Supplemental Material

Supplemental Table 1: Search Strategy used in each database		
Database	Detailed search string	Results
Medline	((("sodium, dietary"[MeSH Terms] OR ("sodium"[All Fields] AND "dietary"[All Fields]) OR "dietary sodium"[All Fields] OR "sodium"[All Fields] OR "sodium"[MeSH Terms] OR "sodiums"[All Fields]) AND ("glucose"[MeSH Terms] OR "glucose"[All Fields] OR "glucoses"[All Fields] OR "glucose s"[All Fields]) AND "cotransporter-2"[All Fields] AND ("antagonists and inhibitors"[MeSH Subheading] OR ("antagonists"[All Fields] AND "inhibitors"[All Fields]) OR "antagonists and inhibitors"[All Fields] OR "inhibitors"[All Fields] OR "inhibitor"[All Fields] OR "inhibitor s"[All Fields])) OR ("sodium glucose transporter 2 inhibitors"[Pharmacological Action] OR "sodium glucose transporter 2 inhibitors"[MeSH Terms] OR "sodium glucose transporter 2 inhibitors"[All Fields] OR ("sglt2"[All Fields] AND "inhibitors"[All Fields]) OR "sglt2 inhibitors"[All Fields]) OR ("sodium glucose transporter 2 inhibitors"[Pharmacological Action] OR "sodium glucose transporter 2 inhibitors"[MeSH Terms] OR "sodium glucose transporter 2 inhibitors"[All Fields] OR ("sglt2"[All Fields] AND "inhibitor"[All Fields]) OR "sglt2 inhibitor"[All Fields]) OR ("sglt2i"[All Fields] OR "sglt2is"[All Fields]) OR "flozins"[All Fields] OR ("empagliflozin"[Supplementary Concept] OR "empagliflozin"[All Fields]) OR ("dapagliflozin"[Supplementary Concept] OR "dapagliflozin"[All Fields] OR "dapagliflozin s"[All Fields])) AND ("heart failure"[MeSH Terms] OR ("heart"[All Fields] AND "failure"[All Fields]) OR "heart failure"[All Fields] OR "HF"[All Fields] OR (("heart failure"[MeSH Terms] OR ("heart"[All Fields] AND "failure"[All Fields]) OR "heart failure"[All Fields]) AND ("reduce"[All Fields] OR "reduced"[All Fields] OR "reduces"[All Fields] OR "reducing"[All Fields]) AND ("eject"[All Fields] OR "ejected"[All Fields] OR "ejecting"[All Fields] OR "ejection"[All Fields] OR "ejectional"[All Fields] OR "ejections"[All Fields] OR "ejects"[All Fields]) AND ("dose fractionation, radiation"[MeSH Terms] OR ("dose"[All Fields] AND "fractionation"[All Fields] AND "radiation"[All Fields]) OR "radiation dose fractionation"[All Fields] OR "fractionation"[All Fields] OR "chemical fractionation"[MeSH Terms] OR ("chemical"[All Fields] AND "fractionation"[All Fields]) OR "chemical fractionation"[All Fields] OR "fraction"[All Fields] OR "fraction s"[All Fields] OR "fractionate"[All Fields] OR "fractionated"[All Fields] OR "fractionates"[All Fields] OR "fractionating"[All Fields] OR "fractionationed"[All Fields] OR "fractionations"[All Fields] OR "fractionator"[All Fields] OR	1,430

	"fractionators"[All Fields] OR "fractioned"[All Fields] OR "fractioning"[All Fields] OR "fractionized"[All Fields] OR "fractions"[All Fields])) OR "HFrEF"[All Fields] OR (("heart failure"[MeSH Terms] OR ("heart"[All Fields] AND "failure"[All Fields]) OR "heart failure"[All Fields]) AND ("preservation, biological"[MeSH Terms] OR ("preservation"[All Fields] AND "biological"[All Fields]) OR "biological preservation"[All Fields] OR "preservation"[All Fields] OR "preserved"[All Fields] OR "preservations"[All Fields] OR "preserve"[All Fields] OR "preserves"[All Fields] OR "preserving"[All Fields]) AND ("eject"[All Fields] OR "ejected"[All Fields] OR "ejecting"[All Fields] OR "ejection"[All Fields] OR "ejectional"[All Fields] OR "ejections"[All Fields] OR "ejects"[All Fields]) AND ("dose fractionation, radiation"[MeSH Terms] OR ("dose"[All Fields] AND "fractionation"[All Fields] AND "radiation"[All Fields]) OR "radiation dose fractionation"[All Fields] OR "fractionation"[All Fields] OR "chemical fractionation"[MeSH Terms] OR ("chemical"[All Fields] AND "fractionation"[All Fields]) OR "chemical fractionation"[All Fields] OR "fraction"[All Fields] OR "fraction s"[All Fields] OR "fractionate"[All Fields] OR "fractionated"[All Fields] OR "fractionates"[All Fields] OR "fractionating"[All Fields] OR "fractionationed"[All Fields] OR "fractionations"[All Fields] OR "fractionator"[All Fields] OR "fractionators"[All Fields] OR "fractioned"[All Fields] OR "fractioning"[All Fields] OR "fractionized"[All Fields] OR "fractions"[All Fields])) OR "HFpEF"[All Fields]) AND ("quality of life"[MeSH Terms] OR ("quality"[All Fields] AND "life"[All Fields]) OR "quality of life"[All Fields] OR "QoL"[All Fields] OR ("health status"[MeSH Terms] OR ("health"[All Fields] AND "status"[All Fields]) OR "health status"[All Fields]) OR (("reference standards"[MeSH Terms] OR ("reference"[All Fields] AND "standards"[All Fields]) OR "reference standards"[All Fields] OR "standardization"[All Fields] OR "standard"[All Fields] OR "standard s"[All Fields] OR "standardisation"[All Fields] OR "standardisations"[All Fields] OR "standardise"[All Fields] OR "standardised"[All Fields] OR "standardises"[All Fields] OR "standardising"[All Fields] OR "standardization s"[All Fields] OR "standardizations"[All Fields] OR "standardize"[All Fields] OR "standardized"[All Fields] OR "standardizes"[All Fields] OR "standardizing"[All Fields] OR "standards"[MeSH Subheading] OR "standards"[All Fields]) AND ("life"[MeSH Terms] OR "life"[All Fields])) OR ("functional status"[MeSH Terms] OR ("functional"[All Fields] AND "status"[All Fields]) OR "functional status"[All Fields]) OR (("diagnosis"[MeSH Subheading] OR "diagnosis"[All Fields] OR "symptoms"[All Fields] OR "diagnosis"[MeSH Terms] OR "symptom"[All Fields] OR "symptom s"[All Fields] OR "symptomes"[All Fields]) AND ("heart failure"[MeSH Terms] OR ("heart"[All Fields] AND "failure"[All Fields]) OR "heart failure"[All Fields]) AND ("patient s"[All Fields] OR "patients"[MeSH Terms] OR "patients"[All Fields] OR "patient"[All Fields] OR "patients s"[All Fields])) OR (("improve"[All Fields] OR "improved"[All Fields] OR "improvement"[All Fields] OR "improvements"[All Fields] OR "improves"[All Fields] OR "improving"[All Fields] OR "improvment"[All Fields]) AND ("dailies"[All Fields] OR "daily"[All Fields]) AND ("life"[MeSH Terms] OR "life"[All Fields])) OR "KCCQ"[All Fields] OR	

	(("kansas"[MeSH Terms] OR "kansas"[All Fields]) AND ("cities"[MeSH Terms] OR "cities"[All Fields] OR "city"[All Fields]) AND ("cardiomyopathie"[All Fields] OR "cardiomyopathies"[MeSH Terms] OR "cardiomyopathies"[All Fields] OR "cardiomyopathy"[All Fields]) AND ("questionnair"[All Fields] OR "questionnaire s"[All Fields] OR "surveys and questionnaires"[MeSH Terms] OR ("surveys"[All Fields] AND "questionnaires"[All Fields]) OR "surveys and questionnaires"[All Fields] OR "questionnaire"[All Fields] OR "questionnaires"[All Fields]))	
Cochrane Central	(sodium glucose cotransporter-2 inhibitors OR SGLT2 inhibitors OR SGLT2 inhibitor OR SGLT2i OR flozins OR empagliflozin OR dapagliflozin) AND (heart failure OR HF OR heart failure with reduced ejection fraction OR HFrEF OR heart failure with preserved ejection fraction OR HFpEF) AND (quality of life OR QoL OR health status OR standard of life OR functional status OR symptoms in heart failure patients OR improvement in daily life OR KCCQ OR Kansas City Cardiomyopathy Questionnaire)	400

Supplemental Table 2. GRADE Scale for Quality Assessment of Evidence for mean change in KCCQ scores									
Outcome	Study Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication bias	Other	Effect Size	Certainty
Short term follow-up									
TSS	Randomized trial	Not serious	Not serious	Not serious	Not serious	serious	None	2.16 [1.67, 2.65]	⊕⊕⊕◯ Moderate
OSS	Randomized trial	Not serious	Not serious	Not serious	Not serious	Not serious	None	1.88 [1.08, 2.68]	⊕⊕⊕⊕ High
CSS	Randomized trial	Not serious	Not serious	Not serious	Not serious	serious	None	2.60 [1.49, 3.71]	⊕⊕⊕◯ Moderate
Mid-term follow-up									
TSS	Randomized trial	Not serious	Not serious	Not serious	Not serious	Not serious	None	1.98 [1.43, 2.54]	⊕⊕⊕⊕ High
OSS	Randomized trial	Not serious	Not serious	Not serious	Not serious	Not serious	None	1.80 [1.34, 2.25]	⊕⊕⊕⊕ High
CSS	Randomized trial	Not serious	Not serious	Not serious	serious	Not serious	None	1.80 [1.16, 2.44]	⊕⊕⊕◯ Moderate
Long term follow-up									
TSS	Randomized trial	Not serious	Not serious	Not serious	Serious	serious	None	1.94 [1.19, 2.69]	⊕⊕◯◯ Low
OSS	Randomized trial	Not serious	Not serious	Not serious	Serious	Serious	None	1.57 [0.88, 2.27]	⊕⊕◯◯ Low
CSS	Randomized trial	Not serious	Not serious	Not serious	Serious	Serious	None	1.54 [0.83, 2.24]	⊕⊕◯◯ Low

Supplemental Table 3. GRADE Scale for Quality Assessment of Evidence for deterioration of greater than five points in participants									
Outcome	Study Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication bias	Other	Effect Size	Certainty
Short term follows up									
TSS	Randomized Trial	Not serious	Serious	Not serious	Not serious	Serious	Not serious	0.77 [0.64, 0.92]	⊕⊕⊕◯ Moderate
OSS	Randomized Trial	Not serious	Not serious	Not serious	Not serious	Serious	Not serious	0.82 [0.75, 0.90]	⊕⊕⊕◯ Moderate
CSS	Randomized Trial	Not serious	Not serious	Not serious	Not serious	Serious	Not serious	0.81 [0.71, 0.91]	⊕⊕⊕◯ Moderate
Mid-term follow up									
TSS	Randomized Trial	Not serious	Not serious	Not serious	Not serious	Serious	Not serious	0.81 [0.77, 0.86]	⊕⊕⊕◯ Moderate
OSS	Randomized Trial	Not serious	Not serious	Not serious	Not serious	Serious	Not serious	0.83 [0.79, 0.87]	⊕⊕⊕◯ Moderate
CSS	Randomized Trial	Not serious	Not serious	Not serious	Not serious	Serious	Not serious	0.84 [0.80, 0.88]	⊕⊕⊕◯ Moderate
Long term follows up									
TSS	Randomized Trial	Not serious	Not serious	Not serious	Not Serious	Serious	Not serious	0.84 [0.76, 0.93]	⊕⊕⊕◯ Moderate
OSS	Randomized Trial	Not serious	Not serious	Not serious	Not Serious	Serious	Not serious	0.81 [0.74, 0.89]	⊕⊕⊕◯ Moderate
CSS	Randomized Trial	Not serious	Not serious	Not serious	Not Serious	Serious	Not serious	0.84 [0.77, 0.92]	⊕⊕⊕◯ Moderate

