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Original article

Efficacy and safety of combination therapy with SGLT2 and DPP4 inhibitors in the treatment of type 2 diabetes: A systematic review and meta-analysis

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ABSTRACT

Background. – This review evaluated the efficacy and safety of a combination therapy comprising a sodium-glucose cotransporter type 2 inhibitor (SGLT2i) and dipeptidyl peptidase-4 inhibitor (DPP4i) in type 2 diabetes.
Methods. – A literature search through to May 2017 was carried out of PubMed, Embase and the Cochrane Central Register of Controlled Trials. Studies were eligible if they were randomized controlled trials (RCTs) comparing SGLT2i plus DPP4i (SGLT2i/DPP4i) against DPP4i ± placebo or SGLT2i ± placebo and published in English. The primary outcome was change in HbA_{1c} from baseline.
Results. – Eight RCTs comparing SGLT2i/DPP4i and DPP4i, and five RCTs comparing SGLT2i/DPP4i and SGLT2i, with three RCTs involving both comparisons, were included in the present review. SGLT2i/DPP4i resulted in a greater mean HbA_{1c} reduction [weighted mean difference (WMD)]: −0.62%] than did DPP4i alone, which was a much less marked reduction (WMD: −0.35%) than with SGLT2i alone. Also, significant differences in body weight loss from baseline were observed only with SGLT2i/DPP4i vs. DPP4i, but not vs. SGLT2i. The risk of hypoglycaemic events was low and similar between treatment groups. When subjects were stratified based on baseline HbA_{1c}, any reduction by SGLT2i/DPP4i in relation to DPP4i was proportional to baseline HbA_{1c} levels. However, compared with SGLT2i, HbA_{1c} reductions with SGLT2i/DPP4i were modest regardless of baseline HbA_{1c}.
Conclusion. – Combination therapy with SGLT2i and DPP4i is both efficacious and safe. In particular, a marked additional glucose-lowering effect is evident when SGLT2i is combined with or added to DPP4i, and not vice versa. However, baseline HbA_{1c} determined the additional glucose-lowering effects of SGLT2i in combined treatment with DPP4i.

Introduction

Many pharmacotherapies are now available for glycaemic control in type 2 diabetes (T2D); however, the management of T2D remains complex and challenging, in part due to the limiting side-effects of current therapies as well as the variable pathogenesis and progressive natural history of T2D [1]. Thus, the quest to develop therapeutic agents with novel mechanisms of action that might

Abbreviations: CI, confidence interval; CVD, cardiovascular disease; DPP4i, dipeptidyl peptidase-4 inhibitor; EGP, endogenous glucose production; FPG, fasting plasma glucose; INS, insulin; OADs, oral antidiabetic drugs; PCB, placebo; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCT, randomized controlled trial; SBP, systolic blood pressure; SGLT2i, sodium-glucose cotransporter type 2 inhibitor; T2D, type 2 diabetes; WMD, weighted mean difference.

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fulfill the unmet needs of the currently available therapies continues. While several novel therapies for T2D are indeed on the horizon, dipeptidyl peptidase-4 inhibitors (DPP4is) and sodium-glucose cotransporter type 2 inhibitors (SGLT2is) are the most recently introduced novel classes of antihyperglycaemic drugs [2].

DPP4is improve glycaemic control by increasing insulin secretion from pancreatic β-cells and decreasing glucagon secretion from pancreatic α-cells, thereby reducing endogenous glucose production (EGP) [3,4]. Placebo-controlled trials of DPP4is have reported that this class of drug as monotherapy improves HbA_{1c} by an average 0.6–0.7% (6.6–7.6 mmol/mol), and has a low risk of hypoglycaemia with weight neutrality [5–7]. SGLT2is reduce plasma glucose concentrations by inhibiting renal glucose reabsorption and promoting urinary glucose excretion, which is also accompanied by weight loss of approximately 2–3 kg due to the resultant negative energy balance [8,9]. Meta-analyses of placebo-controlled trials have demonstrated that an SGLT2i as monotherapy improves glucose control with a 0.5–1.0% (5.4–10.9 mmol/mol) decrease in HbA_{1c} [4,10–12], and a low risk of hypoglycaemia unless co-administered with insulin or insulin secretagogues [4,13].

However, as monotherapy can only marginally address the multiple pathophysiological defects of T2D, its effective treatment eventually requires a combination or sequential addition of glucose-lowering agents [14,15]. In this context, the combination of an SGLT2i with a DPP4i is ideal for T2D therapy, as their complementary mechanisms of action can address multiple pathophysiological disorders [2,4,8,16]. In addition, these agents have no related adverse events or toxicities, and neither agent increases the risk of hypoglycaemia [4,13,17]. Furthermore, this combination therapy has the potential benefit of weight loss, as SGLT2is lead to modest weight reduction whereas DPP4is are weight-neutral [9,17].

Although SGLT2i/DPP4i combination therapy has been reported to obtain greater improvement in glycaemic control than each individual component on its own, the glucose-lowering effects are not additive and far from synergistic with respect to HbA_{1c} reduction [18–20]. The following questions then arise: (1) how efficacious will each individual agent be when combined? (2) Which subset of patients will benefit the most from this combined treatment approach? Therefore, the place of each agent in combination therapy in the management of T2D needs to be more precisely elucidated.

