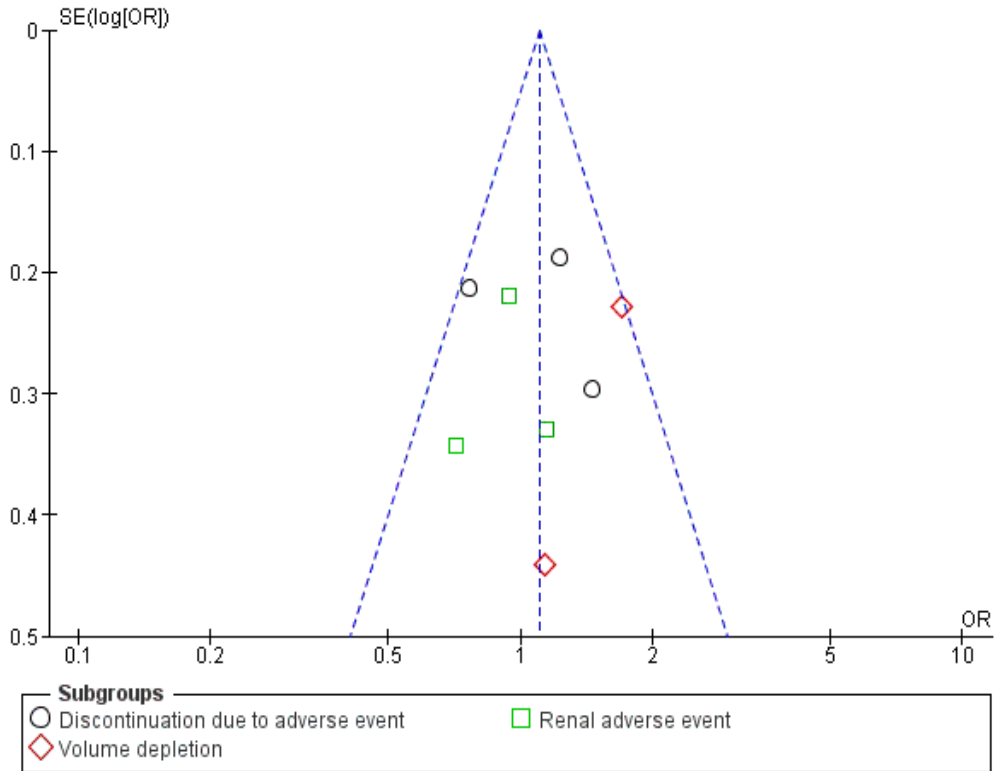
Supplementary Figure 14. A funnel plot comparing the death resulting from any cause in patients with heart failure with reduced ejection fraction and heart failure with preserved ejection fraction, those treated with sodium-glucose co-transporter 2 inhibitor (SGLT2i) and placebo vs. SGLT2i, placebo, and loop diuretics at doses equal to 40 mg.



