Original Article

The effects of sodium glucose co-transporter (SGLT) 2 inhibitors on hematocrit levels: a systematic review and meta-analysis of randomized controlled trials

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Background: Previous studies have suggested benefits of sodium glucose co-transporter 2 (SGLT2) inhibitors including improving glycemic control, lower body weight, uric acid-lowering effect and decreasing blood pressure. The aim of this study was to evaluate the effects of SGLT2 inhibitors on hematocrit (Hct) levels in patients with type 2 diabetes mellitus.

Methods: Embase, CENTRAL, PubMed and other databases were searched from the establishment of the database through to July 2020. Randomized controlled trials (RCTs) involving patients with type 2 diabetes mellitus who were treated with SGLT2 inhibitors were analyzed using the random effects model. Stata 12.0 statistical software was used to estimate the weighted mean difference (WMD) and the 95% confidence intervals (CIs).

Results: A total of 40 RCTs were included, comprising 21,050 patients. SGLT2 inhibitors resulted in a significant increase in Hct levels compared to patients treated with a placebo (WMD 2.67%, 95% CI, 2.53 to 2.82; P<0.001). Treatment with 2.5, 5, and 10 mg of dapagliflozin significantly increased Hct levels (WMD 1.96%, 2.27%, and 2.47%, respectively; P<0.001). Administration of 100 and 300 mg of canagliflozin also resulted in a significant increase in Hct (WMD 2.91% and 2.94%, respectively; P<0.001). Similarly, empagliflozin, at concentrations of 10 and 25 mg, caused a significant increase in Hct (WMD 3.39% and 3.44%, respectively; P<0.001). However, treatment with ipragliflozin (12.5 and 50 mg) and ertugliflozin (5 and 15 mg) only resulted in a slight increase in patient Hct levels (WMD 1.26% and 1.98%, respectively for ipragliflozin, P>0.05; WMD 2.24% and 2.64%, respectively for ertugliflozin; P>0.05).

Discussion: SGLT2 inhibitors, as a class of drugs, increased Hct levels in patients with type 2 diabetes, and this increase was slightly more pronounced at higher doses compared to lower doses.

Trial registration: The protocol of this study has been submitted to the PROSPERO platform (https://www.crd.york.ac.uk/PROSPERO/), and the registration number is CRD42020200699.

Keywords: Sodium glucose co-transporter 2 inhibitors (SGLT2 inhibitors); hematocrit (Hct); type 2 diabetes mellitus; meta-analysis

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Introduction

Type 2 diabetes mellitus is a progressive disease characterized by high glucose levels. It is associated with an increased risk of cardiovascular death, myocardial infarction, stroke, and heart failure (HF) (1,2).

Sodium glucose co-transporter (SGLT) 2 inhibitors reduce blood glucose levels by inhibiting the reabsorption of glucose through the SGLT2 receptors in the proximal tubule of the kidneys (3,4). Large-scale randomized controlled trials (RCTs) including EMPA-REG OUTCOME, CANVAS, DECLARE-TIMI58, DAPA-HF, and CREDENCE, have shown that SGLT2 inhibitors can exert cardiorenal benefits (5).

Hematocrit (Hct) is the volume percentage of red cells in total blood and it may be related to mortality and coronary heart disease (6,7). Previous studies have indicated a dual effect of Hct on all-cause mortality and morbidity from cardiovascular diseases (CVDs), and the effects tend to be J- or U- shaped. Furthermore, Hct was significantly related to the incidence of CVD, myocardial infarction, stroke, and coronary heart disease in younger patients, suggesting that Hct is an important risk factor associated with some CVD events (8). Lowe *et al.* (9) reported that a 3.8% elevation in Hct was associated with a 39% increased risk for stroke, suggesting that high Hct levels are related to an increased risk of cardiovascular outcomes. While the upper limit of Hct level varys, the conclusion is consistently that high hematocrit increases the risk of some cardiovascular disease. In addition, Hct has also been shown to play an important role in blood viscosity and oxygen delivery dynamics. An increased Hct level within normal ranges may be beneficial to the vasculature (8,10-13). This meta-analysis of RCTs was conducted to determine the effects of SGLT2 inhibitors on Hct levels in patients with type 2 diabetes mellitus. We present the following article in accordance with the PRISMA reporting checklist (available at http://dx.doi.org/10.21037/apm-21-1022).

Methods

Search strategy

This meta-analysis was performed according to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) Statement and was registered with the International Prospective Register of Systematic Reviews (CRD42020200699) (14). The following electronic databases were searched from inception to July 2020: Embase, Cochrane Central Register of Controlled Trials (CENTRAL), PubMed, ScienceDirect, Wiley, SpringerLink, and ClinicalTrials.gov. The search terms were as follows: dapagliflozin, canagliflozin, empagliflozin, sotagliflozin, ertugliflozin, ipragliflozin, luseogliflozin, tofogliflozin, SGLT2 inhibitors, and Hct.

Selection criteria

The literature was selected according to the following inclusion criteria: (I) RCTs involving patients with type 2 diabetes mellitus; (II) the study intervention was SGLT2 inhibitor alone or in combination with other antidiabetic drugs (OAD); (III) the study compared SGLT2 inhibitors with OAD or placebo; and (IV) the study measured changes in Hct levels from baseline. Observational studies, cohort studies, trials with less than 4 weeks duration, and trials and with no comparison data were excluded.

Data extraction

Two investigators independently reviewed the titles, abstracts, and full text articles. The following information was collated: first author, year of publication, drug of dosage, intervention drug, comparison (OAD or placebo), total number, baseline Hct, baseline age, baseline hemoglobin (Hb)A1c , baseline body mass index (BMI), duration of therapy, and add-on OAD regimens. Any discrepancies between the two investigators were resolved through discussion and consultation with a third investigator.

Quality assessment

Risk of bias were independently assessed by two investigators according to the Cochrane collaboration tools, and any disagreements were solved by discussion (15). This tool captures six main sources of bias, including random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, and selective reporting. Each item was defined as low risk, high risk, or unclear risk.