In light of these issues, our present review aimed to evaluate this newest combination therapy available of an SGLT2i plus DPP4i, with particular focus on the respective efficacy and safety of each agent on its own. For this purpose, a meta-analysis was performed of randomized controlled trials (RCTs) comparing the efficacy of SGLT2i/DPP4i vs. that of either a DPP4i or a SGLT2i.

Materials and methods

Search strategy and study selection

In preparation of our present meta-analysis, the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist was implemented [21], and a comprehensive search made of PubMed, Embase and the Cochrane Library databases from their inception through to 31 May 2017 to identify eligible studies: RCTs in which the efficacy and safety of SGLT2i/DPP4i as combined treatment were investigated. The search terms are presented in Table S1 (see supplementary material associated with this article online). Also included were RCTs comparing SGLT2i/DPP4i with DPP4i ± placebo or SGLT2i ± placebo. RCTs published in English with at least 12-week follow-up periods and information on HbA_{1c} changes from baseline and results were eligible for inclusion. Studies of extended phases were excluded. Study titles, abstracts and full texts were investigated to confirm whether they met the inclusion criteria. Any disagreements between the examining authors (Y.K.C. and C.H.J.) were resolved by consensus. A flowchart of the study selection process is presented in Fig. S1 (see supplementary material associated with this article online).

Data extraction

The primary outcome was change in HbA_{1c} from baseline to the primary endpoint of each study. Secondary outcomes were changes in fasting plasma glucose (FPG) and body weight, the proportion of subjects achieving the therapeutic goal of an $HbA_{1c} < 7.0\%$ (< 53.0 mmol/mol) and the risk of hypoglycaemia at the same time point as for evaluating the primary endpoint of each study. For studies in which no change from baseline was reported, such changes were calculated as the difference between values at baseline and at the end of treatment. FPG values in mmol/L were converted to mg/dL using the following formula: 1 mmol/L = 18 mg/dL. The various definitions of hypoglycaemia used in the different studies are presented in Table S2 (see supplementary material associated with this article online). In addition to outcome measures, two of the present authors (Y.K.C. and C.H.J.) extracted author and publication-year data for each study as well as any background antidiabetic medications besides SGLT2i or DPP4i, duration of treatment, number of randomized subjects, age, percentage of male participants, body mass index (BMI) and baseline HbA_{1c}. For dose-ranging studies, only the approved maximum doses of the combined or added drugs were selected. For example, although background treatments consisted of two doses (10 mg and 25 mg) of empagliflozin in Tinahones et al. [22], both treatment arms were included, as the added dose of linagliptin was 5 mg, the maximum approved dose. Two authors (Y.K.C. and C.H.J.) independently performed data extraction according to a pre-specified protocol, with any discrepancies resolved by consensus between themselves.

Assessment of methodological quality

The quality of the included RCTs was evaluated according to the Cochrane Collaboration tool for assessing risk of bias [23]. The two independent reviewers (Y.K.C. and C.H.J.) conducted this assessment, and any disagreements were discussed until consensus was reached. A summary of these results is presented in Table S3 (see supplementary material associated with this article online) and Fig. S2 (see supplementary material associated with this article online).

Statistical analysis

Pooled estimates of the weighted mean difference (WMD) and 95% confidence intervals (CIs) were calculated for continuous outcomes, including changes in HbA_{1c}, FPG, body weight and systolic blood pressure (SBP), as well as pooled risk ratios (RRs) and their 95% CIs for dichotomous outcomes, including the proportion of subjects achieving target HbA_{1c}, and risks of hypoglycaemia and genital infections. Studies were combined using a random-effects model, and summary results represented by forest plots. Statistical heterogeneity between studies was evaluated using I^2 statistics. The potential risk of publication bias was evaluated by constructing funnel plots of the primary outcome, with asymmetry assessed by Egger's test. Also, to explore heterogeneity, subgroup analyses were performed of HbA_{1c} reductions, using a baseline HbA_{1c} level of 8.0–8.5% (63.9–69.4 mmol/mol) as the cut-off. Stata version

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11 software (StataCorp LP, College Station, TX, USA) was used for all statistical analyses.

Results

Search results and characteristics

A total of 558 citations for SGLT2i/DPP4i combination therapy were identified through our electronic literature search, of which eight were eligible RCTs involving a total of 2220 T2D patients and investigating the combined efficacy and safety of SGLT2i/DPP4i vs. DPP4i, and five were eligible RCTs involving 1681 T2D patients and investigating the combined efficacy and safety of SGLT2i/DPP4i vs. SGLT2i. Three RCTs [18–20] were included in both meta-analyses as they included both comparisons (SGLT2i/DPP4i vs. DPP4i and SGLT2i/DPP4i vs. SGLT2i). In these three RCTs, the combined efficacy and safety of SGLT2i/DPP4i was evaluated as simultaneous combination treatment vs. DPP4i or SGLT2i alone in metformin-treated (≥ 1500 mg/day) [18,20] or treatment-naïve [19] patients with T2D. In the other seven RCTs [22,24–29], the additional efficacy and safety of SGLT2i [24–28] or DPP4i [22,29] were compared with the equivalent dose of placebo in the metformin-treated (≥ 1500 mg/day) [22,24,26–29] or single-component-treated T2D patients (DPP4i for the SGLT2i add-on trials, and SGLT2i for the DPP4i add-on trials) [25]. As the study by Tinahones et al. [22] comprised two separate trials — one in which subjects received linagliptin 5 mg/empagliflozin 10 mg or placebo/empagliflozin 10 mg plus metformin, and the other in which subjects received linagliptin 5 mg/empagliflozin 25 mg or placebo/empagliflozin 25 mg metformin — these were designated as Tinahones [a] and Tinahones [b], respectively. A flowchart of the study selection process is shown in Fig. S1, and the characteristics of the included studies are presented in Table 1.

