

Supplementary material

Table S1. Search strategy performed on the following databases: PubMed, Embase, the Cochrane Central Register of Controlled Trials (CENTRAL).

1. Randomi*ed study OR random allocation OR Randomi*ed controlled trial OR Random* Control* trial OR RCT Epidemiological study
2. sodium glucose cotransporter 2 OR sodium glucose cotransporter 2 inhibitor* OR sglt2 inhibitor* OR empagliflozin OR dapagliflozin OR canagliflozin OR ipragliflozin OR tofogliflozin OR ertugliflozin OR sotagliflozin OR sergliflozin OR remogliflozin
3. 1 AND 2

Table S2. Safety outcomes of empagliflozin and linagliptin combination therapy compared with empagliflozin or linagliptin monotherapy in treatment naïve type 2 diabetes patients

Safety outcome	Comparator 1	Comparator 2	I ²	RR [95% CI]
	Number of events / total subjects	Number of events / total subjects		
i. Empagliflozin + linagliptin vs empagliflozin monotherapy				
	<i>Empagliflozin + linagliptin</i>	<i>Empagliflozin monotherapy</i>		
≥ 1 AE(s)	202/272	203/270	77%	0.99 [0.81, 1.21]
≥ 1 drug-related AE(s)	37/272	38/270	0%	0.97 [0.64, 1.47]
≥ 1 serious AE(s)	13/272	19/270	0%	0.68 [0.34, 1.35]
Hypoglycaemia*	0/272	5/270	0%	0.18 [0.02, 1.56]
UTI	32/272	25/270	29%	1.28 [0.70, 2.35]
Events suggestive of genital infection	12/272	13/270	9%	0.92 [0.40, 2.09]
i. Empagliflozin + linagliptin vs linagliptin monotherapy				
	<i>Empagliflozin + linagliptin</i>	<i>Linagliptin monotherapy</i>		
≥ 1 AE(s)	202/272	97/135	0%	1.03 [0.91, 1.17]
≥ 1 drug-related AE(s)	37/272	17/135	0%	1.08 [0.63, 1.84]
≥ 1 serious AE(s)	13/272	2/135	0%	3.22 [0.74, 14.07]
Hypoglycaemia*	0/272	1/135	NA	0.17 [0.01, 4.07]
UTI	32/272	12/135	0%	1.32 [0.70, 2.49]
Events suggestive of genital infection	12/272	4/135	0%	1.45 [0.47, 4.47]

RR, relative risk; AE, adverse event; UTI, urinary tract infection. * Hypoglycaemia defined as plasma glucose ≤ 3.9 mmol/L and/or assistance required.