Statistical analysis

For continuous variables (such as Hct), pooled weighted

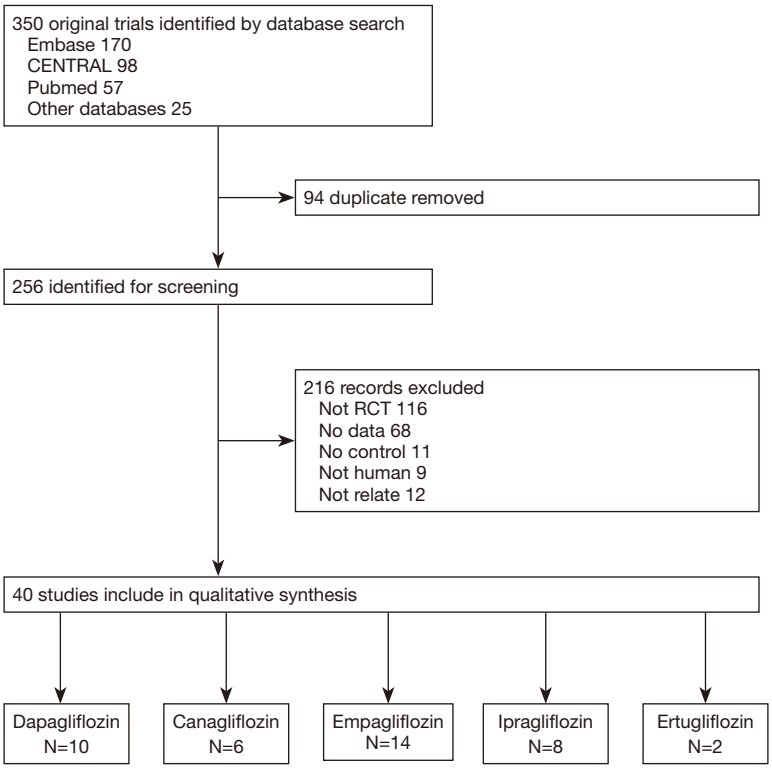

Figure 1 A flowchart summarizing the selection process to identify randomized controlled trials (RCTs) to be included in this meta-analysis.

mean difference (WMD) and 95% confidence interval (CI) between treatment groups were calculated. Heterogeneity between studies was assessed using I^2 statistics. The fixed-effects model was used for analysis if there was no statistical heterogeneity (I^2<50%), otherwise, the random-effects model was used for analysis. Pre-specified subgroup analysis was stratified by type and dosage of SGLT2 inhibitor. The WMD and 95% CI was used to assess the changes in Hct levels from baseline in patients treated with each SGLT2 inhibitor and compared with patients treated with a placebo.

Leave-one-out studies were performed for sensitivity analysis. Meta-regression analyses were performed to evaluate whether the pre-specified covariates of dosage, duration of therapy, add-on therapy, baseline HbA1c, baseline age, and baseline BMI were associated with Hct changes from baseline, corrected for placebo, for each SGLT2 inhibitor. Publication bias was evaluated using Begg's test and Egger's regression analysis. All statistical analyses were conducted with Stata software package (version 12.0; Stata Corp LP, College Station, Texas). The significance level was set at α=0.05.

Results

Summary of the included literature

Figure 1 summarizes the flowchart of the study selection process. A total of 350 articles were identified and 40 RCTs published from 2009 to 2020 were considered appropriate based on the inclusion criteria. Of these, 10 studies compared dapagliflozin with a placebo as monotherapy or add-on OAD, 6 studies compared canagliflozin with a placebo, 14 studies compared empagliflozin with a placebo, 8 studies compared ipragliflozin with a placebo, and 2 studies compared ertugliflozin with a placebo.

The characteristics of the selected trials are shown in *Table 1*. The sample size ranged from 36 to 7,020, totaling 21,050 patients with type 2 diabetes mellitus. The duration of therapy ranged from 4 to 206 weeks. The selected trials enrolled subjects with type 2 diabetes mellitus, hypertension (HP), HF, and chronic kidney disease (CKD).

Risk of bias

Details for the risk of bias assessment are displayed in *Table 2*.

Table 1 The basic information of the included studies involving type 2 diabetes patients

Author	Year	Dose (mg)	Group	n	Baseline Hct (%)	Baseline age (year)	Baseline HbA1c (%)	Baseline BMI (kg/m^2)	Treatment duration	Add-on therapy	Population
List JF	2009	2.5	Dapagliflozin	59	–	55±11	7.6±0.7	32±5	12 w		T2DM
		5	Dapagliflozin	58	–	55±12	8±0.9	32±5			
		10	Dapagliflozin	47	–	54±9	8±0.8	31±5			
		20	Dapagliflozin	59	–	55±10	7.7±0.9	31±5			
		50	Dapagliflozin	56	–	53±10	7.8±1	32±4			
			Placebo	54	–	53±11	7.9±0.9	32±5			
Singh JSS	2020	10	Dapagliflozin	28	40.4±3.9	66.9±7	–	33±5.5	1 y		T2DM, HF
			Placebo	28	41.4±5.4	67.4±6.8	–	32±5.2			
Strojek K	2010	2.5	Dapagliflozin	154	41.97±4.11	59.9±10.1	8.11±0.75	30.0±5.1	24 w	Glimepiride	T2DM
		5	Dapagliflozin	145	41.98±3.23	60.2±9.7	8.12±0.78	29.8±5.2			
		10	Dapagliflozin	151	42.25±3.72	58.9±8.3	8.07±0.79	29.8±5.6			
			Placebo	146	41.83±3.47	60.3±10.2	8.15±0.74	29.7±4.6			
Bailey CJ	2010	2.5	Dapagliflozin	119	42.4±4.0	55±9.3	7.99±0.9	31.6±4.8	24 w	Metformin	T2DM
		5	Dapagliflozin	122	42.1±3.6	54.3±9.4	8.17±0.96	31.4±5			
		10	Dapagliflozin	122	42.8±4	52.7±9.9	7.92±0.82	31.2±5.1			
			Placebo	118	42.6±3.9	53.7±10.3	8.11±0.96	31.8±5.3			
Bailey CJ	2012	1	Dapagliflozin	72	43.18±3.252	53.7±9.04	7.8±0.98	32.53±5.68	24 w		T2DM
		2.5	Dapagliflozin	74	43.26±3.921	53.5±10.61	8.1±1.07	31.13±5.47			
		5	Dapagliflozin	68	42.72±3.82	51.3±11.51	7.9±1.03	30.97±5.68			
			Placebo	68	43.7±3.856	53.5±11.08	7.8±1.12	32.47±4.91			
Bolinder J	2012	10	Dapagliflozin	79	42.1±3.1	60.6±8.2	7.19±0.44	32.1±3.9	24 w	Metformin	T2DM
			Placebo	82	42.1±3.5	60.8±6.9	7.16±0.53	31.7±3.9			
Wilding JPH	2012	2.5	Dapagliflozin	171	40.83±3.78	59.8±7.6	8.46±0.78	33±5.0	24 w	Insulin with/ without OAD	T2DM
		5	Dapagliflozin	171	41.25±3.8	59.3±7.9	8.62±0.89	33±5.3			
		10	Dapagliflozin	163	41.34±3.9	59.3±8.8	8.57±0.82	33.4±5.1			
			Placebo	155	41.75±3.58	58.8±8.6	8.47±0.77	33.1±5.9			
Ji L	2013	5	Dapagliflozin	128	43.73±3.69	53.0±11.07	8.14±0.74	25.17±3.29	24 w	Metformin	T2DM
		10	Dapagliflozin	133	43.93±4.32	51.2±9.89	8.28±0.95	25.76±3.43			
			Placebo	132	43.67±4.03	49.9±10.87	8.35±0.95	25.93±3.64			
Schumm-Draeger PM	2015	2.5	Dapagliflozin	100	41.5±3.741	58.3±9.0	7.77±0.75	33.16±5.16	16 w	Metformin	T2DM
		5	Dapagliflozin	100	41.98±3.286	55.3±9.3	7.78±0.76	33.09±4.94			
		10	Dapagliflozin	99	41.5±3.623	58.5±9.8	7.71±0.71	32.25±5.01			
			Placebo	100	41.44±3.779	58.5±9.4	7.94±0.85	31.74±4.69			