Efficacy

In the meta-analysis of the eight RCTs comparing SGLT2i/DPP4i with DPP4i [18–20,24–28], the combination was associated with a significantly greater reduction in HbA_{1c} than DPP4i alone (WMD: −0.62%, 95% CI: −0.73 to −0.51%; $P < 0.001$). Also, the reduction in HbA_{1c} was slightly greater when SGLT2i was added to DPP4i (WMD: −0.70%, 95% CI: −0.85 to −0.54%; $P < 0.001$) compared with the initial combination of SGLT2i/DPP4i (WMD: −0.51%, 95% CI: −0.65 to −0.37%; $P < 0.001$; Fig. 1A).

In the meta-analysis of the five RCTs comparing SGLT2i/DPP4i with SGLT2i [18–20,22,29], the combination was associated with a significantly greater reduction in HbA_{1c} than SGLT2i alone (WMD: −0.35%, 95% CI: −0.48 to −0.22%; $P < 0.001$). When the reduction in HbA_{1c} was further analyzed, the initial combination showed a similar HbA_{1c} reduction (WMD: −0.32%, 95% CI: −0.58 to −0.06%; $P = 0.016$) as did DPP4i as add-on treatment to SGLT2i (WMD: −0.37%, 95% CI: −0.50 to −0.25%; $P < 0.001$; Fig. 1B). When evaluated by funnel plots and Egger's regression test, no obvious asymmetrical distribution or small-study effect was detected (Fig. S3; see supplementary material associated with this article online). This result, however, was not a clear indication of no publication bias, given the small number of studies and moderate heterogeneity.

Fig. 2 depicts changes in FPG from baseline, as assessed by the eight RCTs of SGLT2i/DPP4i vs. DPP4i ($n = 2220$) [18–20,24–28] and five RCTs of SGLT2i/DPP4i vs. SGLT2i ($n = 1681$) [18–

Table 1
Baseline characteristics of studies included in the meta-analysis.

Author (year)	Background therapy	Interventions	Duration (weeks)	Patients (n)	Age (years)	Male (%)	BMI (kg/m^2)	HbA_{1c} (%)	HbA_{1c} (mmol/mol)	FPG (mg/dL)
Defronzo (2015) [20]	Metformin	Empagliflozin 25 mg + linagliptin 5 mg	24	134	57.1	53.7	30.6	7.9	62.8	154.6
				140	55.5	46.4	31.8	8.0	64.2	159.9
		Empagliflozin 25 mg		128	56.2	50.0	30.6	8.0	64.2	156.3
		Linagliptin 5 mg								
Lewin (2015) [19]	None	Empagliflozin 25 mg + linagliptin 5 mg	24	134	54.2	52.2	31.8	8.0	63.8	156.1
				133	56.0	57.9	31.2	8.0	63.8	152.8
		Empagliflozin 25 mg		133	53.8	56.4	31.9	8.1	64.5	156.0
		Linagliptin 5 mg								
Rosenstock (2015) [18]	Metformin	Dapagliflozin 10 mg + saxagliptin 5 mg	24	179	53	47	31.8	8.9	74.0	180.0
				179	54	53	31.8	9.0	75.2	192.0
		Dapagliflozin 10 mg		176	55	50	31.5	8.9	73.4	185.0
		Saxagliptin 5 mg								
Jabbour (2014) [24]	Metformin + sitagliptin 100 mg	Dapagliflozin 10 mg	24	223	54.8	57.0	NA	7.9	62.8	162.2
		Placebo		224	55.0	52.7	NA	8.0	63.9	163.0
Mathieu (2015) [26]	Metformin + saxagliptin 5 mg	Dapagliflozin 10 mg	24	160	55.2	43.7	31.2	8.2	66.6	179.0
		Placebo		160	55.0	47.5	32.2	8.2	65.8	177.0
Rodbard (2016) [27]	Metformin + sitagliptin 100 mg	Canagliflozin 100 mg or 300 mg	26	107	57.4	61.7	32.3	8.5	69.4	185.5
				106	57.5	51.9	31.7	8.4	68.3	180.4
		Placebo[b]								
Kadowaki (2017) [25]	Teneligliptin 20 mg	Canagliflozin 100 mg	24	70	58.4	77.1	25.5	8.2	65.9	173.9
		Placebo		68	56.0	77.9	26.4	7.9	62.5	166.3
Søfteland (2017) [28]	Metformin + linagliptin 5 mg	Empagliflozin 25 mg	24	110	55.4	64.5	29.9	8.0	63.6	169.2
		Placebo		108	55.9	55.6	29.6	8.0	63.6	163.8
Matthaei (2015) [29]	Metformin + dapagliflozin 10 mg	Saxagliptin 5 mg	24	153	54.7	47.7	31.4	8.0	63.6	164.0
		Placebo		162	54.5	46.9	31.4	7.9	62.4	158.0
Tinahones (a)[a] (2017) [22]	Metformin + empagliflozin 10 mg	Linagliptin 5 mg	24	122	56.6	56.6	31.3	8.0	64.4	159.5
		Placebo		125	56.8	56.0	30.8	8.0	64.3	157.1
Tinahones (b)[a] (2017) [22]	Metformin + empagliflozin 25 mg	Linagliptin 5 mg	24	110	56.6	47.3	30.8	7.8	61.9	152.1
		Placebo		110	56.1	57.3	32.0	7.9	62.6	155.4