Supplemental Table 4. GRADE Scale for Quality Assessment of Evidence for responder analysis of improvement									
Outcome	Study Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication bias	Other	Effect Size	Certainty
Short term follow-up									
TSS ≥ 5 points	Randomized Trial	Not serious	Serious	Not serious	Not serious	Serious	Not serious	1.27 [1.16, 1.38]	⊕⊕◯◯ Low
TSS ≥ 10 points	Randomized Trial	Not serious	Not serious	Not serious	Not serious	Serious	Not serious	1.21 [1.11, 1.32]	⊕⊕⊕◯ Moderate
TSS ≥ 15 points	Randomized Trial	Not serious	Serious	Not serious	Not serious	Serious	Not serious	1.23 [1.14, 1.34]	⊕⊕◯◯ Low
OSS ≥5 points	Randomized Trial	Not serious	Serious	Not serious	Not serious	Serious	Not serious	1.23 [1.13, 1.33]	⊕⊕⊕◯ Moderate
OSS ≥ 10 points	Randomized Trial	Not serious	Not Serious	Not serious	Not serious	Serious	Not serious	1.22 [1.12, 1.32]	⊕⊕⊕◯ Moderate
OSS ≥ 15 points	Randomized Trial	Not serious	Not serious	Not serious	Not serious	Serious	Not serious	1.21 [1.11, 1.32]	⊕⊕⊕◯ Moderate
CSS ≥ 5 points	Randomized Trial	Not serious	Serious	Not serious	Serious	Serious	Not serious	1.30 [1.11, 1.51]	⊕⊕◯◯ Low
CSS ≥ 10 points	Randomized Trial	Not serious	Serious	Not serious	Serious	Serious	Not serious	1.19 [1.09, 1.30]	⊕⊕◯◯ Low
CSS ≥ 15 points	Randomized Trial	Not serious	Serious	Not serious	Not serious	Serious	Not serious	1.20 [1.05, 1.36]	⊕⊕⊕◯ Moderate
Mid-term follow up									
TSS ≥ 5 points	Randomized Trial	Not serious	Not serious	Not serious	Not serious	Serious	Not serious	1.16 [1.10, 1.21]	⊕⊕⊕◯ Moderate
TSS ≥ 10 points	Randomized Trial	Not serious	Not serious	Not serious	Not serious	Serious	Not serious	1.14 [1.09, 1.20]	⊕⊕⊕◯ Moderate
TSS ≥ 15 points	Randomized Trial	Not serious	Not serious	Not serious	Not serious	Serious	Not serious	1.14 [1.09, 1.19]	⊕⊕⊕◯ Moderate
OSS ≥5 points	Randomized Trial	Not serious	Serious	Not serious	Not serious	Serious	Not serious	1.16 [1.10, 1.23]	⊕⊕⊕◯ Moderate
OSS ≥ 10 points	Randomized Trial	Not serious	Not serious	Not serious	Not serious	Serious	Not serious	1.16 [1.11, 1.22]	⊕⊕⊕◯ Moderate
OSS ≥ 15 points	Randomized Trial	Not serious	Not serious	Not serious	Not serious	Serious	Not serious	1.15 [1.09, 1.21]	⊕⊕⊕◯ Moderate

CSS ≥ 5 points	Randomized Trial	Not serious	Not serious	Not serious	Not serious	Serious	Not serious	1.17 [1.11, 1.22]	⊕⊕⊕◯ Moderate
CSS ≥ 10 points	Randomized Trial	Not serious	Not serious	Not serious	Not serious	Serious	Not serious	1.18 [1.13, 1.23]	⊕⊕⊕◯ Moderate
CSS ≥ 15 points	Randomized Trial	Not serious	Serious	Not serious	Not serious	Serious	Not serious	1.14 [1.09, 1.19]	⊕⊕⊕◯ Moderate
Long term follow-up									
TSS ≥ 5 points	Randomized Trial	Not serious	Not serious	Not serious	Not serious	Serious	Not serious	1.19 [1.09, 1.30]	⊕⊕⊕◯ Moderate
TSS ≥ 10 points	Randomized Trial	Not serious	Not serious	Not serious	Not serious	Serious	Not serious	1.18 [1.08, 1.28]	⊕⊕⊕◯ Moderate
TSS ≥ 15 points	Randomized Trial	Not serious	Not serious	Not serious	Not serious	Serious	Not serious	1.20 [1.10, 1.31]	⊕⊕⊕◯ Moderate
OSS ≥5 points	Randomized Trial	Not serious	Not serious	Not serious	Not serious	Serious	Not serious	1.16 [1.06, 1.26]	⊕⊕⊕◯ Moderate
OSS ≥ 10 points	Randomized Trial	Not serious	Not serious	Not serious	Serious	Serious	Not serious	1.10 [1.00, 1.20]	⊕⊕⊕◯ Moderate
OSS ≥ 15 points	Randomized Trial	Not serious	Not serious	Not serious	Not serious	Serious	Not serious	1.18 [1.08, 1.29]	⊕⊕⊕◯ Moderate
CSS ≥ 5 points	Randomized Trial	Not serious	Not serious	Not serious	Not serious	Serious	Not serious	1.20 [1.10, 1.31]	⊕⊕⊕◯ Moderate
CSS ≥ 10 points	Randomized Trial	Not serious	Not serious	Not serious	Not serious	Serious	Not serious	1.17 [1.07, 1.28]	⊕⊕⊕◯ Moderate
CSS ≥ 15 points	Randomized Trial	Not serious	Serious	Not serious	Not serious	Not Serious	Not serious	1.10 [1.01, 1.20]	⊕⊕⊕◯ Moderate

Supplemental Table 5. Baseline characteristics in HFrEF trials										
	Emperor Reduced		DAPA HF		Emperial Reduced		Define HF		Empire HF	
	Empagliflozin	Placebo	Dapagliflzoin	Placebo	Empagliflozin	Placebo	Dapagliflozin	Placebo	Empagliflozin	Placebo
No. of participants	1853	1852	2234	2209	156	156	131	132	95	95
Age, years (SD)	67.2 (10.8)	66.5 (11.2)	66.2 (11)	66.5 (10.8)	69 (2.4)	70 (2.4)	62.2 (11.0)	60.4 (12.0)	64 (2.6)	63 (2.83)
Sex, n (%)										
Male	1416 (76.5)	1396 (75.6)	1670 (74.7)	1664 (75.4)	121 (77.6)	111 (71.2)	95 (72.5)	98 (74.2)	79 (83)	83 (87.3)
Female	437 (23.5)	456 (24.4)	564 (25.2)	545 (24.6)	35 (22.4)	45 (28.8)	36 (27.5)	34 (25.8)	16 (16.9)	12 (12.7)
Duration of heart failure, years (SD)					5.7 (1.2)	5.2 (1.5)	7.1 (5.8)	7.2 (6.8)	2.9 (9.2)	2.25 (8.2)
Type 2 diabetes mellitus, %	927 (49.8)	929 (49.8)	993 (41.8)	990 (41.8)	87 (55.8)	100 (64.1)	81 (61.8)	85 (64.4)	19 (20)	14 (15)
Mean LVEF, %	27.7 (6.0)	27.2 (6.1)	31.2 (6.7)	30.9 (6.9)	30 (1.7)	30 (1.6)	27.2 (8.0)	25.7 (8.2)	30 (1.6)	30 (1.6)
Body mass index, kg/m^2	28.0 (5.5)	27.8 (5.3)	28.2 (6.0)	28.1 (5.9)	29.2 (1.2)	30 (1.2)	30.7(1.4)	30.6 (1.5)	29 (1.0)	29 (1.2)
eGFR, mL/min/1.73m^2	61.8 (21.7)	62.2 (21.5)	66 (19.6)	65.5 (19.3)	56.8 (4.8)	53 (5.4)	66.9 (21.1)	71.2 (23.1)	73 (5.3)	74 (4.8)
NT-proBNP (SD), pg/mL	1887 (392)	1926(395.3)	1428 (299.6)	1446 (297.3)	1458 (344)	1559 (348.2)	1136 (299.5)	1136 (250.6)	582 (119.3)	605 (124.6)
NYHA functional classification, %										
I									5 (5.3)	7 (7.4)
II	1399 (75.1)	1401 (75.0)	1606 (67.7)	1597 (67.4)	101 (64.7)	101 (64.7)	91 (69.5)	82 (62.1)	72 (76)	77 (81)
III	455 (24.4)	455 (24.4)	747 (31.5)	751 (31.7)	55 (35.3)	55 (35.3)	40 (30.5)	50 (37.9)	18 (19)	11 (12)
IV	9 (0.5)	11 (0.6)	20 (0.8)	23 (1.0)						
6-minute walk distance, meters					306.0 (12.2)	309.0 (13.9)	306 (20.8)	305 (24.2)		
KCCQ TSS (SD)			77.1 (6.3)		68.8 (5.4)	68.8 (6.3)			76.9 (19.7)	77.6 (16.1)
KCCQ OSS (SD)							67.4 (22.0)	67.0 (21.1)	75.6 (18.3)	74.9 (17.8)

KCCQ CSS (SD)	70.7 (21.9)					70.8 (21.9)	69.9 (21.4)	78.1 (18.9)	78 (16.1)

HFrEF = heart failure with reduced ejection fraction; LVEF= left ventricular ejection fraction; NT-proBNP= N terminal-pro hormone brain natriuretic peptide; NYHA= New york heart association; KCCQ= Kansas city cardiomyopathy questionnaire; TSS= total symptom score; CSS= clinical summary score; OSS= overall summary score

Supplemental Table 6. Baseline characteristics in HFpEF trials

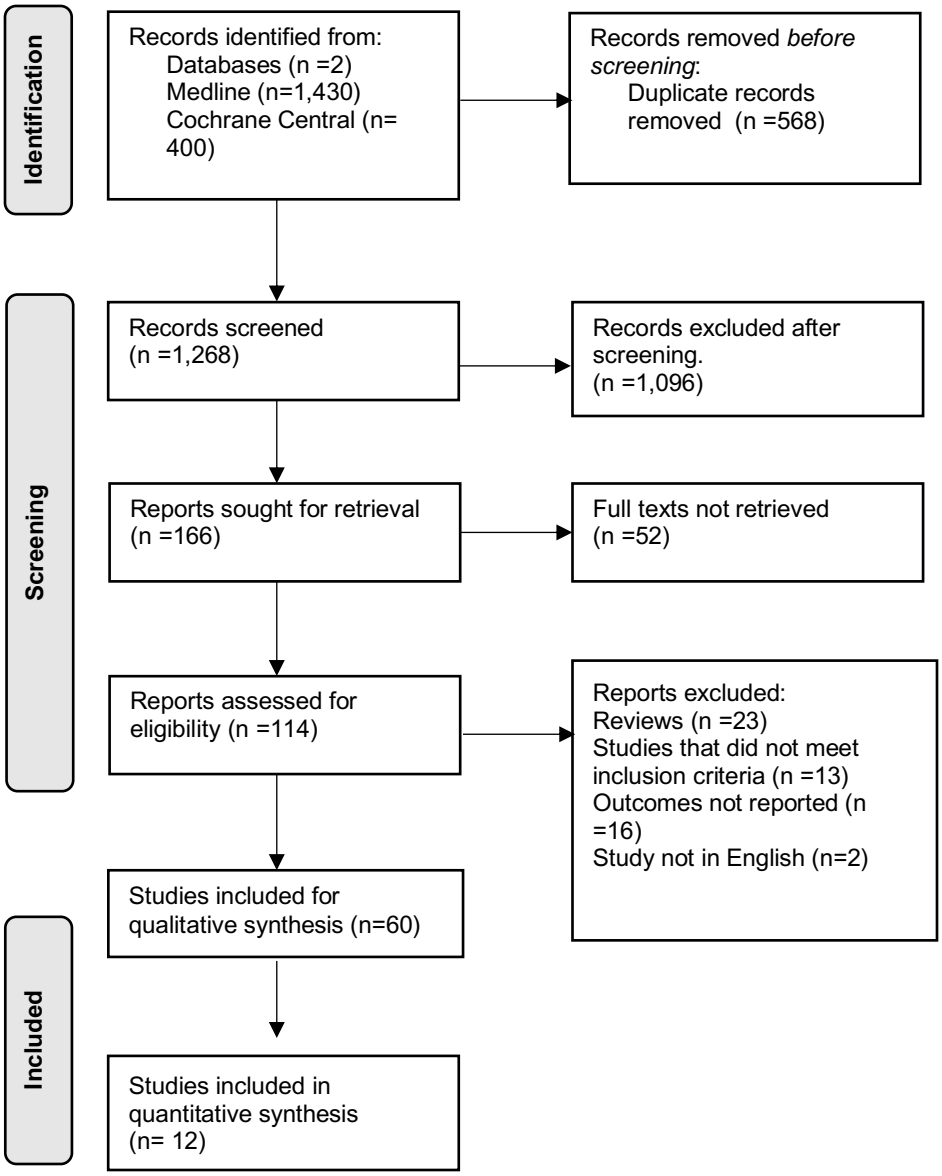
	PRESERVED-HF		EMPERIAL-Preserved		EMPEROR-Preserved		DELIVER	
	Dapagliflozin	Placebo	Empagliflozin	Placebo	Empagliflozin	Placebo	Dapagliflozin	Placebo
No. of participants	162	162	157	158	2997	2991	3131	3132
Age, years (SD)	69 (2.2)	71 (2.5)	74 (1.8)	75 (2.2)	71.8 (9.3)	71.9 (9.6)	71.8±9.6	71.8±9.6
Sex, n (%)								
Male	70 (43.2)	70 (43.2)	87 (55.4)	92 (58.2)	1659 (55.4)	1653 (55.3)	1364 (43.6)	1383 (44.2)
Female	92 (56.8)	92 (56.8)	70 (44.6)	66 (41.8)	1338 (44.6)	1338 (44.7)	1767 (56.4)	1749 (55.8)
Duration of heart failure, years (SD)	3 (1.0)	3.2(1.2)	4.1 (0.8)	3.4 (0.9)				
Type 2 diabetes mellitus, %	90 (55.6)	91 (56.2)	86 (54.8)	75 (47.5)	1466 (48.9)	1472 (49.2)	1401 (44.7)	1405 (44.9)
Mean LVEF, %	60 (1.6)	60 (1.8)	53 (2.2)	53 (2.2)	54.3 (8.8)	54.3 (8.8)	54.0±8.6	54.3±8.9
Body mass index, kg/m^2	35.1 (1.9)	34.6 (1.8)	30.1 (1.3)	28.8 (1.1)	29.7 (5.8)	29.90 (5.9)		
eGFR, mL/min/1.73m^2	56 (4.5)	54 (4.6)	54.5 (4.8)	58.5 (4.6)	60.6 (19.8)	60.6 (19.9)	61±19	61±19
NT-proBNP (SD), pg/mL	641 (139.5)	710 (186.6)	966 (180.2)	843 (251)	994 (206.5)	946 (204.5)		
NYHA functional classification, %								
I					3 (0.1)	1 (<0.1)		
II	96 (59.3)	90 (55.6)	117 (74.5)	126 (79.7)	2432 (81.1)	2451 (81.9)	2314 (73.9)	2399 (76.6)
III			39 (24.8)	32 (20.3)	552 (18.4)	531 (17.8)	807 (25.8)	724 (23.1)
IV					10 (0.3)	8 (0.3)	10 (0.3)	8 (0.3)
6-minute walk distance, meters	244 (27.3)	244 (27.2)	297.0 (13.3)	299.5 (14.3)				
KCCQ TSS (SD) [IQR]			64.6 (6.2)	68.2 (6.2)	73.5 (22)		72.9 [55.2-87.5]	
KCCQ OSS (SD)	63.2 (20.4)	62.3 (20.6)			68.9 (21.1)			
KCCQ CSS (SD)	63.4 (19.7)	61.8 (20.3)			70.4 (21.2)			