Table 1 (*continued*)

Table 1 (*continued*)

Author	Year	Dose (mg)	Group	n	Baseline Hct (%)	Baseline age (year)	Baseline HbA1c (%)	Baseline BMI (kg/m^2)	Treatment duration	Add-on therapy	Population
Araki E	2016	5	Dapagliflozin	122	–	58.3±9.83	8.26±0.792	26.89±4.93	16 w	Insulin	T2DM
			Placebo	60	–	57.6±9.86	8.52±0.937	26.12±3.485			
Inagaki N	2014	100	Canagliflozin	90	–	58.4±10.4	7.98±0.73	25.59±4.2	16 w		T2DM
		200	Canagliflozin	89	–	57.4±11.1	8.04±0.74	25.43±4.18			
			Placebo	93	–	58.2±11	8.04±0.7	25.85±4.39			
Inagaki N	2016	100	Canagliflozin	73	42.77±3.57	59.7±9.4	8.89±0.81	26.88±4.82	16 w	Insulin	T2DM
			Placebo	66	43.63±4.02	56.1±10.9	8.85±0.84	25.99±4.40			
Sha S	2014	300	Canagliflozin	17	41.6±3.09	63.3±4	7.6±0.5	29.4±3.5	12 w	Metformin with/without OAD	T2DM
			Placebo	18	41.6±3.24	62.3±6.8	7.7±0.6	31.2±3.1			
Rosenstock J	2012	100	Canagliflozin	64	–	51.7±8	7.83±0.96	31.7±5	12 w		T2DM
		300	Canagliflozin	64	–	52.3±6.9	7.69±1.02	31.6±4.9			
			Placebo	65	–	53.3±7.8	7.75±0.83	30.6±4.6			
Yale JF	2013	100	Canagliflozin	69	40.1	69.5±8.2	7.9±0.9	32.4±5.5	26 w		T2DM
		300	Canagliflozin	76	39.2	67.9±8.2	8.0±0.8	33.4±6.5			
			Placebo	62	40.8	68.2±8.4	8.0±0.9	33.1±6.5			
Forst T	2014	100	Canagliflozin	93	41.1	56.7±10.4	8.0±0.9	32.3±6.2	52 w	Pioglitazone and metformin	T2DM
		300	Canagliflozin	87	40.4	57.0±10.2	7.9±0.9	32.8±7.7			
			Placebo	77	41.6	58.3±9.6	8.0±1.0	32.5±6.4			
Hafring HU	2015	10	Empagliflozin	225	41.8±5	57±9.2	8.1±0.8	28.3±5.4	52 w	Metformin and sulfonylurea	T2DM
		25	Empagliflozin	216	42.2±4.1	57.1±9.2	8.1±0.8	28.3±5.5			
			Placebo	225	41.7±4.3	56.9±9.2	8.2±0.8	27.9±4.9			
Kovacs CS	2015	10	Empagliflozin	165	41.6±5	54.7±9.9	8.07±0.89	29.2±5.6	24 w	Pioglitazone with/without metformin	T2DM
		25	Empagliflozin	168	40.5±5.3	54.2±8.9	8.06±0.82	29.1±5.5			
			Placebo	165	40.6±4.9	54.6±10.5	8.16±0.92	29.3±5.4			
Merker L	2015	10	Empagliflozin	217	42.4±4.4	55.5±9.9	7.9±0.8	29.1±5.5	72 w	Metformin	T2DM
		25	Empagliflozin	214	41.9±4.7	55.6±10.2	7.9±0.9	29.7±5.7			
			Placebo	207	42.1±4.3	56±9.7	7.9±0.9	28.7±5.2			
Rosenstock J	2015	10	Empagliflozin	169	41.4±4.1	58.6±9.8	8.3±0.8	32.1±5.8	78 w	Insulin with/without metformin	T2DM
		25	Empagliflozin	155	41.4±3.8	59.9±10.5	8.3±0.8	32.7±5.9			
			Placebo	170	41.5±4.3	58.1±9.4	8.2±0.8	31.8±6			

Table 1 (*continued*)

Table 1 (*continued*)