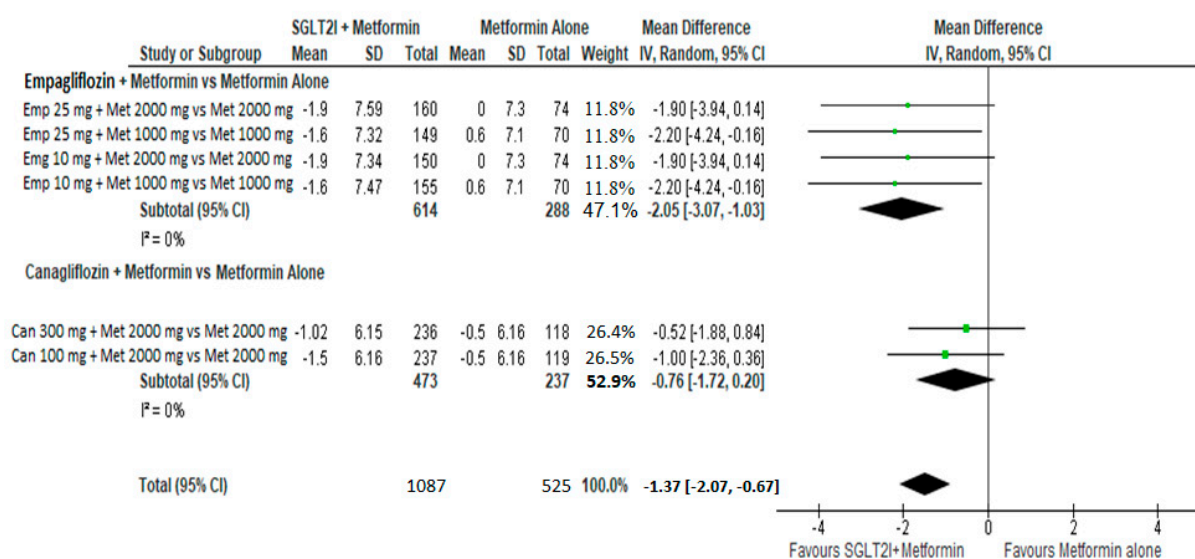
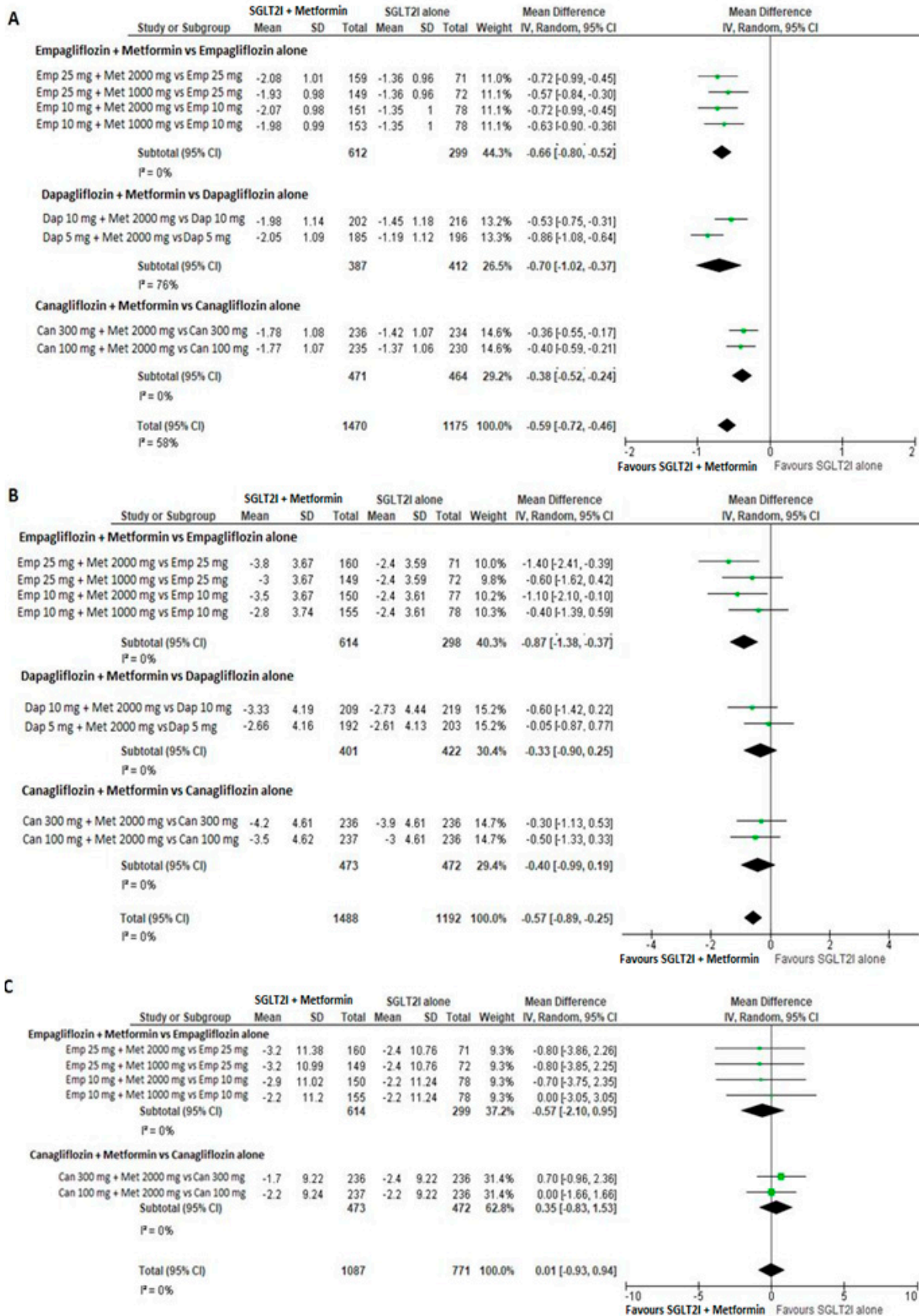