HFrEF = heart failure with reduced ejection fraction; LVEF= left ventricular ejection fraction; NT-proBNP= N terminal-pro hormone brain natriuretic peptide; NYHA= New york heart association; KCCQ= Kansas city cardiomyopathy questionnaire; TSS= total symptom score; CSS= clinical summary score; OSS= overall summary score

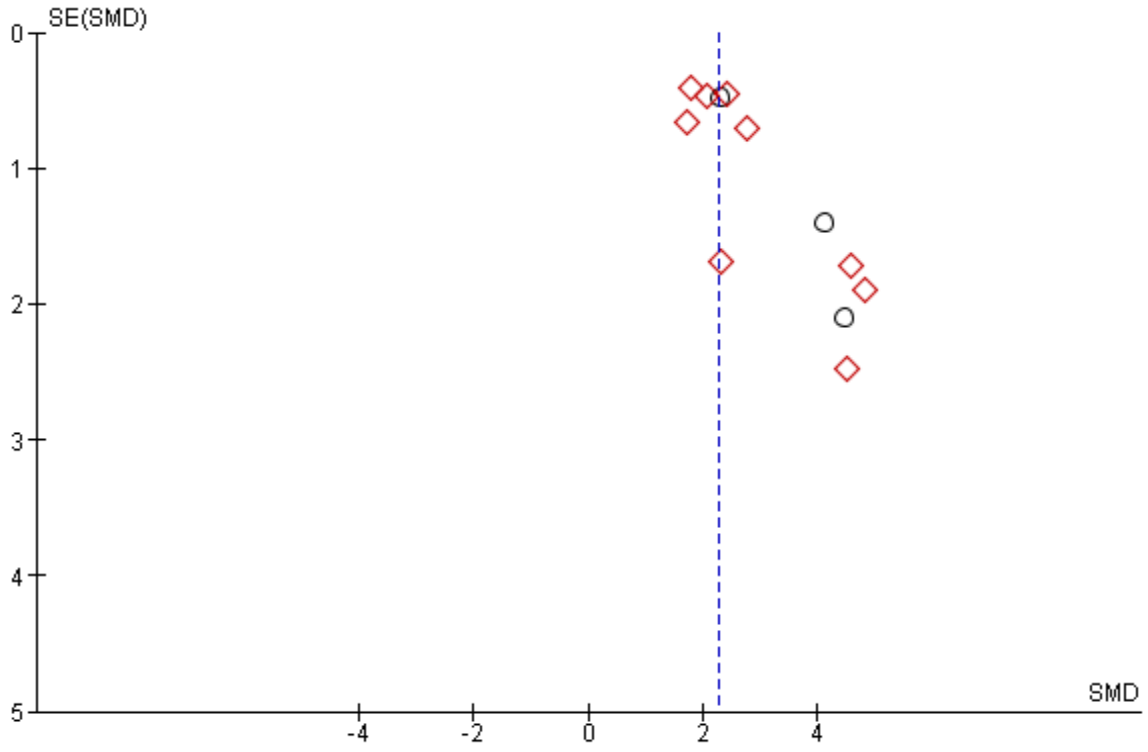
Supplemental Table 7. Baseline characteristics in mixed HFrEF and HFpEF trials						
	CHIEF-HF		EMPULSE		SOLOIST-WHF	
	Canagliflozin	Placebo	Empagliflozin	Placebo	Sotagliflozin	Placebo
No. of participants	222	226	265	265	608	614
Age, years (SD)	62.9±13.2	64±13.5	71 ± 2.6	70 ± 3.17	69 ±2.2	70 ±2
Sex, n (%)						
Male	118 (53.1)	129 (57.1)	179 (67.5)	172 (64.9)	410 (67.4)	400 (65.1)
Female	104 (46.9)	97 (42.9)	86 (32.5)	93 (35.1)	198 (32.6)	214 (34.9)
Duration of heart failure, years (SD)						
Type 2 diabetes mellitus, %	66 (29.7)	59 (26.1)	124 (46.8)	116 (43.8)	608 (100.0)	614 (100.0)
Mean LVEF, %			31.0 ± 3.6	32.0 ± 4.42	35 (3.2)	35 (2.83)
Body mass index, kg/m^2						
eGFR, mL/min/1.73m^2			50.0 ± 4.83	54.0 ± 5.17	30.4 ± 1.3	31.1 ±1.2
NT-proBNP (SD), pg/mL			3,299 (714.5)	3,106 (737.5)	1816.8 (476.3)	1741.0 (456.61)
NYHA functional classification, %						
I			8 (3.0)	6 (2.3)	31 (2.5)	
II			95 (35.8)	91 (34.3)	552 (45.2)	
III			134 (50.6)	145 (54.7)	560 (45.8)	
IV			26 (9.8)	23 (8.7)	54 (4.4)	
6-minute walk distance, meters						
KCCQ TSS (SD)	57.4 ± 21.3	58.0 ± 21.1	37.5 ± 6.25	39.6 ± 5.98	35 ± 2.66	35 ± 3
KCCQ OSS (SD)	52.7 ± 18.3	51.6 ± 18.8				
KCCQ CSS (SD)	56.3 ± 19.5	54.6 ± 19.7				

HFrEF = heart failure with reduced ejection fraction; LVEF= left ventricular ejection fraction; NT-proBNP= N terminal-pro hormone brain natriuretic peptide; NYHA= New york heart association; KCCQ= Kansas city cardiomyopathy questionnaire; TSS= total symptom score; CSS= clinical summary score; OSS= overall summary score

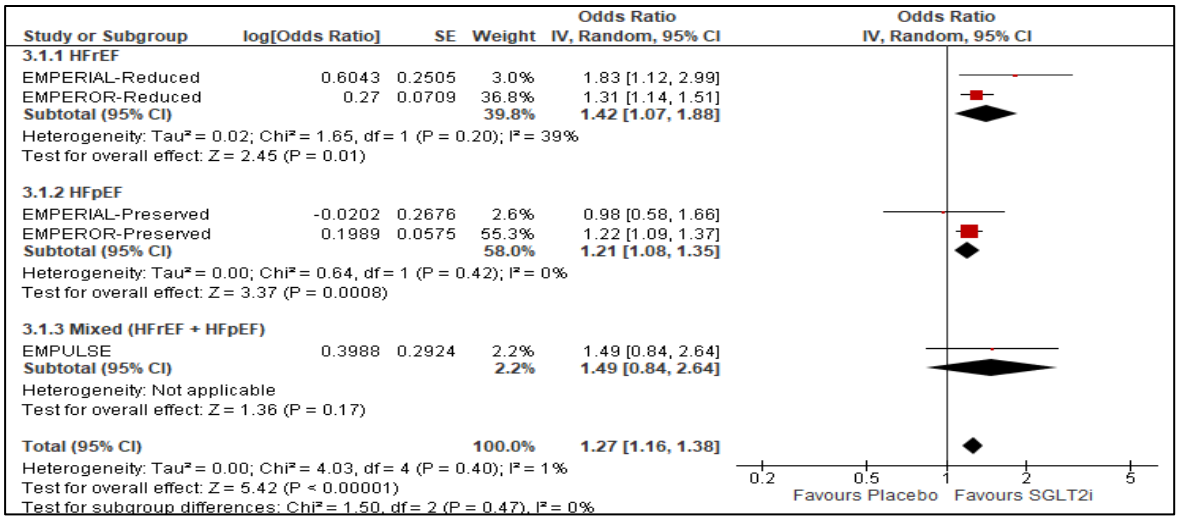
Supplemental Figure 1. PRISMA flowchart showing results of literature search.

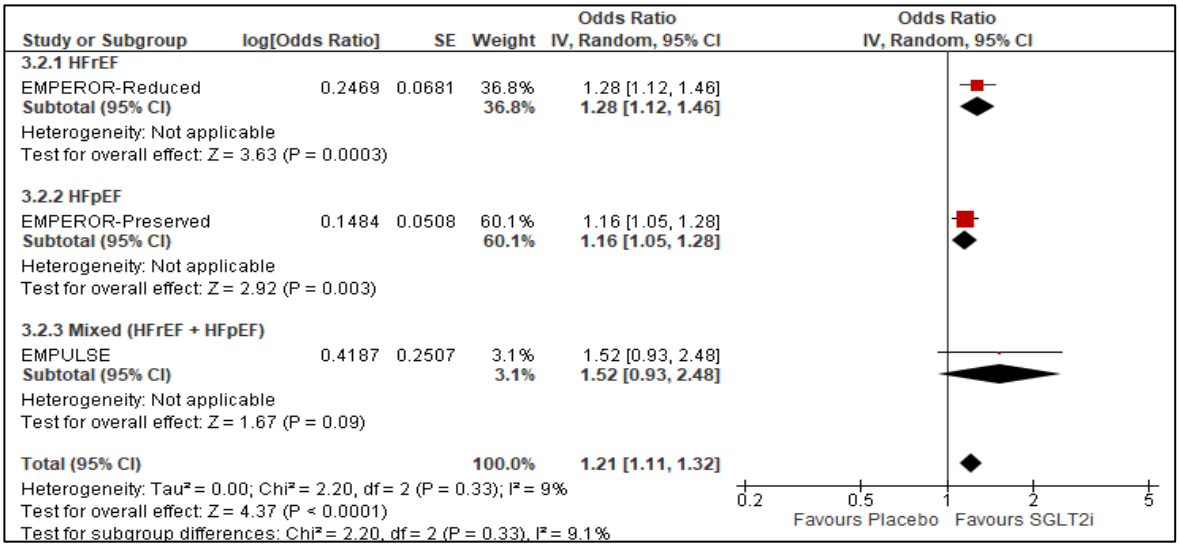


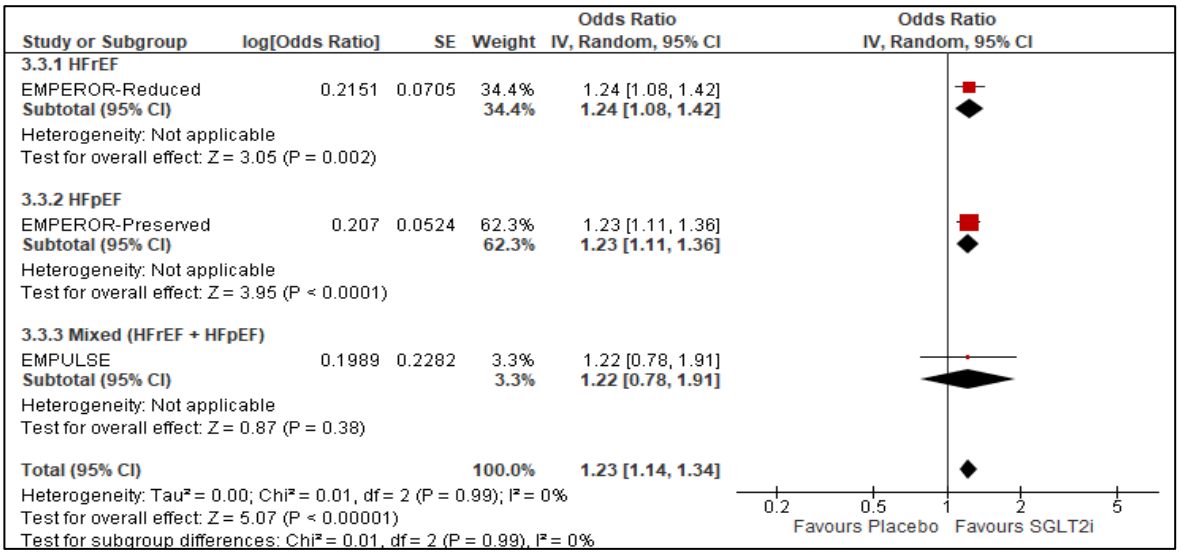
Supplemental Figure 2: Funnel plot for publication bias