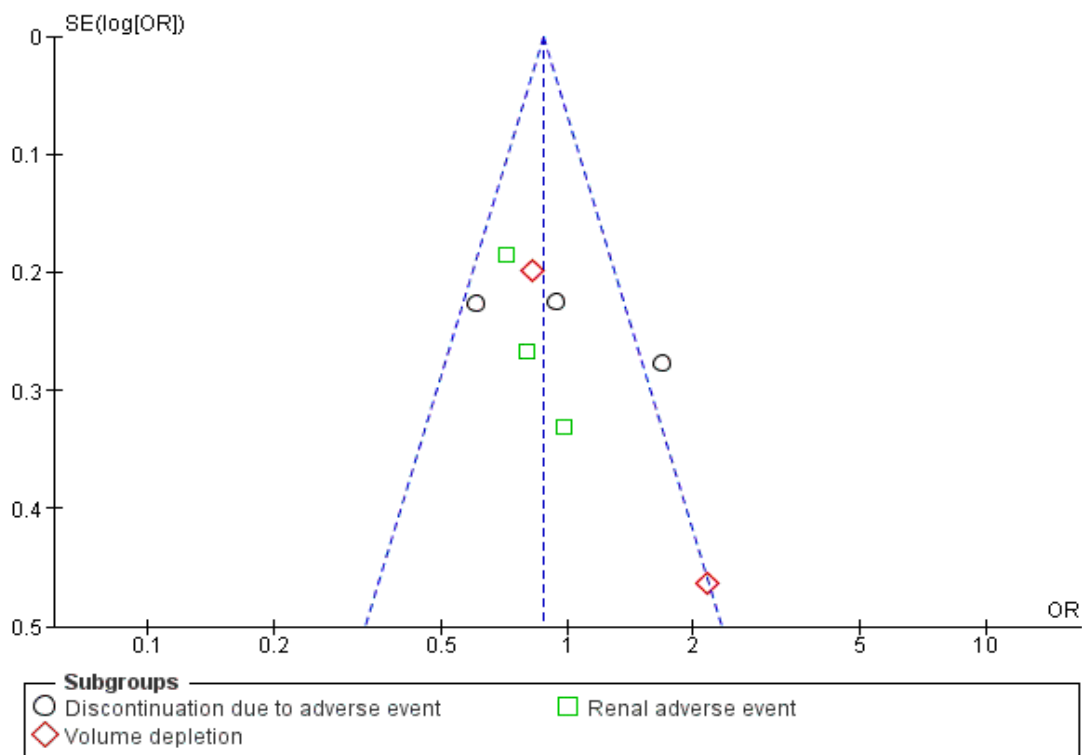
Supplementary Figure 15. A funnel plot comparing the death resulting from any cause in patients with heart failure with reduced ejection fraction and heart failure with preserved ejection fraction, those treated with sodium-glucose co-transporter 2 inhibitor (SGLT2i) and placebo vs. SGLT2i, placebo, and loop diuretics at doses above 40 mg.



Supplementary Figure 16. A funnel plot comparing the discontinuation due to adverse event, volume depletion, renal adverse event in patients with heart failure with reduced ejection fraction and heart failure with preserved ejection fraction, those treated with sodium-glucose co-transporter 2 inhibitor (SGLT2i) and placebo vs. SGLT2i, placebo, and loop diuretics at doses below 40 mg.



Supplementary Figure 17. A funnel plot comparing the discontinuation due to adverse event, volume depletion, renal adverse event in patients with heart failure with reduced ejection fraction and heart failure with preserved ejection fraction, those treated with sodium-glucose co-transporter 2 inhibitor (SGLT2i) and placebo vs. SGLT2i, placebo, and loop diuretics at doses equal to 40 mg.



Supplementary Figure 18. A funnel plot comparing the discontinuation due to adverse event, volume depletion, renal adverse event in patients with heart failure with reduced ejection fraction and heart failure with preserved ejection fraction, those treated with sodium-glucose co-transporter 2 inhibitor (SGLT2i) and placebo vs. SGLT2i, placebo, and loop diuretics at doses above 40 mg.

Supplementary Table 1. Details of risk of bias.

Jackson AM et al 2020		
Methods	Multicenter, Post hoc analysis of Randomized Controlled Trials (RCTs)	
Participants	T2DM with heart failure, NYHA class II-IV, HFrEF < 40% with elevated NT pro-BNP level	
Intervention	SGLT2i +Loop diuretics (<40mg, 40mg, >40mg) + PLCB compared individually versus PLCB+SGLT2i	
Outcome	Primary composite outcome, hospitalization or urgent HF visit, CV death, death resulting from any cause, Discontinuation due to adverse event, Volume depletion, Renal adverse event	
Bias	Author's judgement	Support for judgement
Random sequence generation (Selection bias)	Low risk	A fixed-randomization schedule was followed, using balanced blocks to ensure an approximate 1:1 ratio of the two regimens. Investigators used an interactive voice- or Web-response system to determine treatment assignments.
Allocation concealment (Selection bias)	Low risk	Allocation concealment was done in the study.
Blinding of participants and personnel (Performance bias)	Unclear risk	The blinding of the Physician and Participants was not mentioned.
Blinding of outcome assessment (Detection bias)	Low risk	All outcomes were adjudicated by the members of a clinical events committee, who were unaware of trial-group assignments, according to pre-specified criteria