Data are means (continuous variables) or percentages (dichotomous variables) unless otherwise indicated. BMI: body mass index; FPG: fasting plasma glucose; HbA_{1c}: haemoglobin A_{1c}; NA: not available.

[a] Tinahones et al. [22] comprised two separate trials of linagliptin 5 mg/empagliflozin 10 mg or placebo/empagliflozin 10 mg plus metformin (Tinahones [a]) or linagliptin 5 mg/empagliflozin 25 mg or placebo/empagliflozin 25 mg plus metformin (Tinahones [b])

[b] 6 weeks after starting canagliflozin 100 mg, the dose was increased to 300 mg (or from placebo to matching placebo) if all of the following criteria were met: baseline estimated glomerular filtration rate ≥ 70 mL/min/1.73 m^2; fasting self-monitored blood glucose ≥ 5.6 mmol/L (≥ 100 mg/dL); no volume-depletion-related adverse events within 2 weeks of dose increase.

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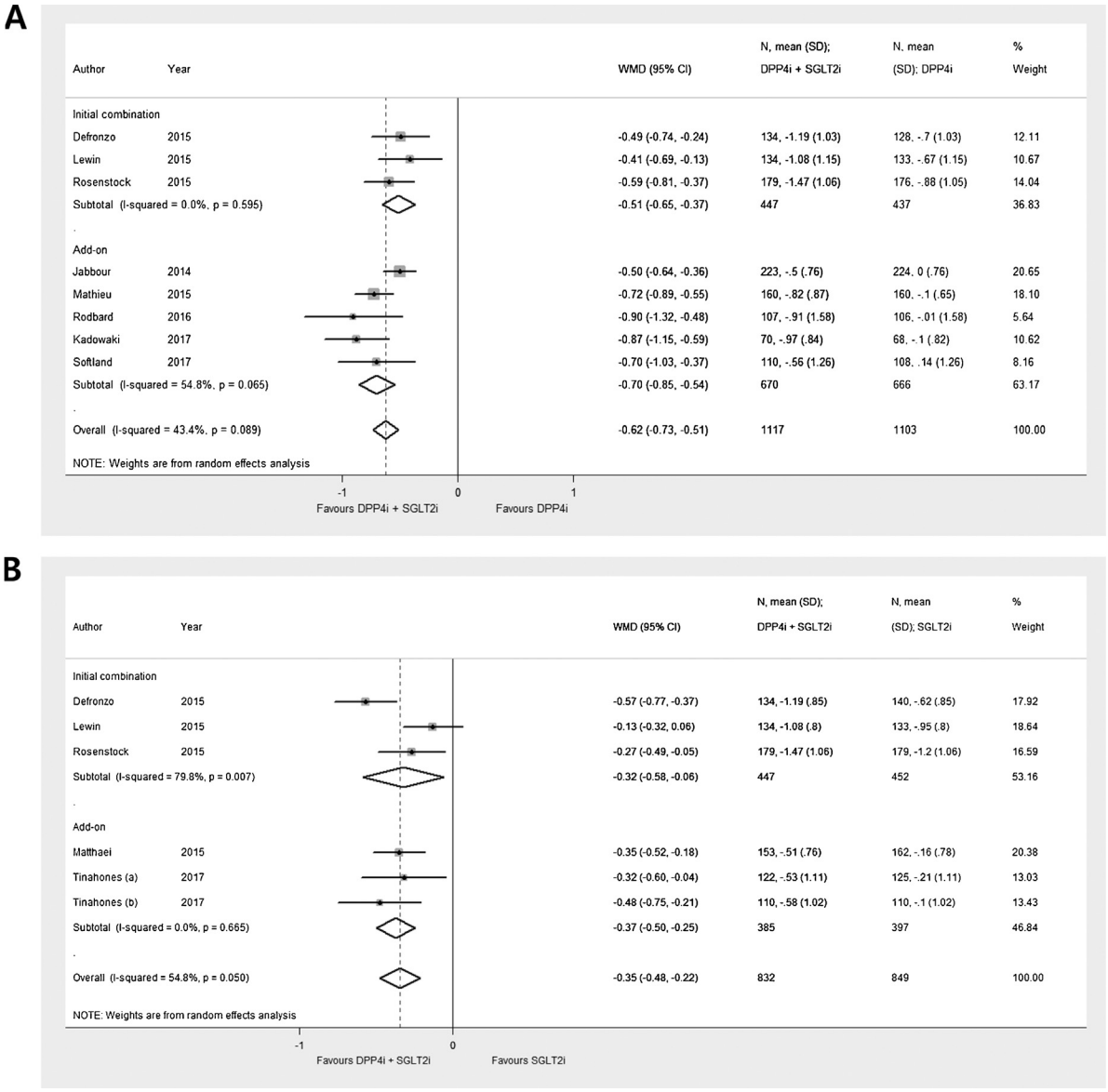

