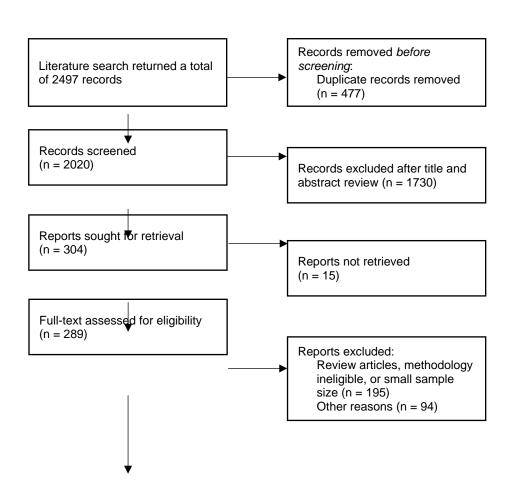
Supplementary Table 1 Diabetic ketoacidosis reported by the reviewed trial across heart failure subtypes

DKA	Trial	event in gliflozins versus placebo groups, respectively
HFrEF	DECLARE-TIMI58	no DKA in either group
	DAPA-HF	3/2368 vs 0/2371
	EMPEROR-Reduced	0/1863 vs 0/1863 (no DKA occurred in either group)
HFpEF	EMPEROR-Preserved	4/2996 vs 5/2989
	DELIVER	46/3126 vs 50/3127
HF(nos)	DAPA-CKD	0/235 vs 0/233 (no DKA in occurred either group)
	SOLOIST-WHF	2/603 vs 4/607
no HF	DAPA-CKD	0/1914 vs 2/1916

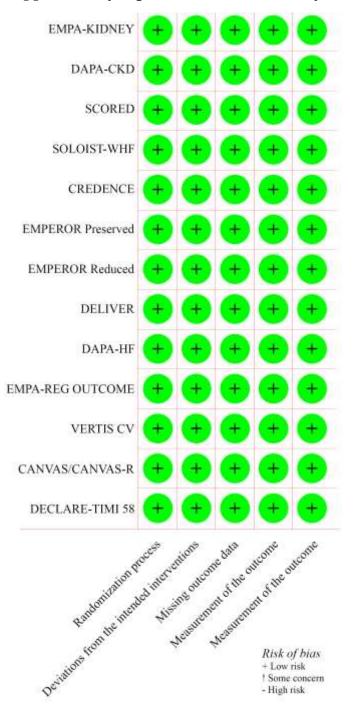
DKA: diabetic ketoacidosis; HF: heart failure; HFpEF: heart failure with preserved ejection fraction; HFrEF: heart failure with reduced ejection fraction; nos: not otherwise specified;



Total randomized controlled trials included in the systematic review (n = 13)

Post hoc analysis studies and comprehensive review articles with novel data (n = 14)

Supplementary Figure 1 Flowchart of the systematic review process.

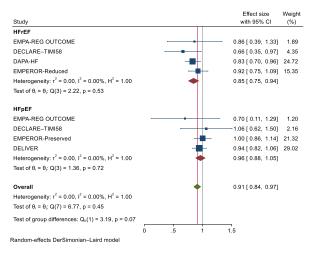


Supplementary Figure 2 Risk of bias assessment of included trials as assessed using Version 2 of the Cochrane Risk-of-Bias tool for randomized trials (ROB2).