Incomplete outcome data (Attrition bias)	Low risk	The attrition rate is low; 2.7% was the attrition rate in the study.
Selective reporting (Reporting bias)	Unclear risk	As of any information regarding past medical as well as medication history has been not mentioned in the study clearly
Other bias	Low risk	No other bias was found.
Nitesh D et al, 2024		
Methods		Multicenter, Post Hoc analysis of EMPEROR - Reduced
Participants		Study population patients with HFrEF 40% and NYHA functional class II-IV
Intervention		SGLT2i +Loop diuretics (<40mg, 40mg, >40mg) + PLCB compared individually versus PLCB+SGLT2i
Outcome		Primary composite outcome, hospitalization or urgent HF visit, CV death, death resulting from any cause, Discontinuation due to adverse event, Volume depletion, Renal adverse event
Bias	Author's judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Patients were randomized in a double- blind fashion to the addition of either empagliflozin 10mg daily or placebo to existing guideline- directed therapy
Allocation concealment (selection bias)	Low risk	Allocation conceal is done
Blinding of participants and personnel (performance bias)	Unclear risk	Blinding of the Physician and Participants were not mentioned
Blinding of outcome assessment (detection bias)	Unclear risk	The details of binding of outcome assessment are not given
Incomplete outcome data (attrition bias)	Low risk	No attrition was found. The data was taken for analysis from EMPEROR study
Selective reporting (reporting bias)	Low risk	All the outcome data were analyzed and reported
Other bias	Low risk	No other bias was found
Chatur S et al, 2023		
Methods		Multicenter Post hoc analysis of Randomized Controlled Trials (RCTs)
Participants		T2DM NYHA class II-IV HFpEF > 40% with elevated NT proBNP level
Intervention		SGLT2i +Loop diuretics (<40mg, 40mg, >40mg) + PLCB compared individually versus PLCB+SGLT2i
Outcome		Primary composite outcome, hospitalization or urgent HF visit, CV death, death resulting from any cause, Discontinuation due to adverse event, Volume depletion, Renal adverse event
Bias	Author's judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The details of random sequence generation were not mentioned.
Allocation concealment (selection bias)	Unclear risk	The details of allocation concealment were not mentioned
Blinding of participants and personnel (Performance bias)	Low risk	It is a double-blind study; both physicians and participants are blinded.
Blinding of outcome assessment	Unclear risk	The details of the binding of outcome assessment are not mentioned.

(Detection bias)		
Incomplete outcome data (Attrition bias)	Low risk	The attrition rate is low, as only 35.9% of patients' data were analyzed.
Selective reporting (Reporting bias)	Low risk	All the outcome data were analyzed and reported.
Other bias	Low risk	No other bias was found
Butler J et al 2023		
Methods		Multicenter, Post hoc analysis of Randomized Controlled Trials (RCTs)
Participants		HFpEF >40%, NYHA class II to IV, Elevated NT-pro BNP level
Intervention		SGLT2i +Loop diuretics (<40mg, 40mg, >40mg) + PLCB compared individually versus PLCB+SGLT2i
Outcome		Primary composite outcome, hospitalization or urgent HF visit, CV death, death resulting from any cause, Discontinuation due to adverse event, Volume depletion, Renal adverse event
Bias	Author's judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	All the patients were randomized to individual groups
Allocation concealment (selection bias)	Low risk	Allocation concealment is done.
Blinding of participants and personnel (performance bias)	Low risk	Both the Physician and participants are blinded
Blinding of outcome assessment (detection bias)	Unclear risk	The blinding of outcome assessment is not mentioned.
Incomplete outcome data (attrition bias)	Low risk	The attrition rate is low, around 2.8%
Selective reporting (reporting bias)	Low risk	All the outcomes were analyzed. Selective reporting was not found
Other bias	Low risk	No other bias was found

Supplementary Table 2. Illustrating the summary findings.