Figure S1. The mean change from baseline (pre-treatment) in diastolic BP (mmHg) between SGLT2 inhibitor and metformin combination therapy versus metformin monotherapy in treatment naïve type 2 diabetes patients. SGLT2i, SGLT2 inhibitor; Emp, empagliflozin; Met, metformin; Dap, dapagliflozin; Can, canagliflozin.



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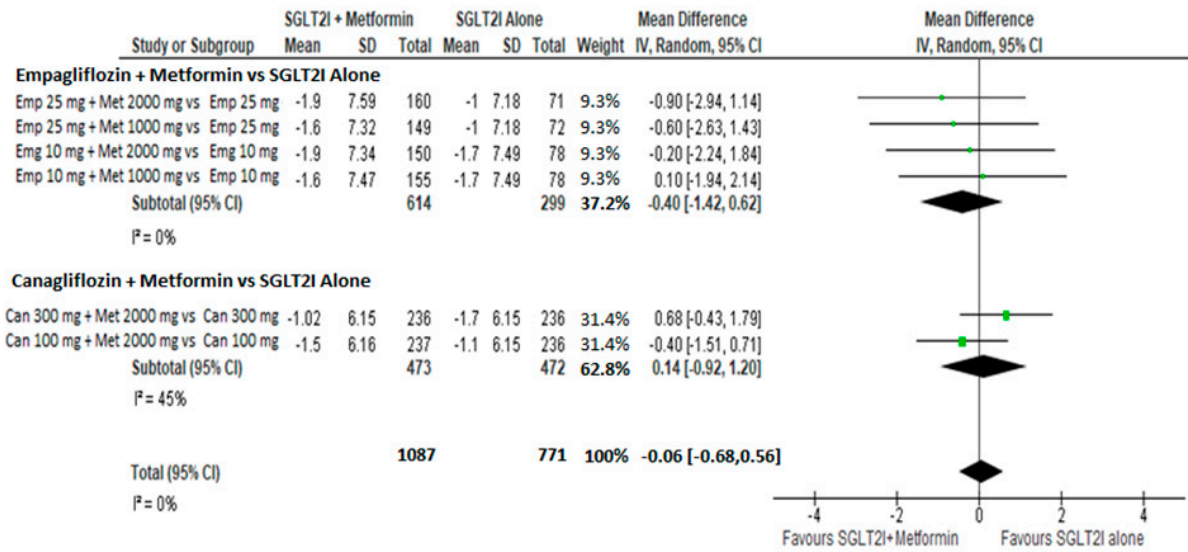


Figure S2. The mean change from baseline (pre-treatment) in: (A) HbA1c (%) (B) body weight (kg) and (C) systolic BP (mmHg) (D) diastolic BP (mmHg) between SGLT2 inhibitor and metformin combination therapy versus SGLT2 inhibitor monotherapy in treatment naïve type 2 diabetes patients. SGLT2i, SGLT2 inhibitor; Emp, empagliflozin; Met, metformin; Dap, dapagliflozin; Can, canagliflozin.