Author	Year	Dose (mg)	Group	n	Baseline Hct (%)	Baseline age (year)	Baseline HbA1c (%)	Baseline BMI (kg/m^2)	Treatment duration	Add-on therapy	Population
Søfteland E	2017	10	Empagliflozin	112	42.3±5.4	54.3±9.6	7.97±0.84	31.2±5.9	24 w	Metformin and linagliptin	T2DM
		25	Empagliflozin	111	42.1±4.4	55.4±9.9	7.97±0.82	29.9±5.3			
			Placebo	110	42.7±5.1	55.9±9.7	7.97±0.85	29.6±5.7			
Roden M	2015	10	Empagliflozin	224	43.6±4.4	56.2±11.6	7.87±0.88	28.3±5.5	76 w		T2DM
		25	Empagliflozin	224	43.8±4.7	53.8±11.6	7.86±0.85	28.2±5.5			
			Placebo	228	43.4±4.7	54.9±10.9	7.91±0.78	28.7±6.2			
Zinman B	2015	10	Empagliflozin	2,345	41.2±5.6	63.0±8.6	8.07±0.86	30.6±5.2	2.6 y	Mono/add-on OAD	T2DM
		25	Empagliflozin	2,342	41.3±5.7	63.2±8.6	8.06±0.84	30.6±5.3			
			Placebo	2,333	41.1±5.7	63.2±8.8	8.08±0.84	30.7±5.2			
Kadowaki T	2014	5	Empagliflozin	110	45.7±4.6	57.3±11.2	7.92±0.70	26.3±4.2	12 w		T2DM
		10	Empagliflozin	109	45.5±4.7	57.9±9.4	7.93±0.71	25.3±4.4			
		25	Empagliflozin	109	45.4±4.7	57.2±9.7	7.93±0.78	25.1±3.8			
		50	Empagliflozin	110	45.1±4.8	56.6±10.3	8.02±0.65	25.0±3.6			
			Placebo	109	45.6±4.5	58.7±8.7	7.94±0.74	25.6±3.4			
Ridderstrale M	2014	25	Empagliflozin	765	42.8±4.8	56.2±10.3	7.92±0.81	29.9±5.3	104 w	Metformin	T2DM
			Placebo	780	42.6±5.2	55.7±10.4	7.92±0.86	30.3±5.3			
Barnett AH	2014	10	Empagliflozin	98	41.5±4.8	63.2±8.5	8.02±0.84	32.4±5.4	52 w		T2DM, CKD 2-4
		25	Empagliflozin	97	41.3±3.5	62.0±8.4	7.96±0.73	31.3±5.8			
			Placebo	97	42.2±5	62.6±8.1	8.09±0.80	30.8±5.6			
		25	Empagliflozin	188	38.7±6.3	64.9±8.5	7.96±0.73	30.2±5.3			
			Placebo	187	40.1±6	65.1±8.2	8.09±0.80	30.3±5.3			
		25	Empagliflozin	37	35.5±8.2	64.1±11.1	8.11±1.01	30.4±5.6			
			Placebo	37	34.5±8.4	62.9±11.9	8.16±0.99	31.8±6.0			
Araki E	2015	10	Empagliflozin	136	42.3±4.6	61.3±9.9	7.99±0.73	24.6±3.8	52 w	OAD	T2DM
		25	Empagliflozin	137	42.4±4.5	61.8±9.6	8.06±0.76	25.2±4.2			
			Placebo	63	42.7±4.6	60.0±10.2	7.93±0.79	25.2±3.6			
DeFronzo RA	2015	10	Empagliflozin	137	41.6±4.3	56.1±10.5	8.00±0.93	30.9±5.4	52 w		T2DM
		25	Empagliflozin	140	41.9±5	55.5±10.0	8.02±0.83	31.8±5.3			
			Placebo	128	41.3±5.5	56.2±10.0	8.02±0.90	30.6±5.4			
Nishimura R	2015	10	Empagliflozin	20	43.6±4.2	64.8±5.9	7.99±0.83	24.1±3.7	28d		T2DM
		25	Empagliflozin	19	43.3±2.8	62.6±7.8	7.73±0.75	24.0±3.2			
			Placebo	21	42.3±4.1	60.7±10.8	8.00±0.82	24.9±2.8			

Table 1 (*continued*)

Table 1 (*continued*)

Author	Year	Dose (mg)	Group	n	Baseline Hct (%)	Baseline age (year)	Baseline HbA1c (%)	Baseline BMI (kg/m^2)	Treatment duration	Add-on therapy	Population
Tikkanen I	2015	10	Empagliflozin	276	41±3	60.6±8.5	7.87±0.77	32.4±5.3	12 w		T2DM, HP
		25	Empagliflozin	276	41±4	59.9±9.7	7.92±0.72	33.0±5.0			
			Placebo	271	42±3	60.3±8.8	7.90±0.72	32.4±4.9			
Kashiwagi A	2014	12.5	Ipragliflozin	73	–	55.3±10.2	8.39±0.9	25.6±3.5	12 w		T2DM
		25	Ipragliflozin	74	–	57±10.4	8.32±0.83	26.2±4.0			
		50	Ipragliflozin	72	–	55.9±11.4	8.33±0.8	25.8±3.5			
		100	Ipragliflozin	72	–	56±10.4	8.25±0.76	25.9±3.8			
			Placebo	69	–	55.2±9.7	8.36±0.79	25.1±3.4			
Lu CH	2016	50	Ipragliflozin	87	–	53.9±11.3	7.74±0.78	26.57±4.3	24 w	Metformin	T2DM
			Placebo	83	–	53.4±11.3	7.75±0.71	27.04±4.06			
Kashiwagi A	2014	50	Ipragliflozin	165	43.86±4.097	59.6±10.02	8.38±0.641	25.81±3.604	24 w	Sulfonylurea	T2DM
			Placebo	75	43.36±3.479	59.8±8.58	8.34±0.727	24.18±2.969			
Kashiwagi A	2015	50	Ipragliflozin	96	43.44±3.758	56.2±10.22	8.24±0.670	27.11±3.851	24 w	Pioglitazone	T2DM
			Placebo	54	43.16±3.608	56.1±11.91	8.39±0.644	27.13±4.312			
Kashiwagi A	2015	50	Ipragliflozin	62	42.54±4.37	60.6±9.4	8.40±0.86	25.3±3.1	16 w		T2DM
			Placebo	67	43.07±3.81	58.3±10.5	8.25±0.68	25.6±3.9			
Wilding JPH	2012	12.5	Ipragliflozin	60	–	56.6±8.5	7.78±0.64	31.9±4.9	12 w		T2DM
		50	Ipragliflozin	62	–	58.6±7.6	7.76±0.66	31.1±4.9			
		150	Ipragliflozin	59	–	58.1±8.2	7.73±0.69	31.8±5.2			
		300	Ipragliflozin	59	–	56.6±8.9	7.87±0.82	31.8±4.6			
			Placebo	55	–	57.3±8.6	7.68±0.60	32.0±4.8			
Han KH	2018	50	Ipragliflozin	74	–	57.62±8.26	7.90±0.69	25.50±3.07	24 w	Metformin and sitagliptin	T2DM
			Placebo	68	–	57.44±7.88	7.92±0.79	26.05±3.79			
Kashiwagi A	2014	50	Ipragliflozin	118	40.89±4.414	63.9±6.59	7.53±0.538	25.84±3.450	24 w		T2DM
			Placebo	46	41.24±4.551	65.7±6.93	7.55±0.526	24.96±3.362			
Aronson R	2018	5	Ertugliflozin	128	46.02±4.4	56.8±11.4	8.2±0.9	33.2±7.4	52 w		T2DM
		15	Ertugliflozin	120	46.09±3.83	56.2±10.8	8.4±1.1	32.5±5.7			
			Placebo	111	43.43±3.83	56.1±10.9	8.1±0.9	33.3±6.8			
Gallo S	2019	5	Ertugliflozin	162	41.92±3.9	56.6±8.2	8.06±0.89	31.1±4.8	104 w		T2DM
		15	Ertugliflozin	163	42.12±3.88	56.9±9.4	8.13±0.93	31.4±4.6			
			Placebo	145	42.26±3.95	56.5±8.7	8.17±0.90	31.0±4.7			

Values are shown as mean ± standard deviation. –, no data; BMI, body mass index; d, day; w, week; y, year; T2DM, type 2 diabetes mellitus; OAD, other antidiabetic drugs; CKD, chronic kidney disease; HP, hypertension.