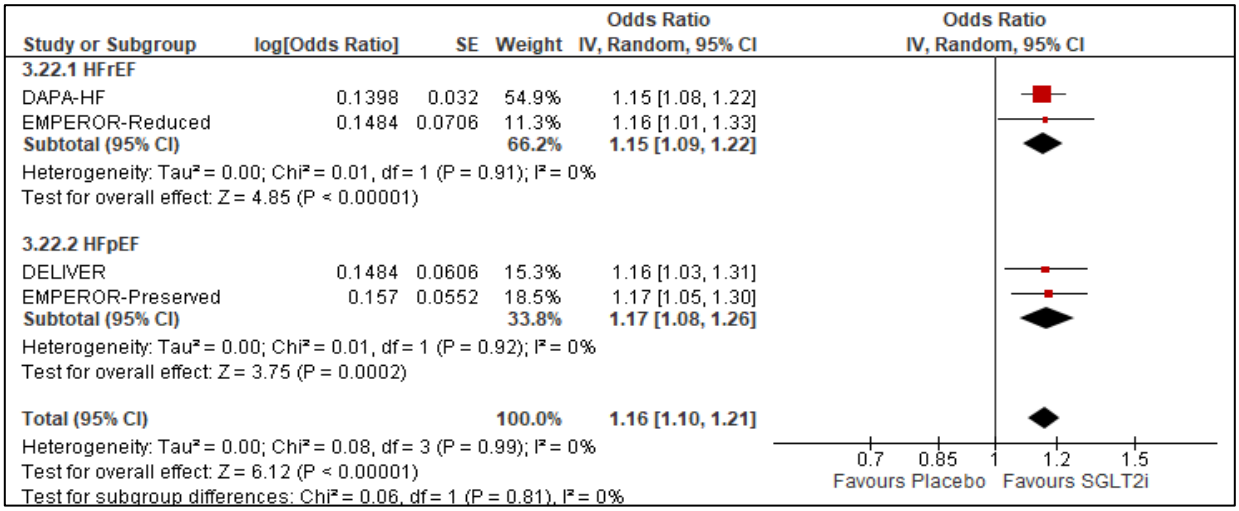
Supplemental Figure 3: Responder analysis; improvement of (A) ≥5 (B) ≥10 and (C) ≥15 points in KCCQ-TSS at 12 weeks

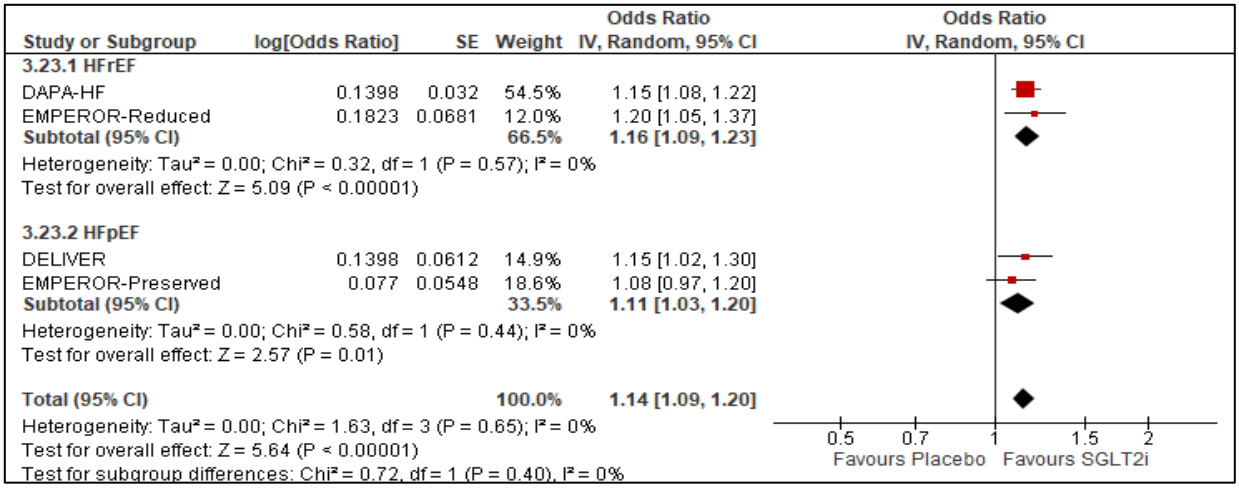


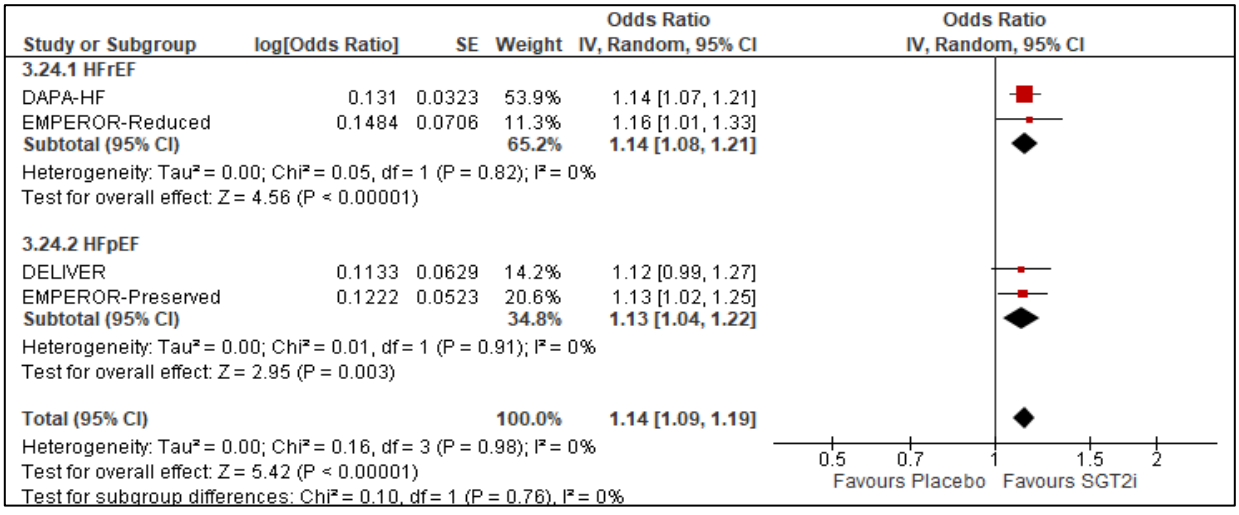




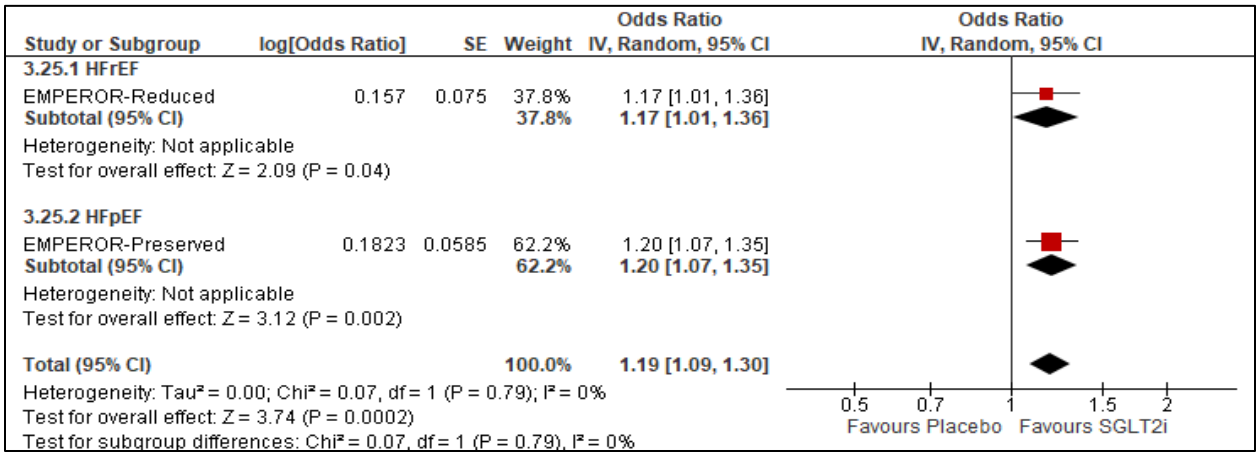
Supplemental Figure 4: Responder analysis; improvement of (A) ≥5 (B) ≥10 and (C) ≥15 points in KCCQ-TSS at 32 weeks