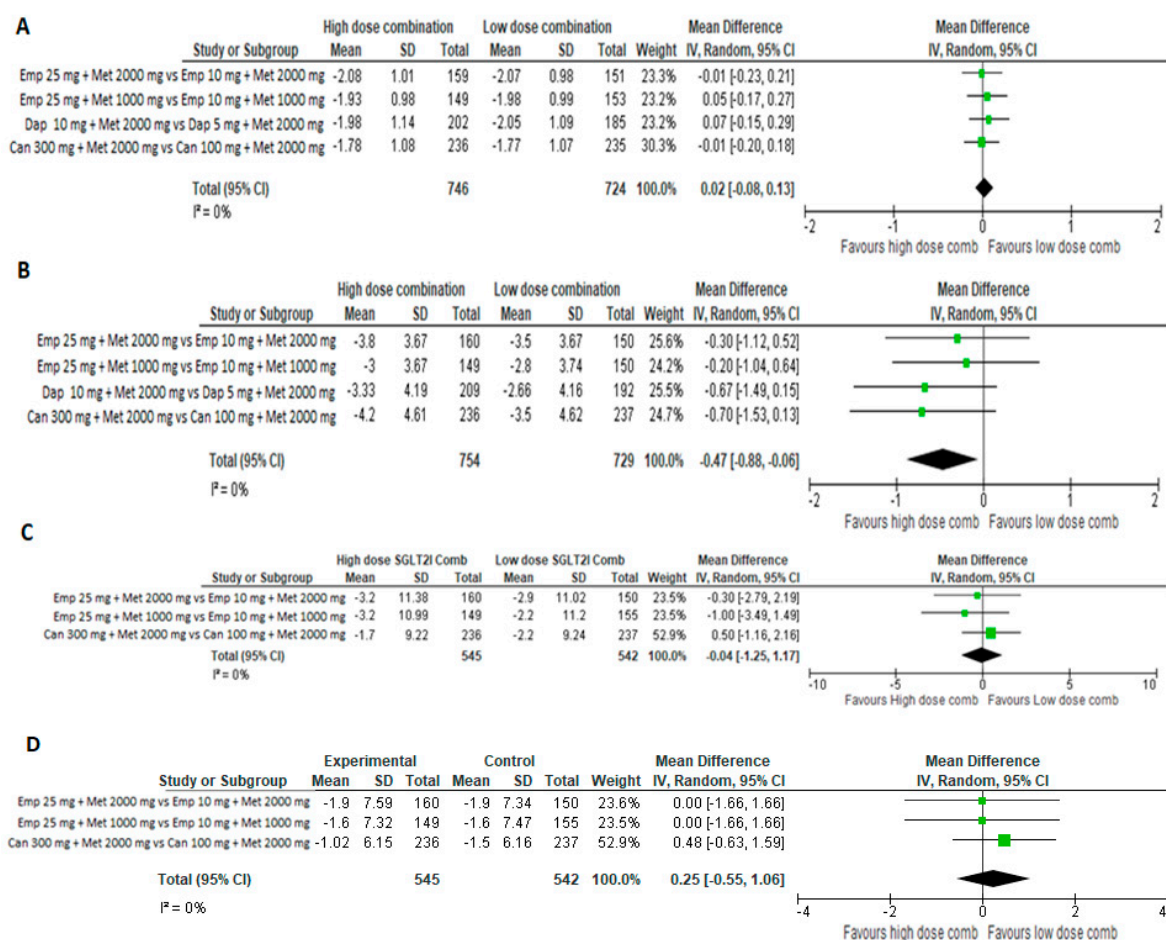


Figure S3. The mean change from baseline (pre-treatment) in: (A) HbA1c (%) (B) body weight (kg) (C) systolic BP (mmHg) and (D) diastolic BP (mmHg) between combination high dose SGLT2 inhibitor and metformin versus combination low dose SGLT2 inhibitor and metformin in treatment naïve type 2 diabetes patients. Emp, empagliflozin; Met, metformin; Dap, dapagliflozin; Can, canagliflozin.