Details of the Comparison groups: SGLT2i+PLCB vs. SGLT2i+PLCB+ Loop diuretics of Furosemide Equivalent dose (Sub-groups: <40mg, 40mg and >40mg)					
Patient or population: T2DM, NYHA class II-IV, HFrEF < 40% or HFpEF >40% with elevated NT pro-BNP level					
Intervention: SGLT2i+PLCB+ Loop Diuretics (<40mg, 40mg and >40mg)					
Comparison: SGLT2i+PLCB					
Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)
	Risk with a placebo	Risk with SGLT2i+PLCB v/s SGLT2i+PLC+ LD			
Details of the Adjusted Hazard Ratios for Comparisons of Primary Composite Outcome, Hospitalization or Urgent HF visit, CV death and death resulting from any other cause in Patients with HFrEF and HFpEF: SGLT2i+ Placebo Vs. SGLT2i+Loop Diuretic Furosemide Equivalent Dose of Less Than 40 Mg.					

SGLT2i+PLCB vs SGLT2i+PLCB+ <40mg Loop Diuretics - Primary Composite Outcomes-Reduced <40%EF	594 per 1,000	491 per 1,000 (412 to 575)	aHR 0.75 (0.59 to 0.95)	3260 (2 RCTs)	⊕⊕⊕⊕ High
SGLT2i+PLCB vs SGLT2i+PLCB+ <40mg Loop Diuretics - Primary Composite Outcomes- Preserved>40%EF	174 per 1,000	139 per 1,000 (117 to 165)	aHR 0.78 (0.65 to 0.94)	5398 (2 RCTs)	⊕⊕⊕⊕ High
SGLT2i+PLCB vs SGLT2i+PLCB+ <40mg Loop Diuretics - Hospitalization or Urgent HF visit- Reduced <40%EF	610 per 1,000	458 per 1,000 (345 to 587)	aHR 0.65 (0.45 to 0.94)	3260 (2 RCTs)	⊕⊕⊕⊕ High
SGLT2i+PLCB vs SGLT2i+PLCB+ <40mg Loop Diuretics - Hospitalization or Urgent HF visit- Preserved >40%EF	223 per 1,000	181 per 1,000 (147 to 221)	aHR 0.79 (0.63 to 0.99)	5398 (2 RCTs)	⊕⊕⊕⊕ High
SGLT2i+PLCB vs SGLT2i+PLCB+ <40mg Loop Diuretics - Cardiovascular death-Reduced <40%EF	597 per 1,000	542 per 1,000 (441 to 651)	aHR 0.86 (0.64 to 1.16)	3260 (2 RCTs)	⊕⊕⊕⊕ High
SGLT2i+PLCB vs SGLT2i+PLCB+ <40mg Loop Diuretics - Cardiovascular death- Preserved>40% EF	287 per 1,000	258 per 1,000 (203 to 325)	aHR 0.88 (0.67 to 1.16)	5398 (2 RCTs)	⊕⊕⊕⊕ High
SGLT2i+PLCB vs SGLT2i+PLCB+ <40mg Loop Diuretics - Death resulting from any cause-Reduced <40% EF	594 per 1,000	526 per 1,000 (433 to 625)	aHR 0.83 (0.63 to 1.09)	3260 (2 RCTs)	⊕⊕⊕⊕ High
SGLT2i+PLCB vs SGLT2i+PLCB+ <40mg Loop Diuretics - Death resulting from any cause- Preserved>40% EF	195 per 1,000	202 per 1,000 (170 to 238)	aHR 1.04 (0.86 to 1.25)	5398 (2 RCTs)	⊕⊕⊕⊕ High
Details of the Adjusted Hazard Ratios for Comparisons of Primary Composite Outcome, Hospitalization or Urgent HF visit, CV death and death resulting from any other cause in Patients with HFpEF and HFpEF: SGLT2i+ Placebo Vs. SGLT2i+Loop Diuretic Furosemide Equivalent Dose equal to 40 Mg.					
SGLT2i+PLCB vs SGLT2i+PLCB+ 40mg Loop Diuretics - Primary composite outcomes-Reduced <40%EF	594 per 1,000	468 per 1,000 (412 to 526)	aHR 0.70 (0.59 to 0.83)	3994 (2 RCTs)	⊕⊕⊕⊕ High
SGLT2i+PLCB vs SGLT2i+PLCB+ 40mg Loop Diuretics - Primary composite outcomes- Preserved>40%EF	174 per 1,000	144 per 1,000 (125 to 166)	aHR 0.81 (0.70 to 0.95)	5536 (2 RCTs)	⊕⊕⊕⊕ High
SGLT2i+PLCB vs SGLT2i+PLCB+ 40mg Loop Diuretics - Hospitalization or urgent HF visit- Reduced <40%EF	610 per 1,000	432 per 1,000 (364 to 507)	aHR 0.60 (0.48 to 0.75)	3994 (2 RCTs)	⊕⊕⊕⊕ High
SGLT2i+PLCB vs SGLT2i+PLCB+ 40mg Loop Diuretics - Hospitalization or urgent HF visit- Preserved>40%EF	223 per 1,000	170 per 1,000 (143 to 205)	aHR 0.74 (0.61 to 0.91)	5536 (2 RCTs)	⊕⊕⊕⊕ High
SGLT2i+PLCB vs SGLT2i+PLCB+ 40mg Loop Diuretics - Cardiovascular death-Reduced <40%EF	597 per 1,000	525 per 1,000 (446 to 611)	aHR 0.82 (0.65 to 1.04)	3994 (2 RCTs)	⊕⊕⊕⊕ High
SGLT2i+PLCB vs SGLT2i+PLCB+ 40mg Loop Diuretics - Cardiovascular death -Preserved >40%EF	287 per 1,000	260 per 1,000 (216 to 311)	aHR 0.89 (0.72 to 1.10)	5536 (2 RCTs)	⊕⊕⊕⊕ High