Fig. 1. Weighted mean differences in changes from baseline HbA_{1c} levels (%) with: (A) and sodium-glucose cotransporter type 2 inhibitor (SGLT2i)/dipeptidyl peptidase-4 inhibitor (DPP4i) vs. DPP4i; and (B) SGLT2i/DPP4i vs. SGLT2i. Squares indicate effects of an individual study, their size reflects study weight and horizontal lines represent 95% confidence intervals (CI); diamonds indicate pooled estimates. The study by Tinahones et al. [22] comprised two separate trials in which subjects received linagliptin 5 mg/empagliflozin 10 mg or placebo/empagliflozin 10 mg plus metformin (Tinahones [a]) or linagliptin 5 mg/empagliflozin 25 mg or placebo/empagliflozin 25 mg plus metformin (Tinahones [b]) [Tinahones et al. Linagliptin as add-on to empagliflozin and metformin in patients with type 2 diabetes: two 24-week randomized, double-blind, double-dummy, parallel-group trials. Diabetes Obes Metab, 2017;19:266–74].

20,22,29]. SGLT2i/DPP4i together lowered FPG (WMD: −28.30 mg/dL, 95% CI: −32.31 to −24.28 mg/dL; $P < 0.001$) significantly more than did DPP4i alone. This was significant regardless of whether the two inhibitors were combined stepwise (WMD: −31.29 mg/dL, 95% CI: −36.18 to −26.39 mg/dL; $P < 0.001$, Fig. 2A, lower) or simultaneously (WMD: −23.42 mg/dL, 95% CI: −28.77 to −18.08 mg/dL; $P < 0.001$; Fig. 2A, upper). SGLT2i/DPP4i also lowered FPG (WMD: −7.47 mg/dL, 95% CI: −11.01 to −3.92 mg/dL; $P < 0.001$; Fig. 2B) significantly more than did SGLT2i alone and, again, regardless of whether they were combine stepwise (WMD: −6.63 mg/dL, 95% CI: −12.05 to −1.21 mg/dL; $P < 0.001$; Fig. 2B, lower) or simultaneously (WMD: −8.56 mg/dL, 95% CI −14.91 to −2.22 mg/dL; $P < 0.001$; Fig. 2B, upper).

Except for one previous report of SGLT2i/DPP4i vs. DPP4i [24], all studies to date [18–20,22,25–29] ($n = 1773$ for SGLT2i/DPP4i vs. DPP4i and $n = 1682$ for SGLT2i/DPP4i vs. SGLT2i) have reported the proportion of participants attaining the HbA_{1c} target of < 7.0% (< 53.0 mmol/mol; Fig. S4; see supplementary material associated with this article online). A greater proportion of the SGLT2i/DPP4i group attained this HbA_{1c} target compared with either the DPP4i group (RR: 2.03, 95% CI: 1.73–2.39; $P < 0.001$; Fig. S4A) or SGLT2i group (RR: 1.74, 95% CI: 1.46–2.08; $P < 0.001$; Fig. S4B). Again, the difference was significant regardless of the manner of combination (Fig. S4).

All of the RCTs assessed changes in body weight from baseline (Fig. S5; see supplementary material associated with this article online) [18–20,22,24–29]. Significant differences in weight reduction from baseline were observed with SGLT2i/DPP4i vs. DPP4i (WMD: −1.75 kg, 95% CI: −2.02 to −1.49 kg; $P < 0.001$; Fig. S5A), but not with SGLT2i (WMD: 0.29 kg, 95% CI: −0.14 to 0.71 kg; $P = 0.191$; Fig. S5B), and the result was similar regardless of how SGLT2i and DPP4i were combined (Fig. S5).

Notably, four studies of SGLT2i/DPP4i vs. DPP4i [18–20,24] and four studies of SGLT2i/DPP4i vs. SGLT2i [18–20,29] reported HbA_{1c}