Table 2 Risk of bias assessment of the included studies according to the Cochrane guideline

Study	Sequence generation	Allocation concealment	Blinding of participants, personnel	Outcome assessors	Incomplete outcome data	Selective outcome reporting	Other bias
List JF 2009	U	U	L	U	L	L	L
Singh JSS 2020	U	U	U	U	L	L	U
Strojek K 2010	L	L	L	L	L	L	L
Bailey CJ 2010	L	L	L	L	L	L	L
Bailey CJ 2012	L	L	L	L	L	L	L
Wilding JPH 2012	L	L	L	L	L	L	L
Ji L 2014	L	L	L	U	L	L	L
Schumm-Draeger PM 2015	L	L	L	L	L	L	L
Araki E 2016	U	U	L	U	L	L	U
Bolinder J 2012	L	L	L	U	L	L	L
Inagaki N 2014	L	L	L	L	L	L	L
Inagaki N 2016	L	L	L	L	L	L	U
Sha S 2014	H	U	L	U	L	L	U
Rosenstock J 2012	U	U	L	L	L	L	U
Yale JF 2013	L	L	L	L	L	L	L
Forst T 2014	L	L	L	L	L	L	L
Haering HU 2015	U	U	L	L	L	L	U
Kovacs CS 2015	L	L	L	U	L	L	L
Merker L 2015	U	U	L	U	L	L	U
Rosenstock J 2015	L	L	L	U	H	L	L
Søfteland E 2017	L	L	L	L	L	L	L
Roden M 2015	U	U	L	U	L	L	U
Zinman B 2015	L	L	L	U	L	L	L
Kadowaki T 2014	L	L	L	U	L	L	L
Ridderstrale M 2014	L	L	L	L	L	L	L
Barnett AH 2014	L	L	L	L	L	L	L
Araki E 2015	L	L	L	U	L	L	L
Defronzo RA 2015	L	L	L	U	L	L	L
Nishimura R 2015	U	U	L	U	H	L	U
Tikkanen I 2015	L	L	L	U	H	L	L
Kashiwagi A 2014	U	U	L	L	U	L	U
Lu CH 2016	L	L	L	L	L	L	L
Kashiwagi A 2014	L	L	L	L	L	L	L
Kashiwagi A 2015	L	L	L	L	L	L	L
Kashiwagi A 2015	H	U	L	U	L	L	U
Wilding JPH 2012	H	U	L	L	L	L	L
Han KH 2018	L	L	L	L	L	L	L
Kashiwagi A 2014	H	L	L	L	U	L	U
Aronson R 2018	L	L	L	L	U	L	L
Gallo S 2019	L	L	L	L	L	L	L

L, low risks of bias; H, high risks of bias; U, unclear risks of bias.

The majority of included studies had a low risk of bias for random sequence generation, allocation concealment, and blinding of participants and personnel. However, 17 included studies showed insufficient information regarding blinding of outcome assessment. Additionally, 3 clinical trials showed a high risk of bias for incomplete outcome data, and 3 clinical trials had an uncleared risk of bias. Finally, all studies showed a low risk of bias for selective outcome reporting. There was no evidence of publication bias, as demonstrated by Begg's test (P=0.898) and Egger's regression analysis (P=0.162).

The effect of SGLT2 inhibitors on Hct levels

This meta-analysis demonstrated that overall, the SGLT2 inhibitors caused a significant increase in Hct levels (WMD 2.67%, 95% CI, 2.53 to 2.82, I^2=98.5%, P<0.001). Furthermore, each of the following SGLT2 inhibitors significantly increased Hct levels, including dapagliflozin (WMD 2.25%, 95% CI, 2.02 to 2.48, I^2=99.5%, P<0.001), canagliflozin (WMD 2.63%, 95% CI, 2.30 to 2.96, I^2=83.7%, P<0.001), and empagliflozin (WMD 3.42%, 95% CI, 3.09 to 3.75, I^2=86.8%, P<0.001). Ipragliflozin (WMD 1.85%, 95% CI, 1.62 to 2.07, I^2=0%, P>0.05), and ertugliflozin (WMD 2.45%, 95% CI, 2.14 to 2.76, I^2=0%, P>0.05) only slightly increased Hct levels. Details are presented in *Figure 2*.

The Hct level increased slightly more in high-dose patients compared to low-dose patients. Compared with placebo, dapagliflozin at 2.5, 5, and 10 mg led to a significant increase in Hct levels (WMD 1.96%, 2.27%, and 2.47%, respectively; P<0.001; *Figure 3*). Treatment with canagliflozin 100 and 300 mg also resulted in a notable increase in Hct levels (WMD 2.91% and 2.94%, respectively; P<0.001; *Figure 4*). Patients treated with empagliflozin at 10 and 25 mg also demonstrated an apparent increase in Hct levels (WMD 3.39% and 3.44%, respectively; P<0.001; *Figure 5*). However, treatment with ipragliflozin at 12.5 and 50 mg (WMD 1.26% and 1.98%, respectively; P>0.05; *Figure 6*) and treatment with ertugliflozin at 5 and 15 mg (WMD 2.24% and 2.64%, respectively; P>0.05; *Figure 7*) only resulted in a slight increase in Hct levels.

Sensitivity analysis and meta-regressions

The sensitivity analysis demonstrated that all included trials showed a similar consistent trend with the pooled analysis, and none of the studies were omitted. Several meta-regression analyses were performed to evaluate whether the pre-specified covariates of dosage, duration of therapy, add-on therapy, baseline HbA1c, baseline age, and baseline BMI were associated with Hct changes from baseline, corrected for placebo, for each SGLT2 inhibitor. In patients who received canagliflozin treatment, the increase in Hct levels was associated with the duration of therapy. In patients who received empagliflozin treatment, elevated Hct levels were associated with add-on therapy. No other associations were detected between each SGLT2 inhibitor and the aforementioned factors. β coefficients and P values are shown in *Table 3*.

Discussion

The present meta-analysis of 40 RCTs quantified the ability of SGLT2 inhibitors to increase Hct levels in patients with type 2 diabetes mellitus. Dapagliflozin, canagliflozin, and empagliflozin significantly increased the levels of Hct, while ipragliflozin and ertugliflozin led to a slight increase, suggesting that SGLT2 inhibitors displayed a class effect. The increase in Hct levels was slightly more pronounced at high doses compared to low doses.