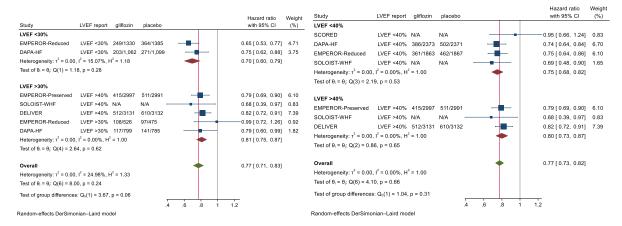
Study		Effect size with 95% CI	Weight (%)
HFrEF			
EMPA-REG OUTCOME		0.82 [0.31, 1.33]	1.47
DECLARE-TIMI58		0.61 [0.27, 0.95]	2.99
DAPA-HF	-	0.82 [0.67, 0.97]	11.57
EMPEROR-Reduced	-	0.92 [0.74, 1.11]	8.35
Heterogeneity: $\tau^2 = 0.00$, $I^2 = 0.00\%$, $H^2 = 1.00$	•	0.83 [0.73, 0.94]	
Test of $\theta_i = \theta_j$: Q(3) = 2.49, p = 0.48			
HFmrEF			
EMPEROR-Preserved & Reduced (LVEF 35%-45%)		0.86 [0.66, 1.06]	7.73
DELIVER & DAPA-HF (LVEF 38%-51%)		0.86 [0.68, 1.04]	8.68
Heterogeneity: $\tau^2 = 0.00$, $I^2 = 0.00\%$, $H^2 = 1.00$	•	0.86 [0.73, 0.99]	
Test of $\theta_i = \theta_j$: Q(1) = 0.00, p = 1.00			
HFpEF			
EMPA-REG OUTCOME		0.48 [-0.10, 1.06]	1.15
DECLARE-TIMI58		1.44 [0.61, 2.27]	0.56
EMPEROR-Preserved	-	0.91 [0.75, 1.08]	9.79
DELIVER	-	0.88 [0.73, 1.03]	10.64
Heterogeneity: τ ² = 0.00, I ² = 19.17%, H ² = 1.24	•	0.89 [0.75, 1.02]	
Test of $\theta_i = \theta_j$: Q(3) = 3.71, p = 0.29			
HF (nos)			
DECLARE-TIMI58		1.33 [0.42, 2.25]	0.47
VERTIS-CV		0.94 [0.63, 1.25]	3.62
DAPA-CKD		0.65 [0.23, 1.07]	2.09
SOLOIST-WHF		0.84 [0.50, 1.18]	3.07
Heterogeneity: $\tau^2 = 0.00$, $I^2 = 0.00\%$, $H^2 = 1.00$	•	0.86 [0.66, 1.06]	
Test of $\theta_i = \theta_j$: Q(3) = 2.24, p = 0.52			
no HF			
EMPA-REG OUTCOME	· -	0.60 [0.45, 0.75]	11.09
DECLARE-TIMI58		0.97 [0.76, 1.18]	6.91
VERTIS-CV	-	0.92 [0.71, 1.13]	6.91
DAPA-CKD		0.87 [0.52, 1.22]	2.92
Heterogeneity: $\tau^2 = 0.03$, $I^2 = 71.79\%$, $H^2 = 3.55$	•	0.83 [0.62, 1.03]	
Test of $\theta_i = \theta_j$: Q(3) = 10.64, p = 0.01			
Overall	•	0.84 [0.78, 0.90]	
Heterogeneity: τ^2 = 0.00, I^2 = 19.92%, H^2 = 1.25			
Test of $\theta_i = \theta_j$: Q(17) = 21.23, p = 0.22			
Test of group differences: $Q_b(4) = 0.44$, p = 0.98			
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Random-effects DerSimonian-Laird model

Supplementary Figure 3 Meta-analysis of cardiovascular death as the outcome of patients receiving gliflozins versus placebo across heart failure subtypes. HF: heart failure; HFpEF: heart failure with preserved ejection fraction; HFrEF: heart failure with reduced ejection fraction; nos: not otherwise specified; *



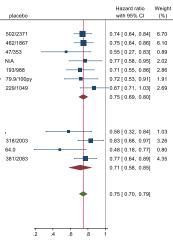
Supplementary Figure 4 Differential effects of gliflozins on all-cause mortality between patients with HFrEF and HfpEF. HF: heart failure; HFpEF: heart failure with preserved ejection fraction; HFrEF: heart failure with reduced ejection fraction; nos: not otherwise specified;