SGLT2i+PLCB vs SGLT2i+PLCB+40 mg Loop Diuretics - Death resulting from any cause-Reduced <40%EF	594 per 1,000	505 per 1,000 (433 to 582)	aHR 0.78 (0.63 to 0.97)	3994 (2 RCTs)	⊕⊕⊕⊕ High
SGLT2i+PLCB vs SGLT2i+PLCB+40 mg Loop Diuretics - Death resulting from any cause-Preserved >40%EF	195 per 1,000	165 per 1,000 (143 to 190)	aHR 0.83 (0.71 to 0.97)	5536 (2 RCTs)	⊕⊕⊕⊕ High
Details of the Adjusted Hazard Ratios for Comparisons of Primary Composite Outcome, Hospitalization or Urgent HF visit, CV death and death resulting from any other cause in Patients with HFrEF and HFpEF: SGLT2i+ Placebo Vs. SGLT2i+Loop Diuretic Furosemide Equivalent Dose of More Than 40 Mg.					
SGLT2i+PLCB+>40mg Loop diuretic - Primary composite outcomes-Reduced <40%EF	594 per 1,000	522 per 1,000 (468 to 579)	aHR 0.82 (0.70 to 0.96)	3454 (2 RCTs)	⊕⊕⊕⊕ High
SGLT2i+PLCB+>40mg Loop diuretic - Primary composite outcomes-Preserved >40%EF	174 per 1,000	144 per 1,000 (124 to 165)	aHR 0.81 (0.69 to 0.94)	4099 (2 RCTs)	⊕⊕⊕⊕ High
SGLT2i+PLCB+>40mg Loop diuretic - Hospitalization or urgent HF visit-Reduced <40%EF	610 per 1,000	547 per 1,000 (478 to 621)	aHR 0.84 (0.69 to 1.03)	3454 (2 RCTs)	⊕⊕⊕⊕ High
SGLT2i+PLCB+>40mg Loop diuretic - Hospitalization or urgent HF visit-Preserved >40%EF	223 per 1,000	179 per 1,000 (149 to 211)	aHR 0.78 (0.64 to 0.94)	4099 (2 RCTs)	⊕⊕⊕⊕ High
SGLT2i+PLCB+>40mg Loop diuretic - Cardiovascular death-Reduced <40%EF	597 per 1,000	570 per 1,000 (494 to 648)	aHR 0.93 (0.75 to 1.15)	3454 (2 RCTs)	⊕⊕⊕⊕ High
SGLT2i+PLCB+>40mg Loop diuretic - Cardiovascular death- Preserved >40%EF	287 per 1,000	263 per 1,000 (211 to 322)	aHR 0.90 (0.70 to 1.15)	4099 (2 RCTs)	⊕⊕⊕⊕ High
SGLT2i+PLCB+>40mg Loop diuretic - Death resulting from any cause-Reduced <40%EF	594 per 1,000	563 per 1,000 (496 to 635)	aHR 0.92 (0.76 to 1.12)	3454 (2 RCTs)	⊕⊕⊕⊕ High
SGLT2i+PLCB+>40mg Loop diuretic - Death resulting from any cause-Preserved>40%EF	195 per 1,000	205 per 1,000 (176 to 241)	aHR 1.06 (0.89 to 1.27)	4099 (2 RCTs)	⊕⊕⊕⊕ High
Details of the adjusted odds ratio for pooled adverse effects, discontinuation of the drug due to adverse events, volume depletion, and renal adverse events among patients SGLT2i with placebo, vs. SGLT2i and placebo plus loop diuretics of Furosemide equivalent dose of less than 40 mg					
Outcomes.	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)
	Risk with placebo	Risk with SGLT2i+PLCB v/s SGLT2i+PLC+ LD			
Adverse events of LD <40mg	38 per 1,000	42 per 1,000 (35 to 50)	aOR 1.11 (0.92 to 1.33)	12816 (3 RCTs)	⊕⊕⊕⊕ High
Adverse events of LD <40mg - Discontinuation due to adverse event	57 per 1,000	69 per 1,000 (49 to 96)	aOR 1.21 (0.84 to 1.74)	4847 (3 RCTs)	⊕⊕⊕⊕ High
Adverse events of LD <40mg - Volume depletion	29 per 1,000	31 per 1,000 (21 to 47)	aOR 1.08 (0.72 to 1.63)	3122 (2 RCTs)	⊕⊕⊕⊕ High
Adverse events of LD <40mg - Renal adverse event	25 per 1,000	22 per 1,000 (15 to 31)	aOR 0.86 (0.59 to 1.25)	4847 (3 RCTs)	⊕⊕⊕⊕ High
Details of the adjusted odds ratio for pooled adverse effects, discontinuation of the drug due to adverse events, volume depletion, and renal adverse events among patients SGLT2i with placebo, vs. SGLT2i and placebo plus loop diuretics of Furosemide equivalent dose of 40 mg					