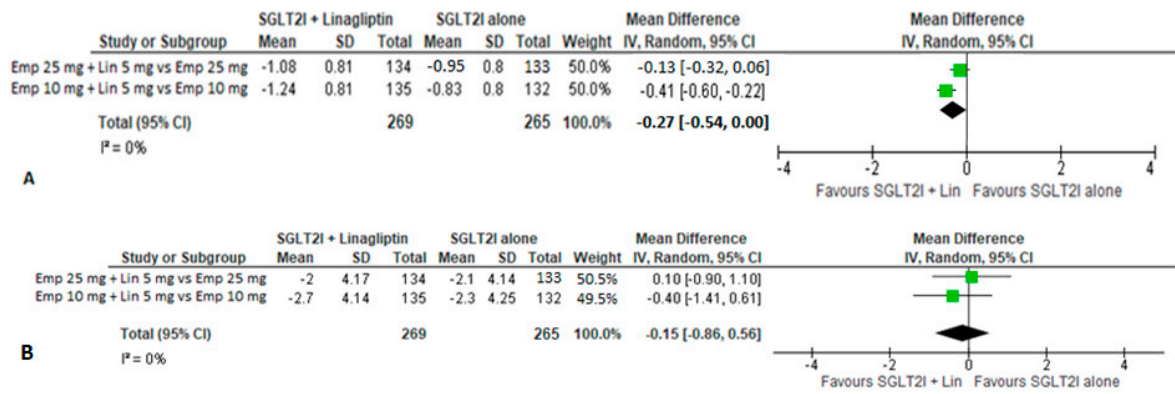


Figure S4. The mean change from baseline (pre-treatment) in: (A) HbA1c (%) (B) body weight (kg) between empagliflozin and linagliptin combination therapy versus empagliflozin monotherapy in treatment naïve type 2 diabetes patients. SGLT2i, SGLT2 inhibitor; Emp, empagliflozin; Lin, Linagliptin.

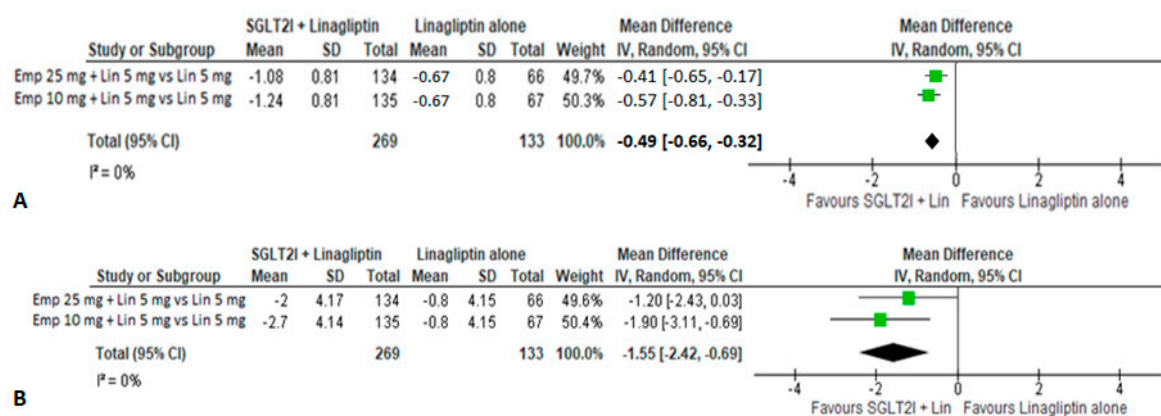


Figure S5. The mean change from baseline in: (A) HbA1c (%) (B) body weight (kg) between empagliflozin and linagliptin combination therapy versus linagliptin monotherapy in treatment naïve type 2 diabetes patients. SGLT2i, SGLT2 inhibitor; Emp, empagliflozin; Lin, Linagliptin.