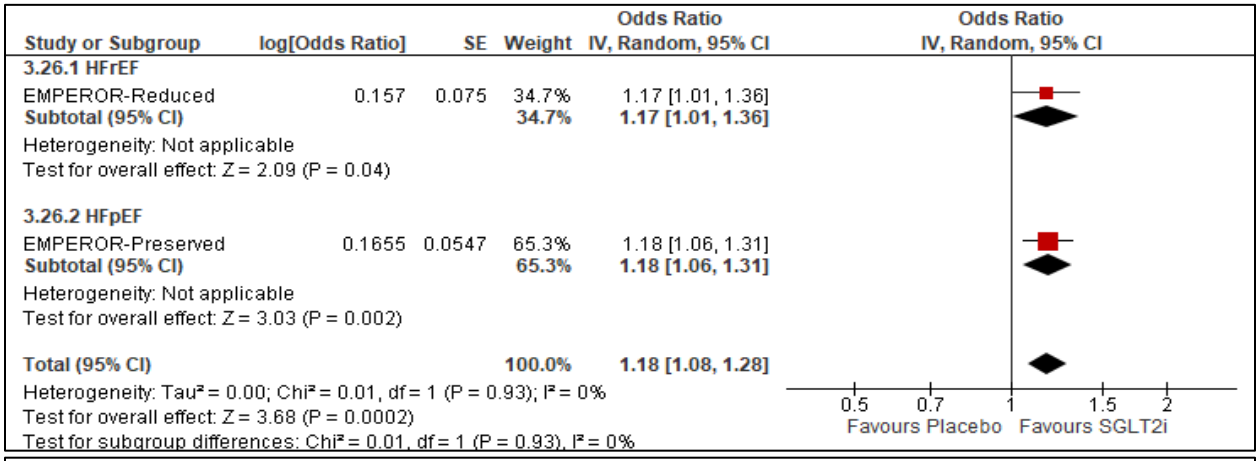


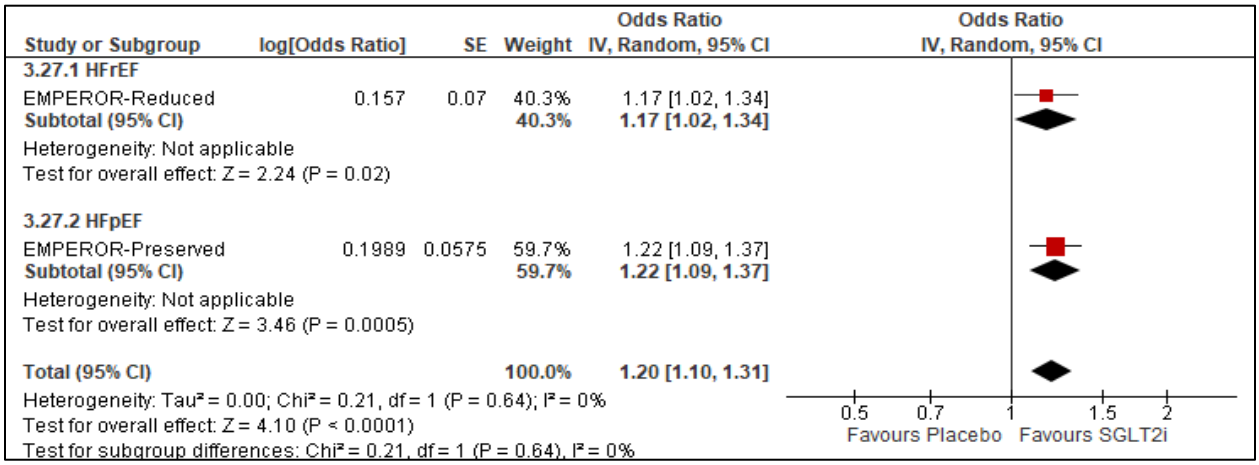




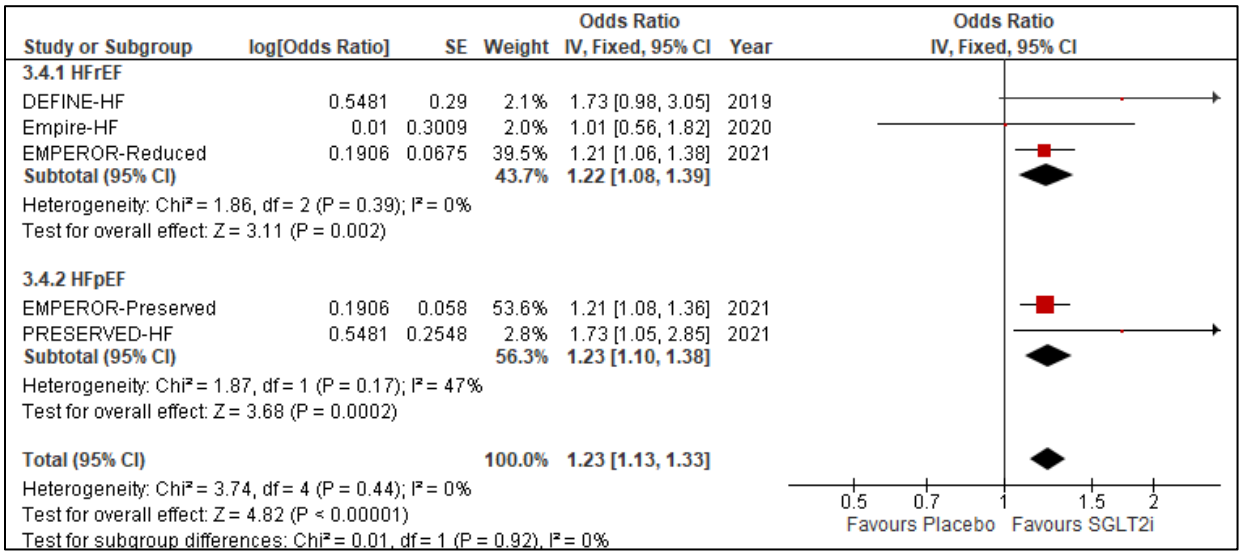
Supplemental Figure 5: Responder analysis; improvement of (A) ≥5 (B) ≥10 and (C) ≥15 points in KCCQ-TSS at 52 weeks

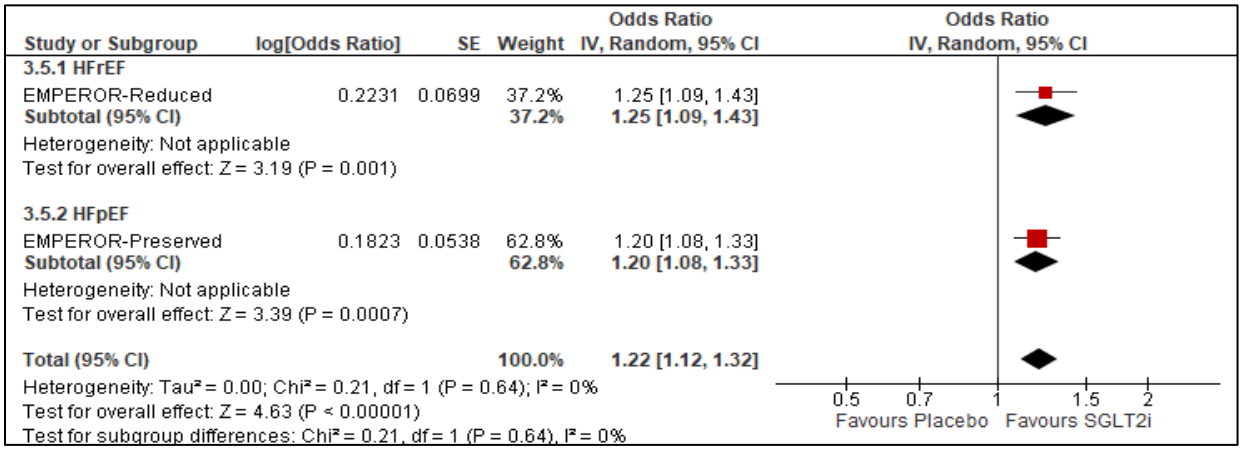


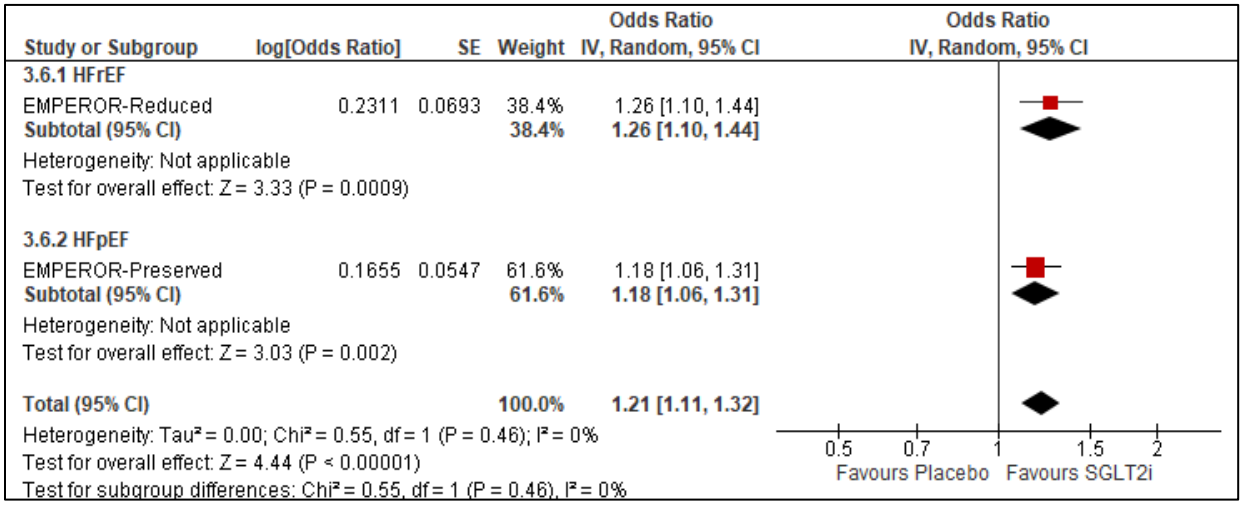




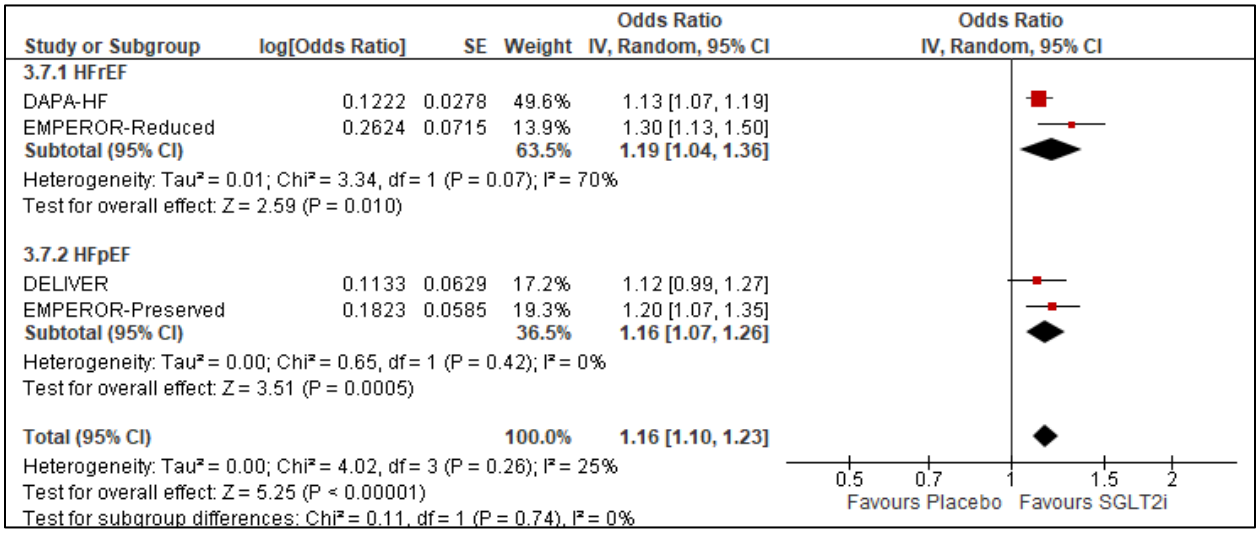
Supplemental Figure 6: Responder analysis; improvement of (A) ≥5 (B) ≥10 and (C) ≥15 points in KCCQ-OSS at 12 weeks