Adverse events of LD (40mg)	39 per 1,000	42 per 1,000 (34 to 52)	aOR 1.10 (0.89 to 1.36)	13345 (3 RCTs)	⊕⊕⊕⊕ High
Adverse events of LD (40mg) - Discontinuation due to adverse event	51 per 1,000	55 per 1,000 (39 to 77)	aOR 1.08 (0.75 to 1.55)	5039 (3 RCTs)	⊕⊕⊕⊕ High
Adverse events of LD (40mg) - Volume depletion	26 per 1,000	40 per 1,000 (27 to 59)	aOR 1.56 (1.05 to 2.31)	3267 (2 RCTs)	⊕⊕⊕⊕ High
Adverse events of LD (40mg) - Renal adverse event	34 per 1,000	31 per 1,000 (23 to 42)	aOR 0.93 (0.68 to 1.27)	5039 (3 RCTs)	⊕⊕⊕⊕ High
Details of the adjusted odds ratio for pooled adverse effects, discontinuation of the drug due to adverse events, volume depletion, and renal adverse events among patients SGLT2i with placebo, vs. SGLT2i and placebo plus loop diuretics of Furosemide equivalent dose of more than 40 mg					
Adverse events of LD >40mg	72 per 1,000	66 per 1,000 (52 to 83)	aOR 0.91 (0.71 to 1.17)	8644 (3 RCTs)	⊕⊕⊕⊕ High
Adverse events of LD >40mg - Discontinuation due to adverse event	73 per 1,000	71 per 1,000 (41 to 117)	aOR 0.97 (0.55 to 1.69)	3261 (3 RCTs)	⊕⊕⊕⊕ High
Adverse events of LD >40mg - Volume depletion	63 per 1,000	76 per 1,000 (31 to 170)	aOR 1.22 (0.48 to 3.06)	2122 (2 RCTs)	⊕⊕⊕⊕ High
Adverse events of LD >40mg - Renal adverse event	77 per 1,000	61 per 1,000 (47 to 79)	aOR 0.78 (0.59 to 1.02)	3261 (3 RCTs)	⊕⊕⊕⊕ High