Previous studies have shown the ability of SGLT2 inhibitors to increase Hct levels from baseline (16). This meta-analysis demonstrated that SGLT2 inhibitors may have a class effect on Hct levels, with empagliflozin exerting the largest increase in Hct levels, followed by canagliflozin, ertugliflozin, dapagliflozin, and ipragliflozin.

There are several possible mechanisms by which SGLT2 inhibitors increase Hct levels. Sano *et al.* attributed the Hct increase to diuretic effects (17). This latter study demonstrated that SGLT2 inhibitors increased urine volume, reaching a peak at 24 hours and recovering to baseline about 1 week later, while the Hct continued to increase beyond 2 months (17). Lambers Heerspink *et al.* (18) suggested that the increase in Hct was related to erythropoiesis. Treatment with dapagliflozin increased erythropoietin levels, reaching a peak range at 2 to 4 weeks after treatment. Meanwhile, the number of reticulocytes was elevated, followed by an increase in hemoglobin and Hct levels. Under normal conditions, fibroblasts near the proximal tubule in the kidneys produce erythropoietin. When proximal tubular epithelial cells are selectively injured, this induces the transdifferentiation of fibroblasts into myofibroblasts, thereby reducing the production of erythropoietin (13,17). SGLT2 inhibitors improve ATP

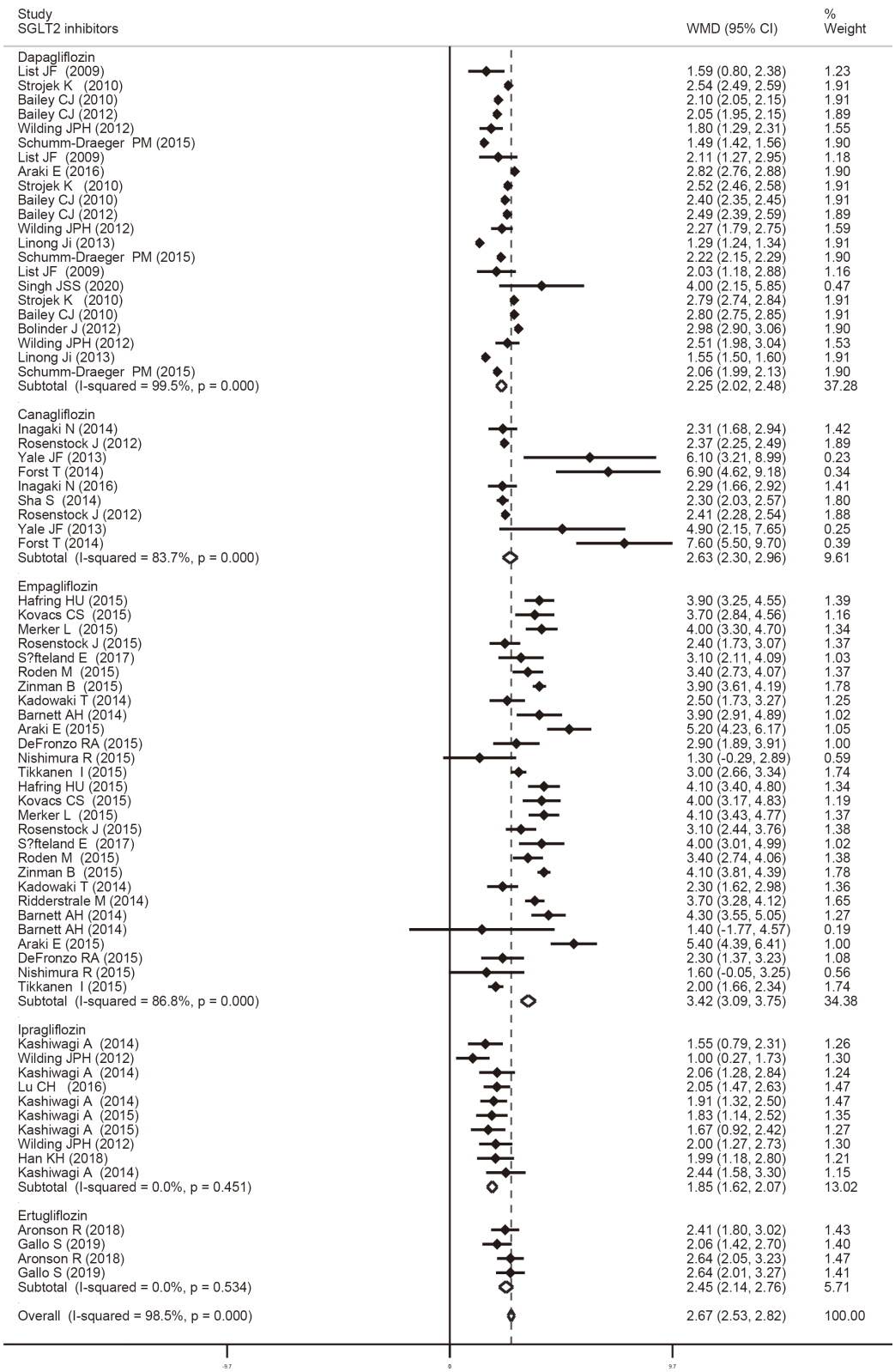

Figure 2 The weighted mean difference (WMD) and 95% confidence intervals (CI) for the effects of SGLT2 inhibitors on hematocrit levels, stratified by dosage. SGLT2, sodium glucose co-transporter 2.