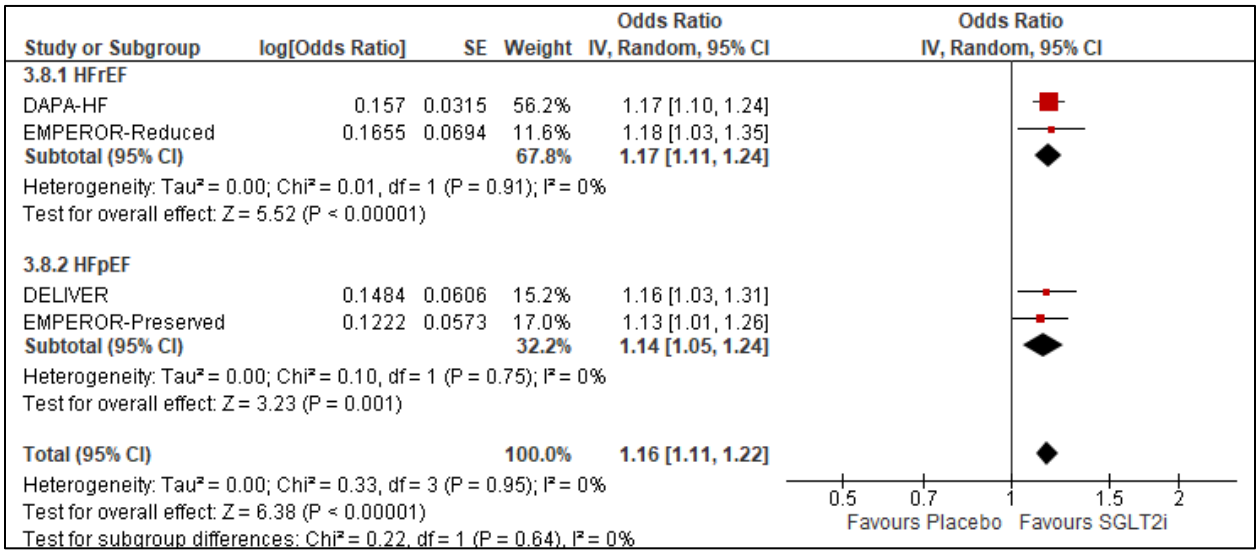


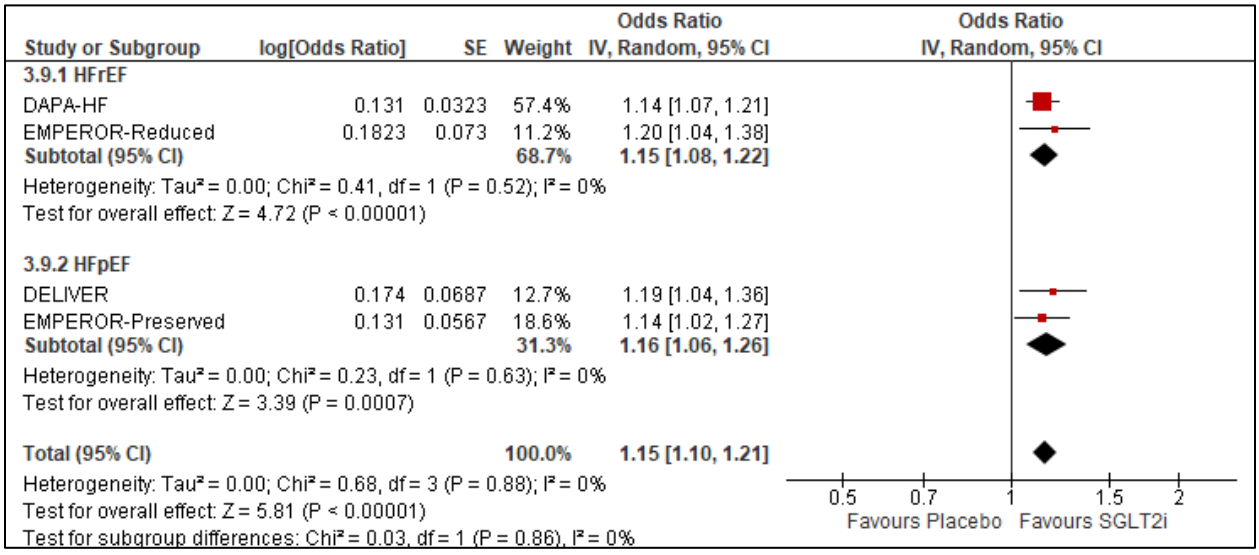




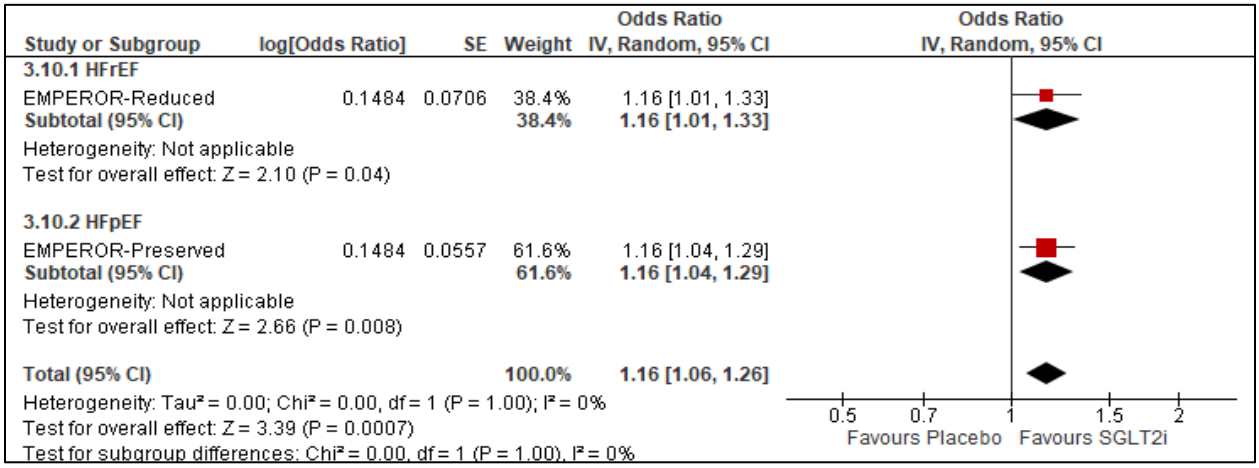
Supplemental Figure 7: Responder analysis; improvement of (A) ≥5 (B) ≥10 and (C) ≥15 points in KCCQ-OSS at 32 weeks

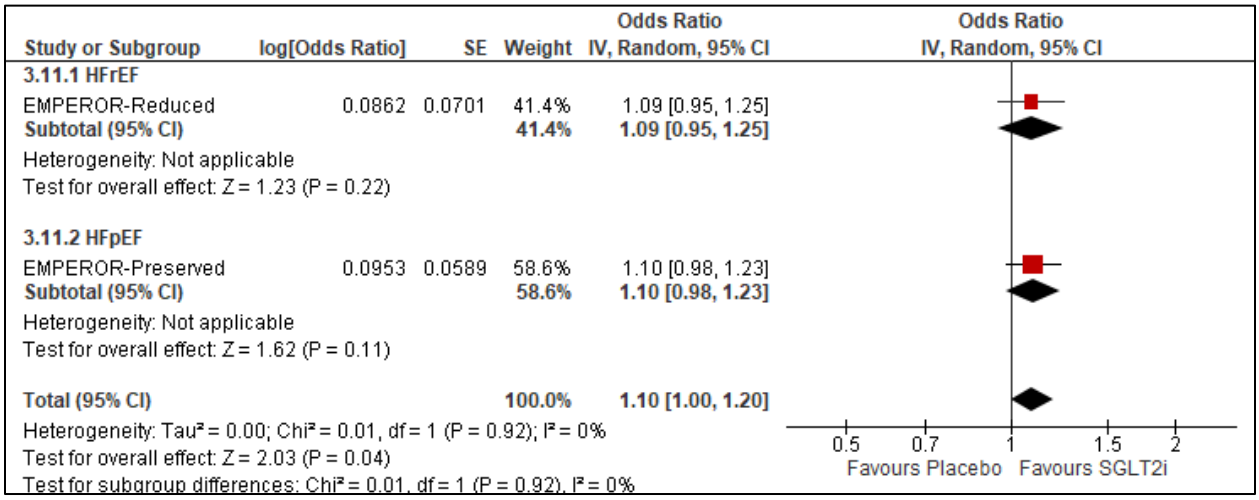


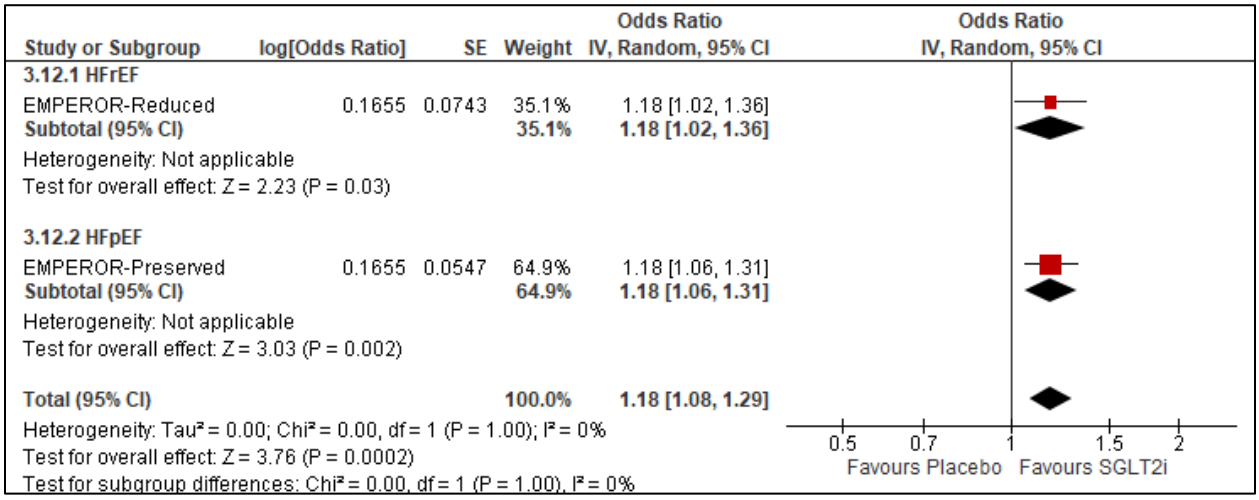




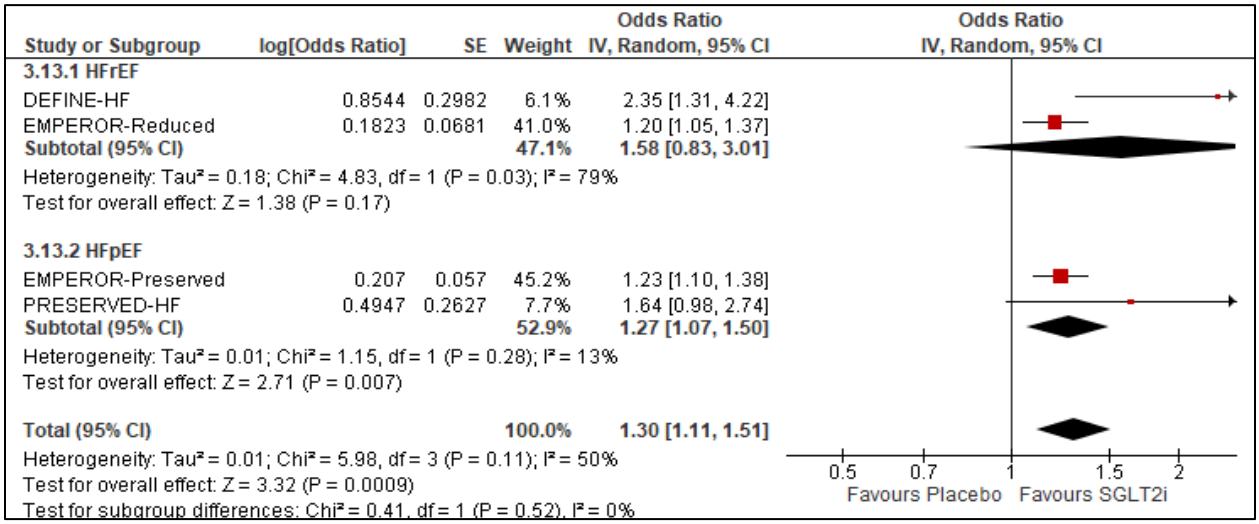
Supplemental Figure 8: Responder analysis; improvement of (A) ≥5 (B) ≥10 and (C) ≥15 points in KCCQ-OSS at 52 weeks.