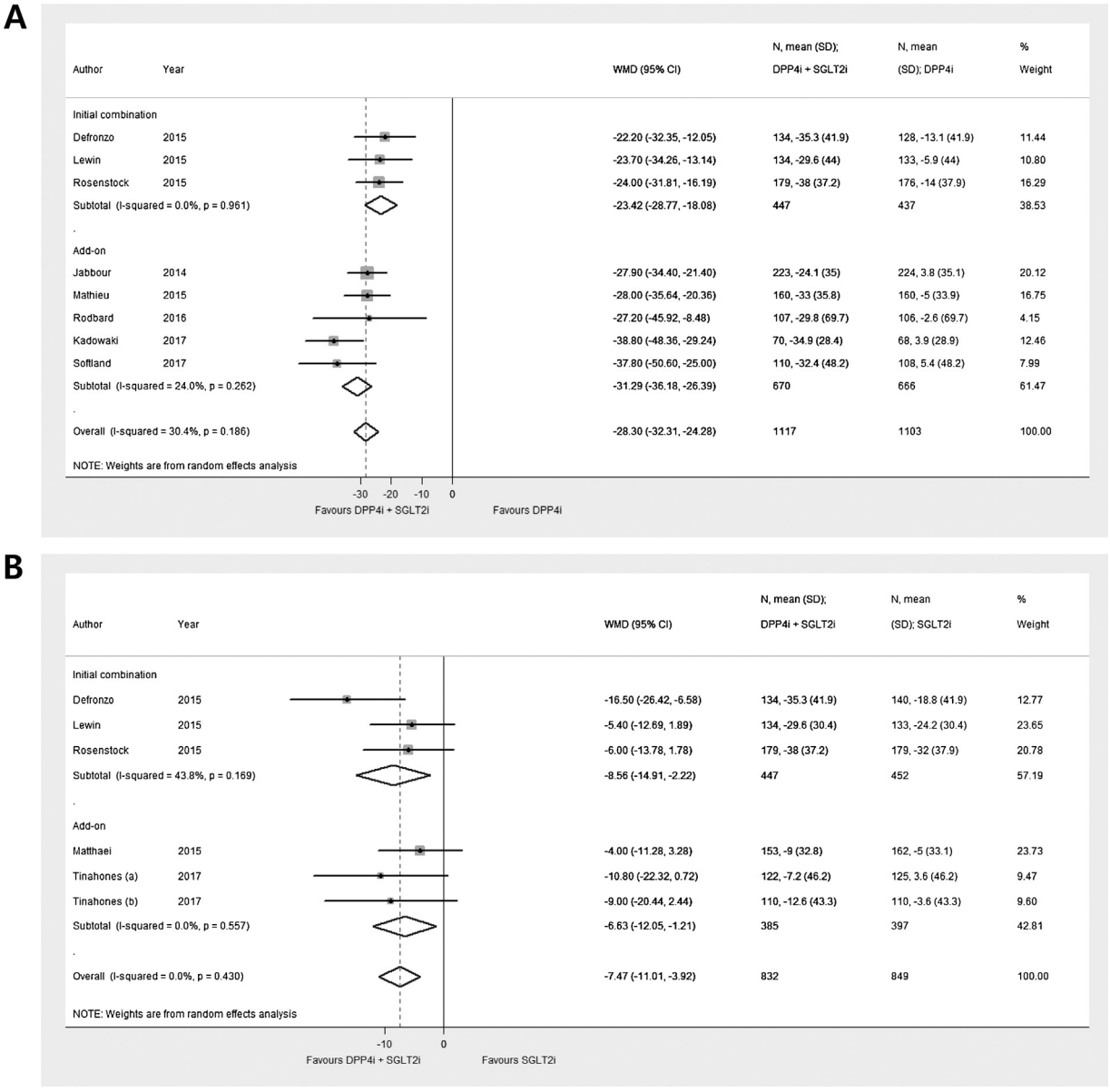

Fig. 2. Weighted mean differences in changes in fasting plasma glucose levels (mg/dL) from baseline with: (A) sodium-glucose cotransporter type 2 inhibitor (SGLT2i)/dipeptidyl peptidase-4 inhibitor (DPP4i) vs. DPP4i; and (B) with SGLT2i/DPP4i vs. SGLT2i. Squares indicate effects of an individual study, their size reflects study weight and horizontal lines represent 95% confidence intervals (CI); diamonds indicate pooled estimates. The study by Tinahones et al. [22] comprised two separate trials wherein subjects received linagliptin 5 mg/empagliflozin 10 mg or placebo/empagliflozin 10 mg plus metformin (Tinahones [a]) or linagliptin 5 mg/empagliflozin 25 mg or placebo/empagliflozin 25 mg plus metformin (Tinahones [b]) [Tinahones et al. Linagliptin as add-on to empagliflozin and metformin in patients with type 2 diabetes: two 24-week randomized, double-blind, double-dummy, parallel-group trials. Diabetes Obes Metab, 2017;19:266–74].

reductions according to baseline levels. When participants were stratified by baseline HbA_{1c} [with 8.0–8.5% (63.9–69.4 mmol/mol) as the cut-off], HbA_{1c} reduction due to SGLT2i/DPP4i vs. DPP4i was proportional to baseline HbA_{1c}: WMD: −0.78%, 95% CI: −0.93 to −0.62% vs. WMD: −8.5 mmol/mol, 95% CI: −10.1 to −6.8 mmol/mol ($P < 0.001$) for moderate-to-high baseline HbA_{1c}; and WMD: −0.20%, 95% CI: −0.40 to −0.01% vs. WMD: −2.2 mmol/mol, 95% CI: −4.3 to −0.1 mmol/mol ($P = 0.065$) for low baseline HbA_{1c} (Fig. 3A). On the other hand, compared with SGLT2i alone, the HbA_{1c} reduction with SGLT2i/DPP4i was modest regardless of baseline HbA_{1c}: WMD: −0.29%, 95% CI: −0.53 to −0.05% ($P = 0.001$) for moderate-to-high baseline HbA_{1c}; and WMD: −0.36%, 95% CI: −0.57 to −0.16% ($P = 0.018$) for low baseline HbA_{1c} (Fig. 3B).