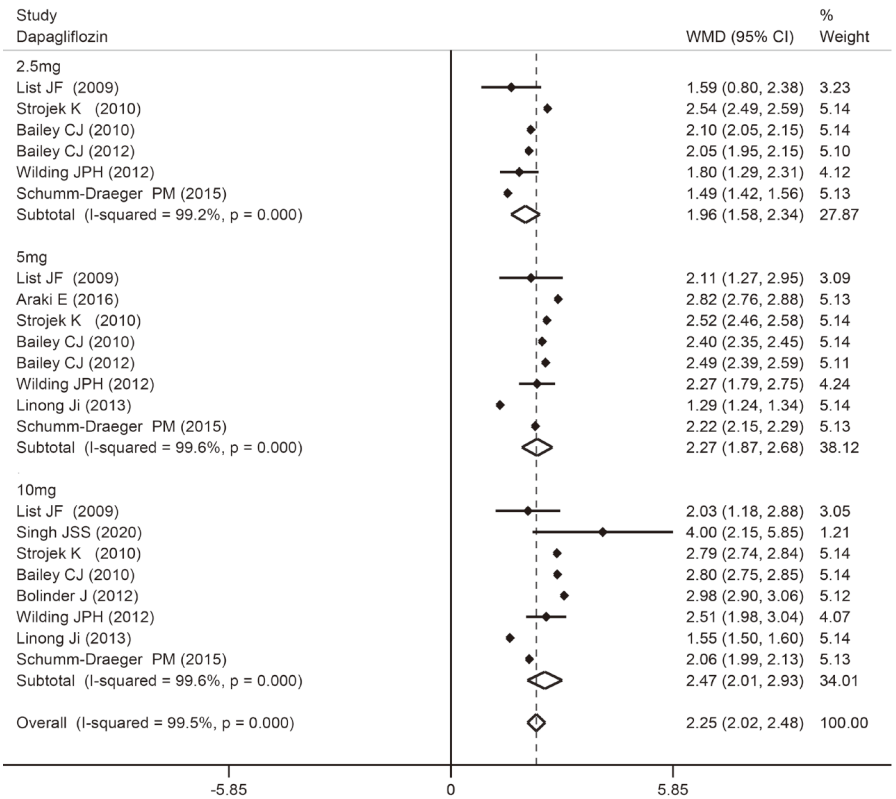

Figure 3 The weighted mean difference (WMD) and 95% confidence intervals (CI) for the effects of dapagliflozin treatment on Hct levels, stratified by dosage.

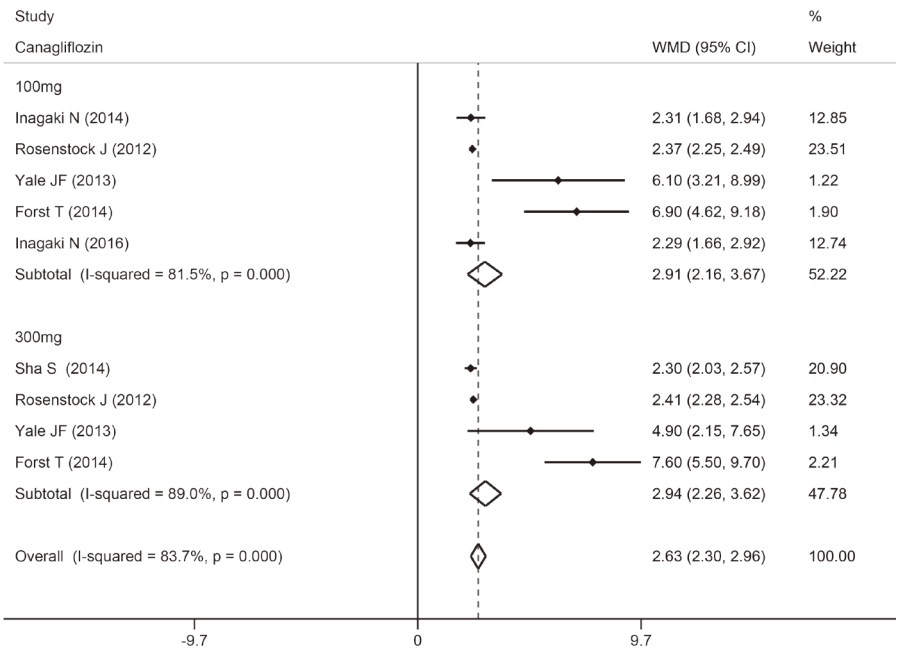

Figure 4 The weighted mean difference (WMD) and 95% confidence intervals (CI) for the effects of canagliflozin treatment on Hct levels, stratified by dosage.

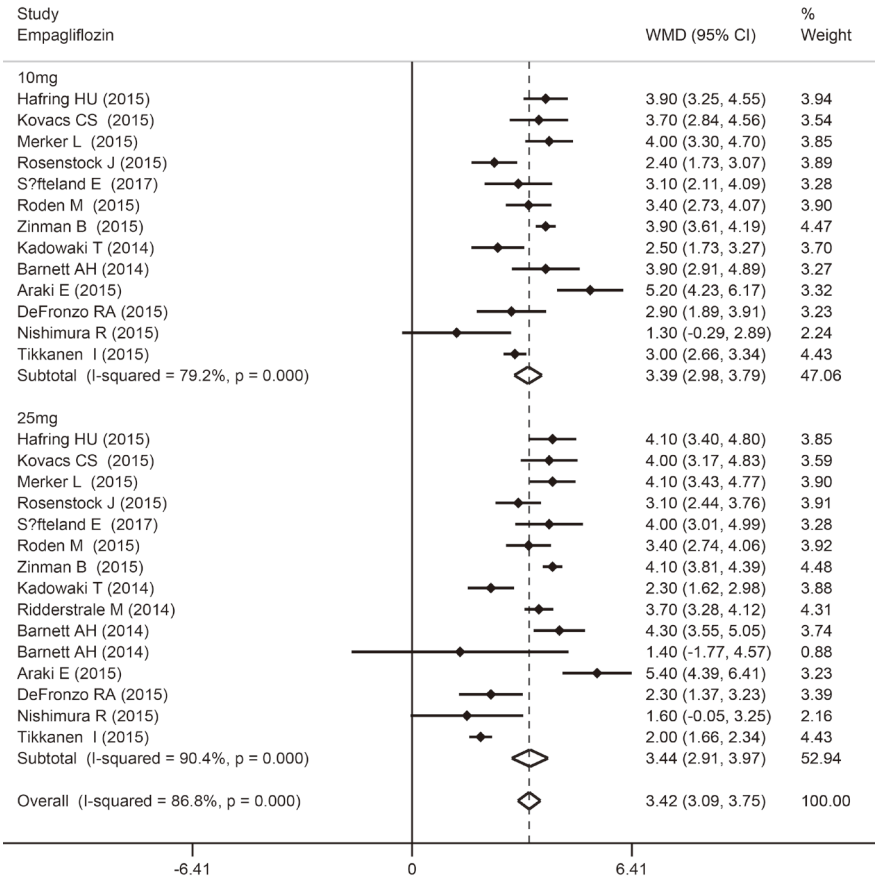

Figure 5 The weighted mean difference (WMD) and 95% confidence intervals (CI) for the effects of empagliflozin treatment on Hct levels, stratified by dosage.

consumption via the sodium/potassium (Na^+/K^+) pump and mitigate metabolic stress to the proximal tubular epithelial cells, which may reverse the transdifferentiating fibroblasts into erythropoietin-producing fibroblasts, thereby increasing Hct levels (19-21).