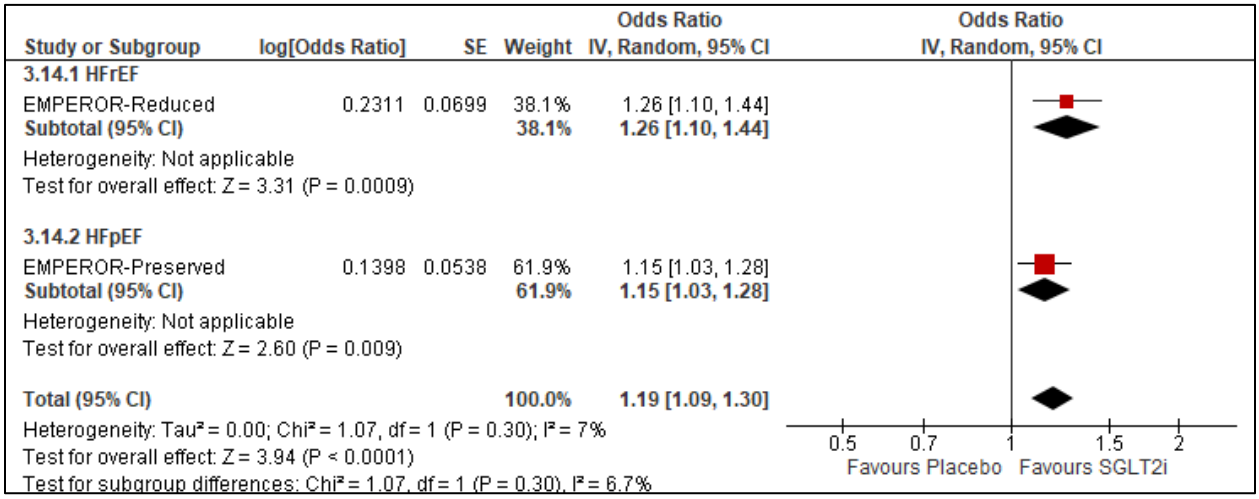


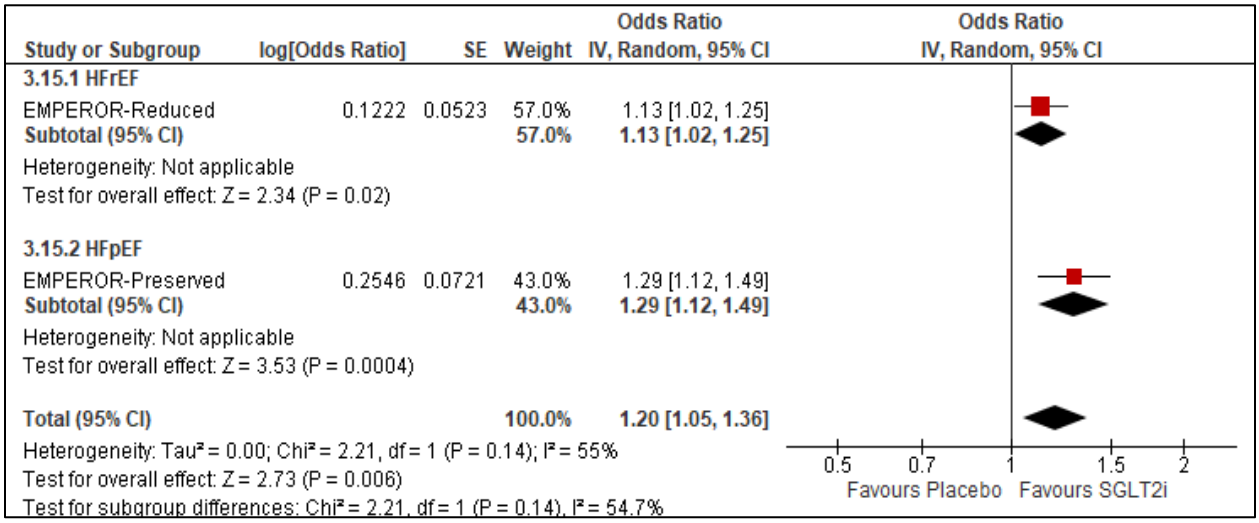




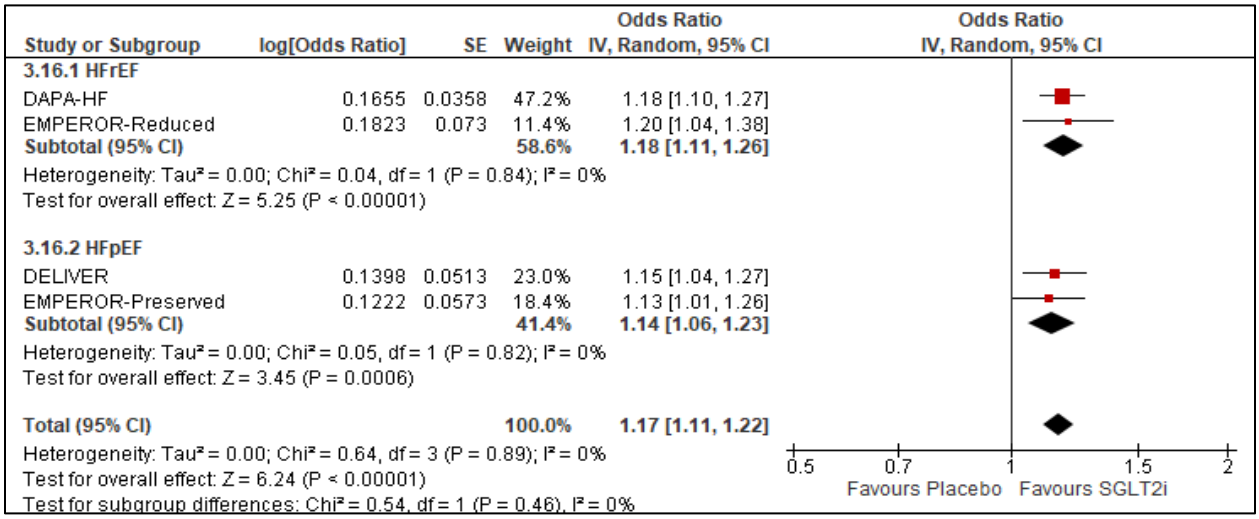
Supplemental Figure 9: Responder analysis; improvement of (A) ≥5 (B) ≥10 and (C) ≥15 points in KCCQ-CSS at 12 weeks.

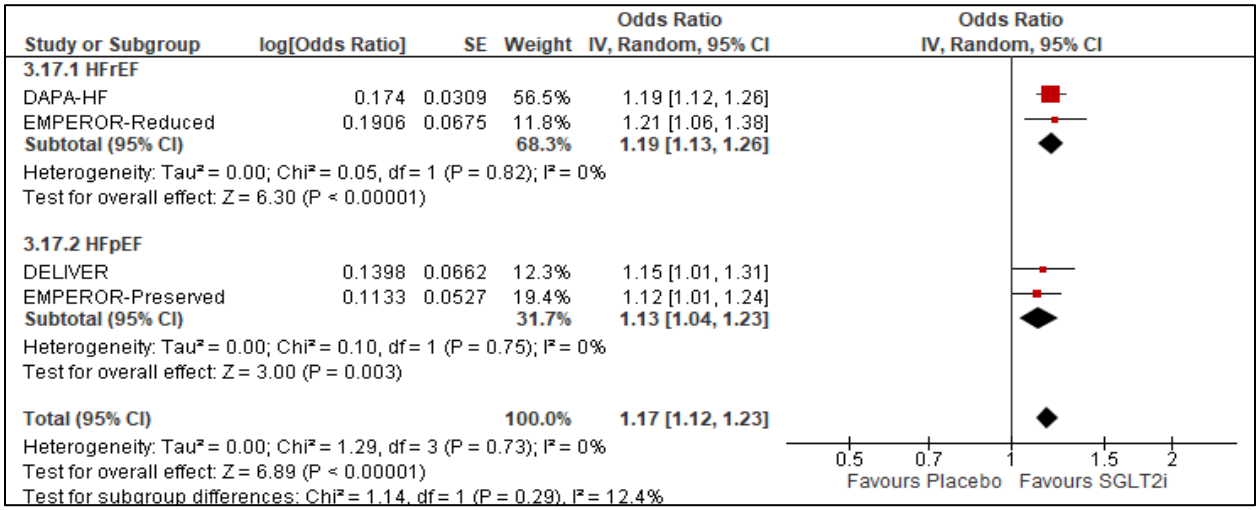


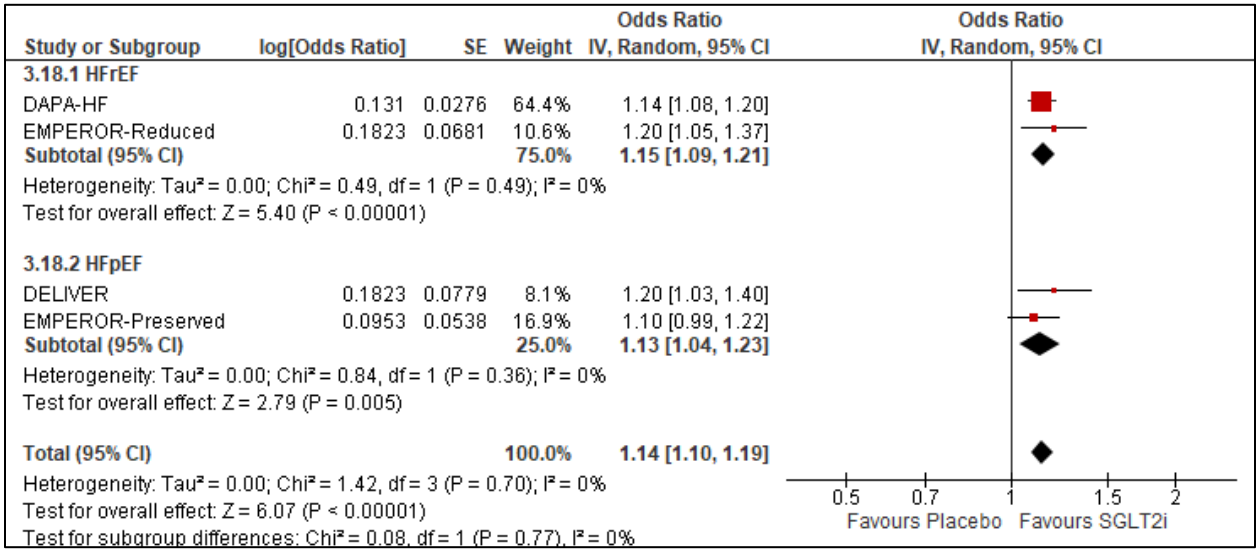




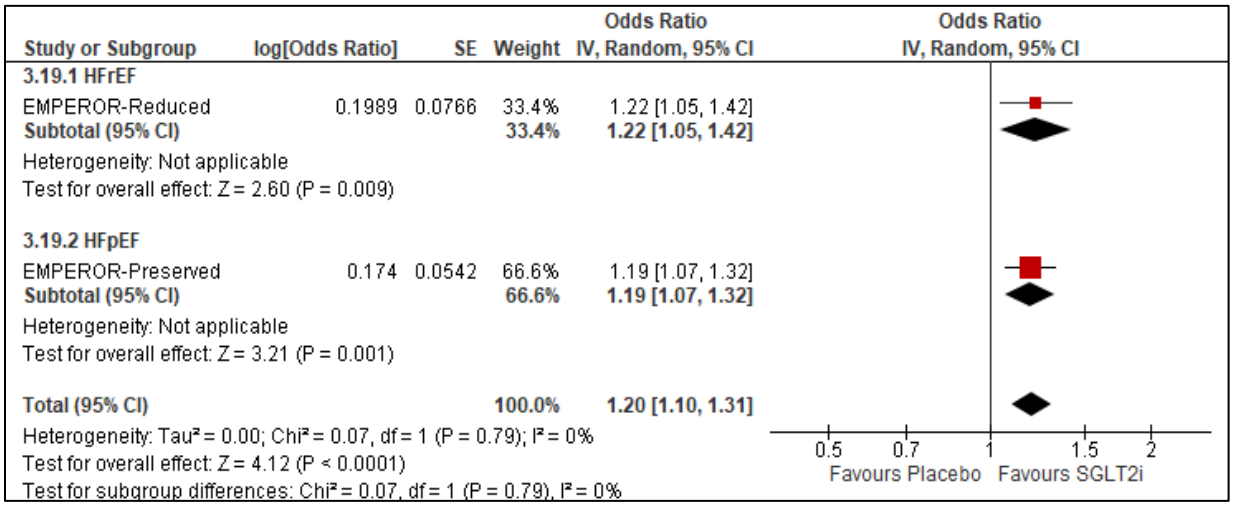
Supplemental Figure 10: Responder analysis; improvement of (A) ≥5 (B) ≥10 and (C) ≥15 points in KCCQ-CSS at 32 weeks.