Study	LVEF report	gliflozin	placebo		Hazard ratio with 95% CI	Weigh (%)
VEF <45%						
CORED	LVEF <40%	N/A	N/A			0.83
OLOIST-WHF	LVEF <40%	N/A	N/A		0.69 [0.48, 0.90]	1.65
APA-HF plus DELIVER	LVEF <45%	473/2824	595/2784		0.81 [0.72, 0.90]	8.19
MPEROR (Re- & Pr-)	LVEF <45%	423/2253	537/2251		0.74 [0.63, 0.85]	6.10
leterogeneity: r ² = 0.00, I ²	² = 1.47%, H ² =	1.01		+	0.78 [0.72, 0.84]	
test of $\theta_i = \theta_i$: Q(3) = 3.04,	p = 0.38					
VEF >45%						
MPEROR-Preserved	LVEF >45%	353/2610	436/2607		0.78 [0.66, 0.90]	4.71
DELIVER	LVEF >45%	[440/2680]	[533/2687]		0.85 [0.75, 0.95]	6.70
leterogeneity: τ ² = 0.00, l ²	² = 0.00%, H ² =	1.00		+	0.82 [0.74, 0.90]	
Test of $\theta_i = \theta_j$: Q(1) = 0.77,	, p = 0.38					
Overall				↓	0.80 [0.75, 0.85]	
leterogeneity: τ ² = 0.00, l ²	² = 0.00%, H ² =	1.00				
Test of $\theta_i = \theta_i$: Q(5) = 4.48,	p = 0.48					
est of group differences:	Q _b (1) = 0.66, p	= 0.42				

Study	LVEF report	gliflozin	placebo	
LVEF <50%				
DAPA-HF	LVEF <40%	386/2373	502/2371	
EMPEROR-Reduced	LVEF <40%	361/1863	462/1867	
DECLARE-TIMI58	LVEF <50%	25/318	47/353	
SCORED	LVEF <50%	N/A	N/A	-
EMPEROR-Preserved	LVEF <50%	145/995	193/988	
SOLOIST-WHF	LVEF <50%	56.9/100py	79.9/100py	
DELIVER	LVEF <50%	207/1067	229/1049	
Heterogeneity: r ² = 0.00	, I ² = 0.00%, H ²	² = 1.00		
Test of $\theta_i = \theta_j$: Q(6) = 4.5	i5, p = 0.60			
LVEF >50%				
SCORED	LVEF >50%			
EMPEROR-Preserved	LVEF >50%	270/2002	318/2003	
SOLOIST-WHF	LVEF >50%	30.6**	64.0	
DELIVER	LVEF >50%	305/2064	381/2083	
Heterogeneity: r ² = 0.01	, I ² = 50.98%, H	$H^2 = 2.04$		-
Test of $\theta_i = \theta_j$: Q(3) = 6.1	2, p = 0.11			
Overall				
Heterogeneity: T ² = 0.00	$I^2 = 6.28\%$ H ⁴	= 1.07		
Test of $\theta_i = \theta_j$: Q(10) = 1				
Test of group differences	s: Q _b (1) = 0.22,	p = 0.64		