Several limitations of this meta-analysis should be considered. First, the inclusion criteria and the baseline characteristics, such as ethnicity, age, BMI, HbA1c, baseline Hct, duration of therapy, and add-on therapy, may vary across studies resulting in a high level of heterogeneity. While the random-effects model, sensitivity analyses, and several meta-regression analyses were performed, these results should be interpreted with caution. The inter-study heterogeneity of ipragliflozin and ertugliflozin were low , and thus the related meta-regressions could not be conducted. Second, the complete data set was not available for all studies. For example, in the study by Yale and colleagues (5), 100 and 300 mg canagliflozin were compared with the same placebo group. Finally, ertugliflozin was only included in two studies. Therefore, future clinical trials are warranted to comprehensively determine the effects of ertugliflozin treatment on Hct levels.

In conclusion, SGLT2 inhibitors demonstrated a class effect by increasing Hct levels. Empagliflozin had the most significantly effect on Hct levels, followed by canagliflozin, ertugliflozin, dapagliflozin, and ipragliflozin. Hence, it can be suggested that patients with high baseline Hct or excessive Hct elevation should be carefully treated with SGLT2 inhibitors. However, further clinical trials are necessary to clarify these results.

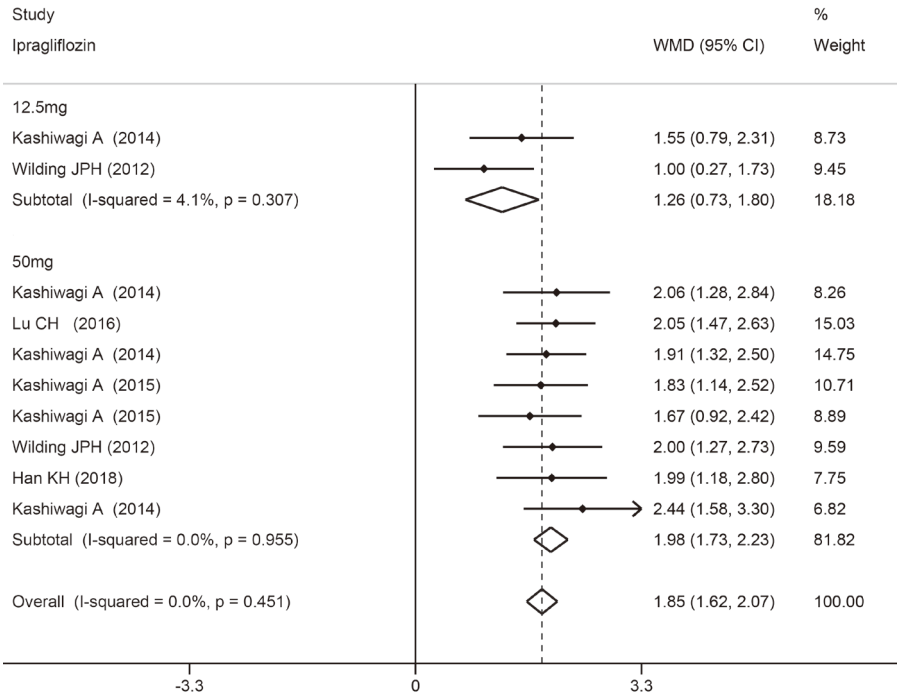

Figure 6 The weighted mean difference (WMD) and 95% confidence intervals (CI) for the effects of ipragliflozin treatment on Hct levels, stratified by dosage.

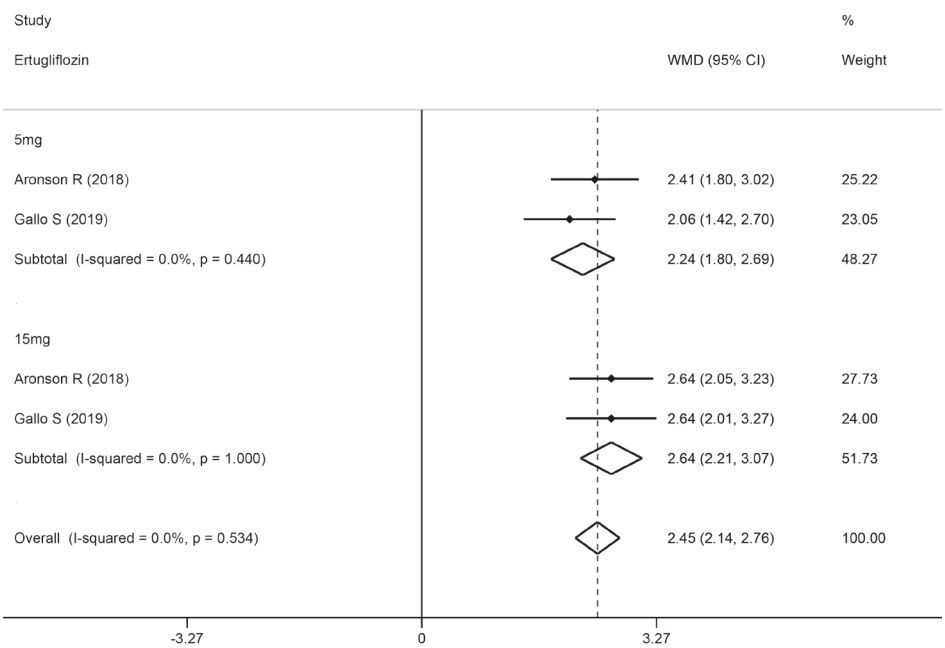

Figure 7 The weighted mean difference (WMD) and 95% confidence intervals (CI) for the effects of ertugliflozin treatment on Hct levels, stratified by dosage.

Table 3 Meta-regression analysis of the association between changes in hematocrit (Hct), corrected for placebo, and dosage, duration of therapy, add-on therapy, baseline HbA1c, baseline age, and baseline body mass index (BMI) for a specific sodium glucose co-transporter (SGLT) 2 inhibitor (β coefficient values and P values are displayed)

Variables	Dapagliflozin	Canagliflozin	Empagliflozin
Dosage	0.07 (0.068)	0.002 (0.827)	0.005 (0.839)
Duration of therapy	0.88 (0.116)	2.53 (0.001)	0.28 (0.053)
Add-on therapy	−0.15 (0.57)	1.14 (0.476)	0.89 (0.009)
Baseline HbA1c	−0.12 (0.642)	0.90 (0.603)	0.34 (0.359)
Baseline age	0.69 (0.057)	0.41 (0.817)	0.47 (0.229)
Baseline BMI	0.09 (0.738)	2.4 (0.113)	−0.38 (0.294)

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Footnote

Reporting Checklist: The authors have completed the PRISMA reporting checklist. Available at http://dx.doi.org/10.21037/apm-21-1022

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/apm-21-1022). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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