Fig. S6 (see supplementary material associated with this article online) presents the changes in SBP from baseline, as assessed in seven studies of SGLT2i/DPP4i vs. DPP4i ($n = 2082$) [18–20,24,26–28] and four studies of SGLT2i/DPP4i vs. SGLT2i ($n = 1366$) [18–20,22]. The combination therapy lowered SBP significantly more than did DPP4i on its own (WMD: −2.50 mmHg, 95% CI: −3.77 to −1.24 mmHg; $P < 0.001$; Fig. S6A). However, compared with SGLT2i alone, SBP reduction with SGLT2i/DPP4i was not significant (WMD: −0.90 mmHg, 95% CI: −2.44 to 0.64; $P = 0.251$; Fig. S6B).

Safety

Although all of the RCTs reviewed reported the number of hypoglycaemic events, Kadowaki et al. [25] and the Tinahones et al. [22] arm using background treatment with empagliflozin 10 mg were omitted from the combined RR calculation, as they reported no hypoglycaemic events between the two groups. As presented in Fig. S7 (see supplementary material associated with this article online), the risk of hypoglycaemia was low and similar between

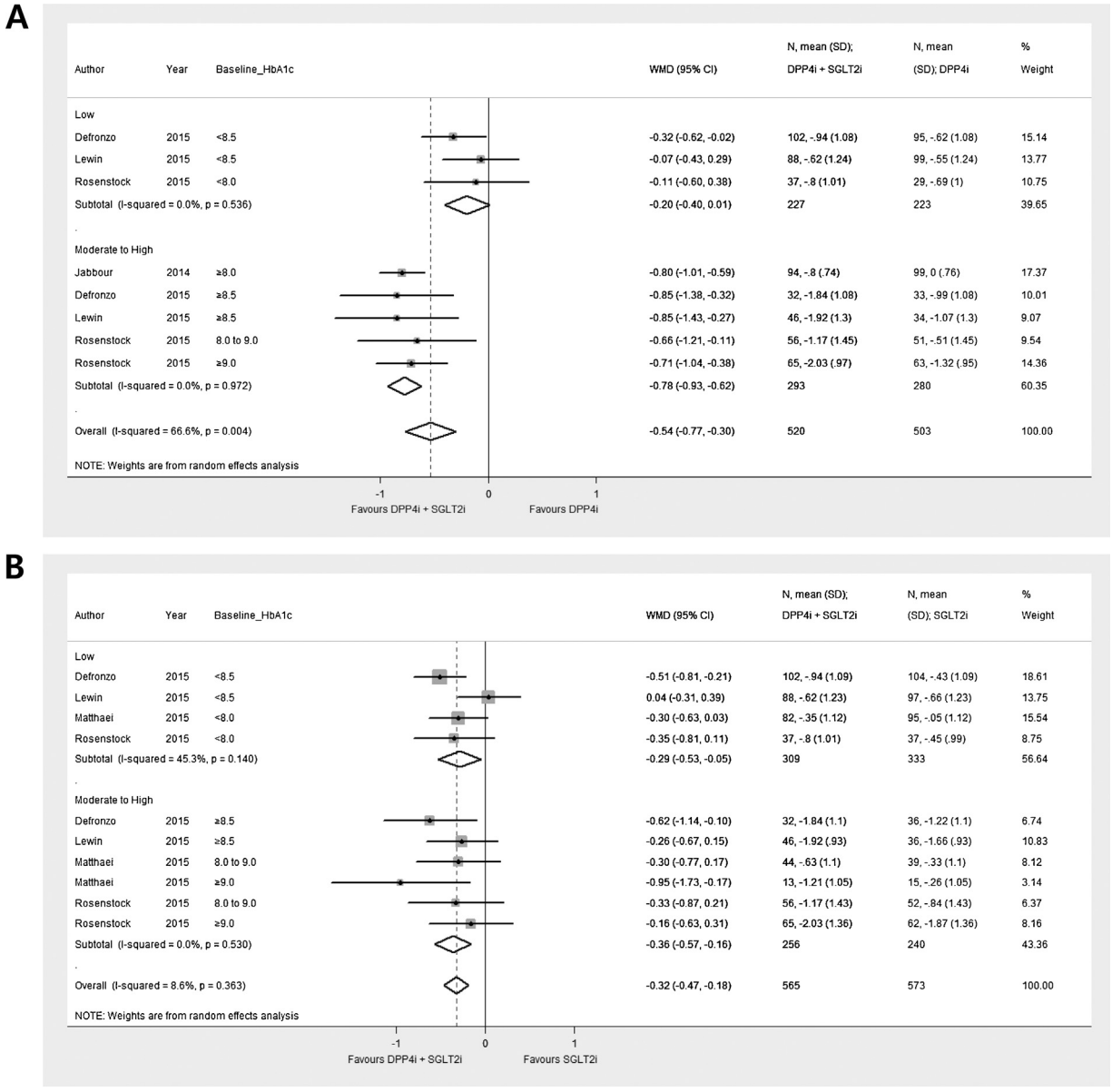

Fig. 3. Weighted mean differences in changes from baseline HbA_{1c} (%) according to baseline HbA_{1c}, using a cut-off of 8.0–8.5%, with: (A) sodium–glucose cotransporter type 2 inhibitor (SGLT2i)/dipeptidyl peptidase-4 inhibitor (DPP4i) vs. DPP4i; and (B) with SGLT2i/DPP4i vs. SGLT2i. Squares indicate effects of an individual study, their size reflects study weight and horizontal lines represent 95% confidence intervals (CI); diamonds indicate pooled estimates.

treatment groups: RR: 1.60, 95% CI: 0.81–3.15 ($P = 0.176$) for SGLT2i/DPP4i vs. DPP4i; and RR: 0.76, 95% CI: 0.33–1.75 ($P = 0.519$) for SGLT2i/DPP4i vs. SGLT2i.