Random-effects DerSimonian-Laird model



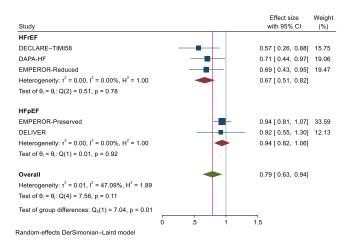
Random-effects DerSimonian-Laird model

Study	LVEF report	gliflozin	placebo				Hazard ratio with 95% CI	Weight (%)
LVEF <60%								
DAPA-HF	LVEF <40%	386/2373	502/2371			-	0.74 [0.64, 0.84]	6.70
EMPEROR-Reduced	LVEF <40%	361/1863	462/1867		-	-	0.75 [0.64, 0.86]	6.10
DECLARE-TIMI58	LVEF <50%	25/318	47/353	 -		_	0.55 [0.27, 0.83]	0.89
SCORED	LVEF <50%	N/A	N/A	-	-		0.77 [0.58, 0.95]	2.02
EMPEROR-Preserved	LVEF <60%	283/2023	366/2018		_		0.73 [0.61, 0.86]	4.35
DELIVER	LVEF <60%	381/2200	440/2172		-		0.83 [0.72, 0.94]	5.58
Heterogeneity: $\tau^2 = 0.00$, I ² = 0.00%, H ²	= 1.00					0.76 [0.70, 0.81]	
Test of $\theta_i = \theta_j$: Q(5) = 4.1	12, p = 0.53							
LVEF >60%								
EMPEROR-Preserved	LVEF >60%	132/974	145/973			_	0.87 [0.66, 1.08]	1.65
DELIVER	LVEF >60%	131/931	170/960	-			0.78 [0.60, 0.96]	2.13
Heterogeneity: $\tau^2 = 0.00$, I ² = 0.00%, H ²	= 1.00			-		0.82 [0.68, 0.95]	
Test of $\theta_i = \theta_j$: Q(1) = 0.4	12, p = 0.52							
Overall							0.76 [0.72, 0.81]	
Heterogeneity: $\tau^2 = 0.00$	$I^2 = 0.00\%, H^2$	= 1.00						
Test of $\theta_i = \theta_j$: Q(7) = 5.2								
Test of group differences	s: Q _b (1) = 0.73,	p = 0.39	ŗ	,		.8	1	
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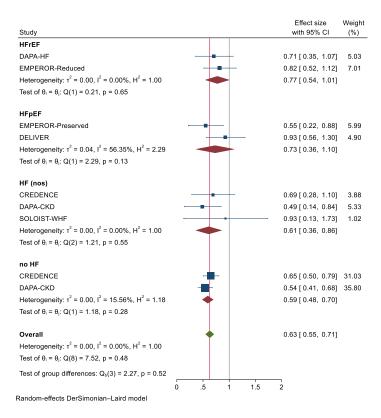
Supplementary Figure S4. Differential primary composite outcomes across the patients' baseline left ventricular ejection fraction stratums

HF: heart failure; HFpEF: heart failure with preserved ejection fraction; HFrEF: heart failure with reduced ejection fraction; nos: not otherwise specified; * per 1000 person-years; ** per 100 person-years; N/A: not available;

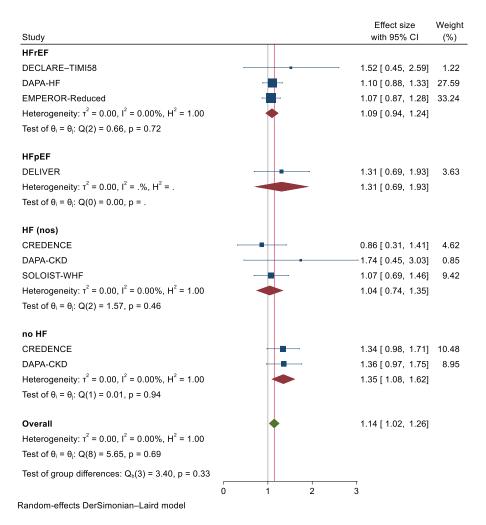
Random-effects DerSimonian-Laird model



Supplementary Figure 5 Differential effects of SGLT2 inhibitors on the incident acute kidney injury (acute renal failure) between patients with heart failure with either preserved or reduced left ventricular ejection fraction. HFpEF: heart failure with preserved ejection fraction; HFrEF: heart failure with reduced ejection fraction;



Supplementary Figure 6 the impact of SGLT2inhibitors on the renal disease progression (worsening renal function) across the heart failure subgroups. HF: heart failure; HFpEF: heart failure with preserved ejection fraction; HFrEF: heart failure with reduced ejection fraction; nos: not otherwise specified;



Supplementary Figure 7 Volume depletion in response to gliflozins across the heart failure status and subtypes. HF: heart failure; HFpEF: heart failure with preserved ejection fraction; HFrEF: heart failure with reduced ejection fraction; nos: not otherwise specified;