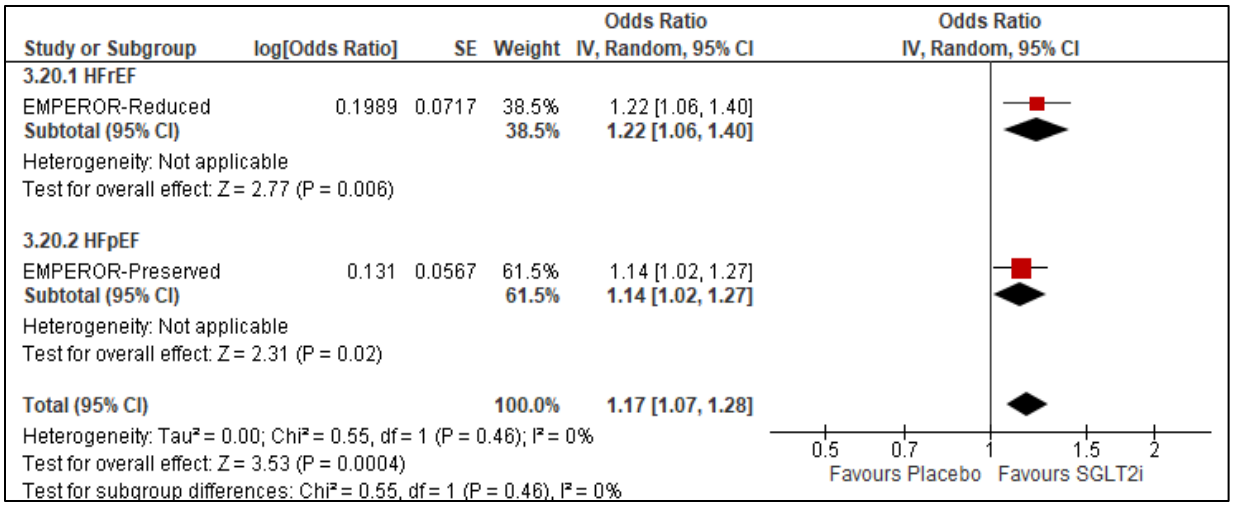


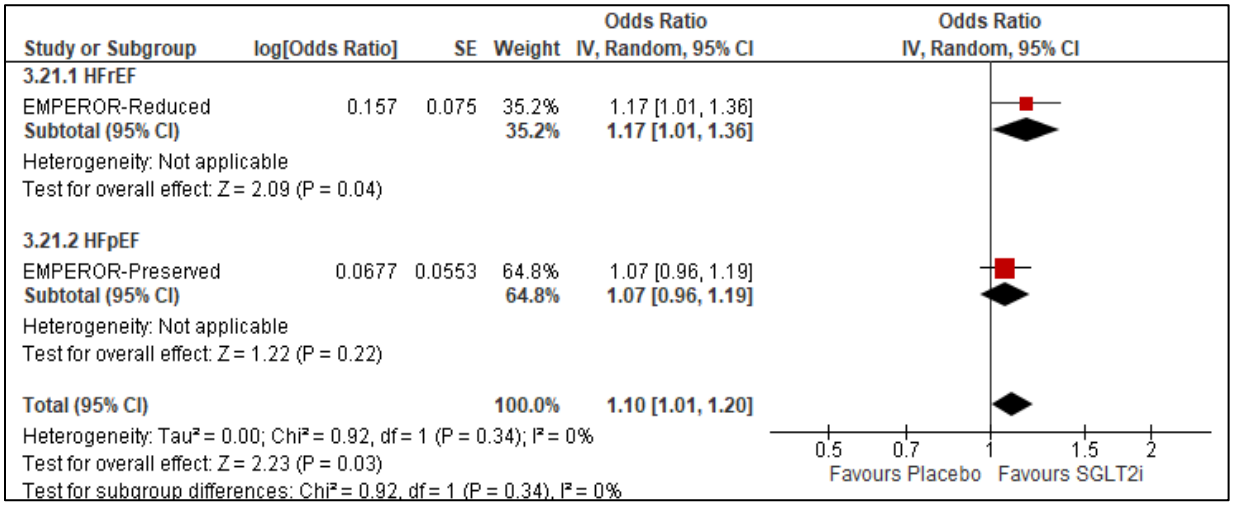




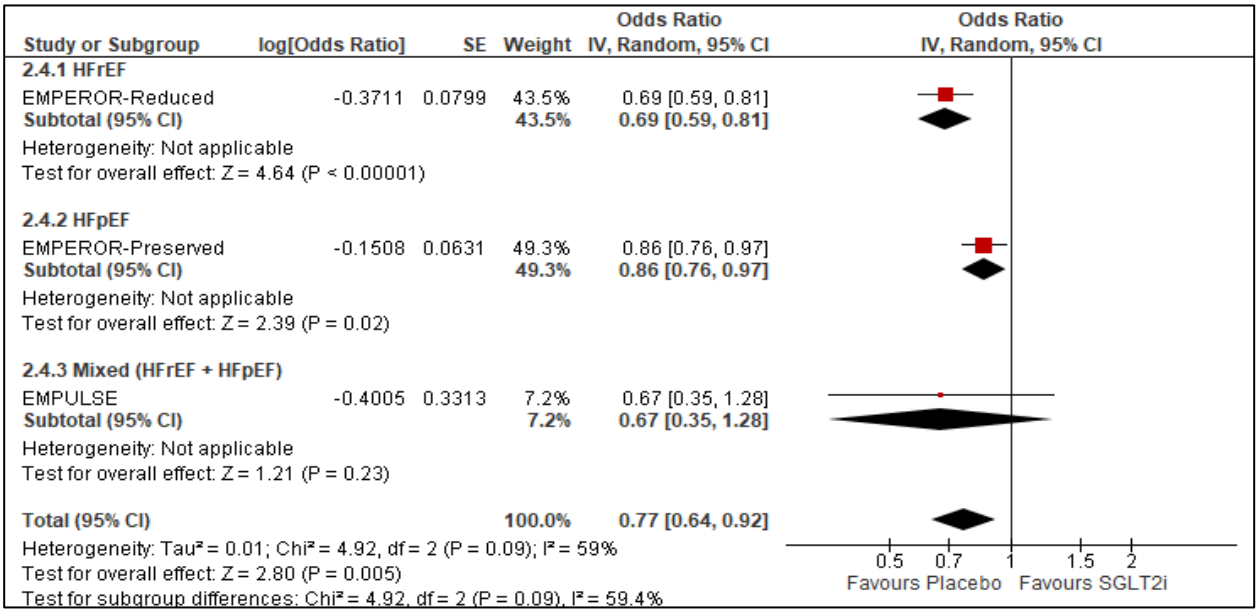
Supplemental Figure 11: Responder analysis; improvement of (A) ≥5 (B) ≥10 and (C) ≥15 points in KCCQ-CSS at 52 weeks

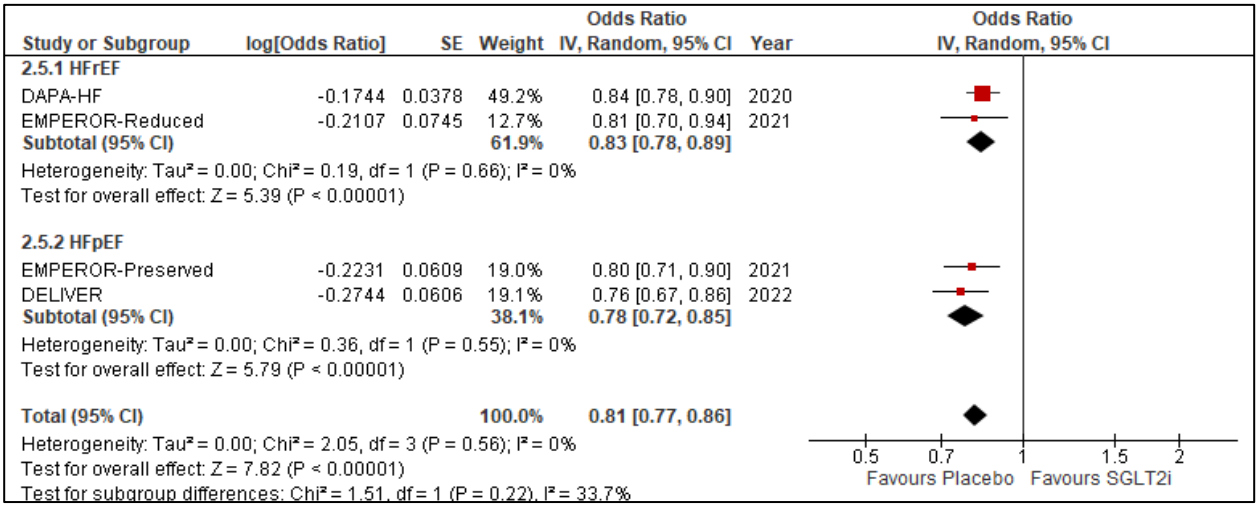


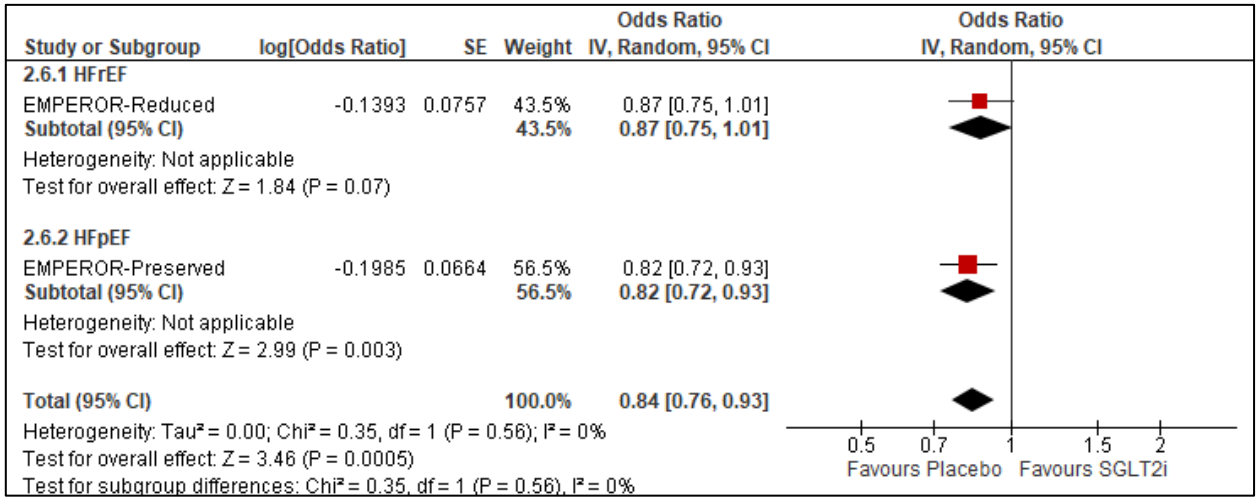




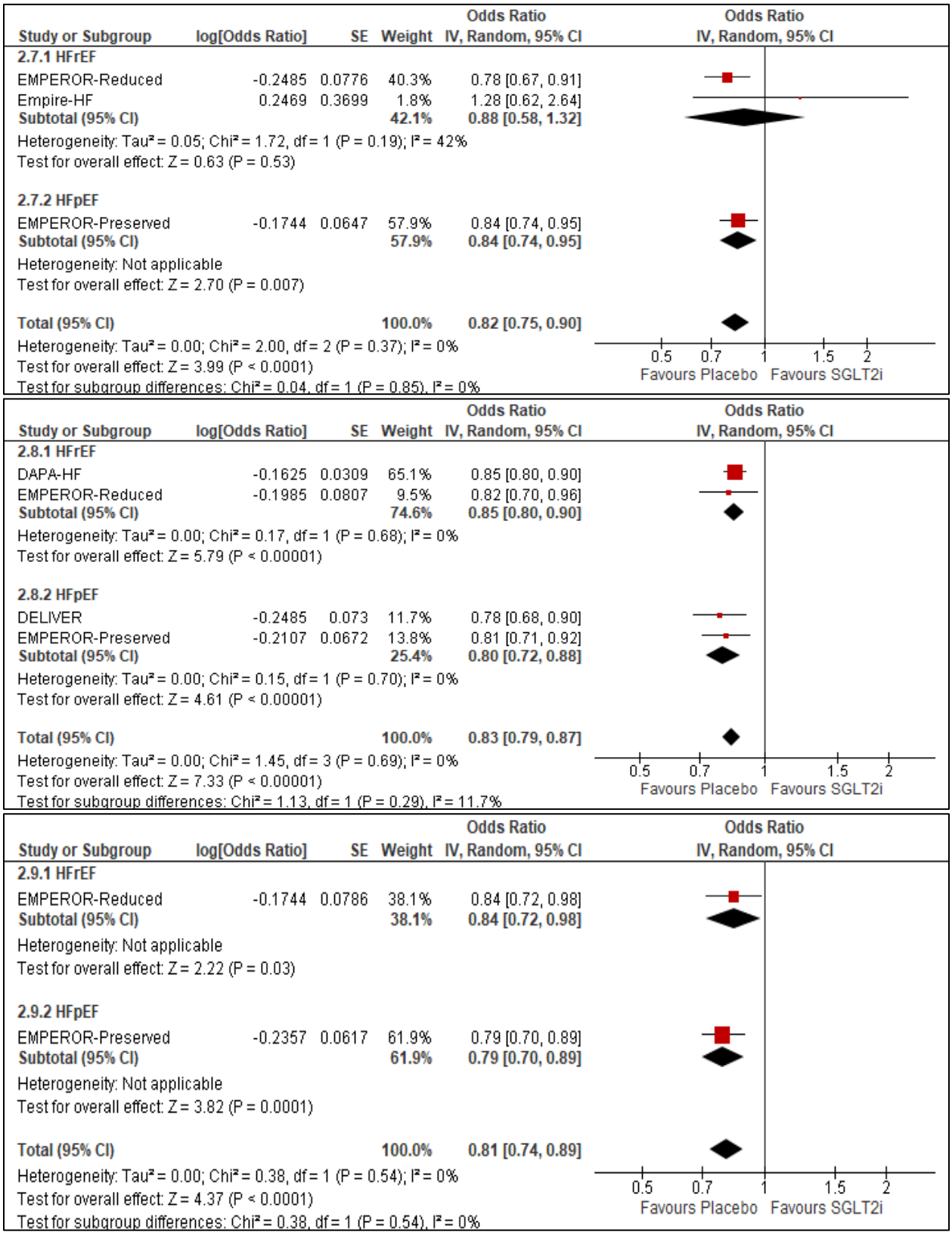
Supplemental Figure 12: Responder analysis; KCCQ-TSS deterioration by ≥5 points at (A) 12, (B) 32 and (C) 52 weeks.







Supplemental Figure 13: Responder analysis; KCCQ-OSS deterioration by ≥5 points at (A) 12, (B) 32 and (C) 52 weeks.



Supplemental Figure 14: Responder analysis; KCCQ-CSS deterioration by ≥5 points at (A) 12, (B) 32 and (C) 52 weeks.