Regarding genital infections, all RCTs reported the number of such events. However, Kadowaki et al. [25] was not included when the combined RR was calculated, as they reported no genital infections between the two groups. As shown in Fig. S8 (see supplementary material associated with this article online), the RR of genital infection was significantly higher with SGLT2i/DPP4i vs. DPP4i (RR: 2.94, 95% CI: 1.23 to 7.00; $P = 0.015$; Fig. S8A), whereas SGLT2i/DPP4i resulted in a lower combined RR compared with SGLT2i alone (RR: 0.42, 95% CI: 0.18 to 0.99; $P = 0.046$, Fig. S8B).

Discussion

Our present meta-analysis was designed to evaluate the efficacy and safety of SGLT2i/DPP4i combination therapy in patients with T2D. The combination resulted in greater reductions in HbA_{1c} and FPG than did DPP4i alone, whereas additional reductions in HbA_{1c} and FPG were less marked when SGLT2i/DPP4i was compared with SGLT2i (Figs. 1 and 2A). The risk of hypoglycaemic events was low and similar among treatment groups (Fig. S7). Interestingly, when subjects were stratified by baseline HbA_{1c} [with 8.0–8.5% (63.9–69.4 mmol/mol) as the cut-off], the additional HbA_{1c} reduction due to SGLT2i, as estimated by comparing results with SGLT2i/DPP4i vs. DPP4i, was directly proportional to baseline HbA_{1c} (Fig. 3A). In contrast, the added HbA_{1c} reduction with SGLT2i/DPP4i compared with SGLT2i alone indicated that the effects of DPP4i were modest regardless of baseline HbA_{1c} (Fig. 3B). Our results suggest that, while the combination of SGLT2i and DPP4i resulted in clinically meaningful reductions in HbA_{1c} and FPG with a low risk of hypoglycaemia, the additional glucose control was significant when SGLT2i was combined with or added to DPP4i, but not vice versa, as already suggested in a previous review [16]. Our findings also demonstrate that baseline HbA_{1c}

determines the glucose-lowering effects of SGLT2i in combination with DPP4i.

The progressive deterioration of β-cell function in T2D often requires combination therapy to address hyperglycaemia [2]. The ideal combination of glucose-lowering agents needs to meet certain criteria, such as complementary physiological pathways and good safety profiles, with low risks of hypoglycaemia, weight gain and cardiovascular events [4,8,15,30,31]. As the combination of SGLT2i and DPP4i targets different pathophysiological defects associated with T2D through their different mechanisms of action, combination therapy with SGLT2i and DPP4i is very appealing [8,16]. In addition, both drug classes have good tolerability profiles, including low risk of hypoglycaemia, and weight neutrality with DPP4i and weight loss with SGLT2i [4,7,10–12,32,33].

Given these factors, several RCTs have investigated the efficacy and safety of combination therapy with SGLT2i and DPP4i in patients with T2D [18–20,22,24–29]. In 2015, three similar RCTs investigating the combined efficacy and safety of SGLT2i and DPP4i were published [18–20]. Interestingly, they compared the efficacy and safety of the initial combination of SGLT2i/DPP4i with SGLT2i or DPP4i alone in T2D drug-naïve [19] or metformin-treated patients [18,20]. Remarkably, the combination of SGLT2i/DPP4i failed to produce any synergistic or additive reduction in HbA_{1c} [18–20]. Instead, in general, the HbA_{1c} reductions were even smaller than the additional effects of each agent alone [18–20]. In Rosenstock et al. [18], the addition of dapagliflozin 10 mg or saxagliptin 5 mg in metformin-treated subjects lowered HbA_{1c} by −1.20% (−13.1 mmol/mol) and −0.88% (−9.6 mmol/mol), respectively, whereas the initial combination of both agents led to a reduction of −1.47% [difference vs. dapagliflozin and saxagliptin: −0.27% (−3.0 mmol/mol) and −0.59% (−6.4 mmol/mol), respectively]. Based on these results, it was suggested that initial expectations of SGLT2i/DPP4i as combination therapy were overly optimistic [8].

Our present results have shown that the additional HbA_{1c} reduction by DPP4i was modest, regardless of baseline HbA_{1c} (Figs. 1 and 3B). One possible explanation for this finding may be the compensatory increases in glucagon and EGP levels associated with the use of SGLT2i [34,35]. As DPP4i lowers plasma glucose concentrations by suppressing glucagon secretion and inhibiting EGP, it may be speculated that stimulation of EGP by SGLT2i-induced glycosuria is so powerful that it overwhelms the effects of DPP4i [35]. On the other hand, as the key mechanism of SGLT2i is increased glucose excretion by the kidney, the action of SGLT2i is less likely to be affected by its combined use with DPP4i. Thus, SGLT2i may display glucose-lowering effects regardless of the use of DPP4i in combination.

In addition, it has also been suggested that the impact of higher baseline HbA_{1c} on the clinical efficacy of SGLT2i is greater than on DPP4i [18,20,36]. In Defronzo et al. [20], the additional benefit of empagliflozin 25 mg over linagliptin 5 mg was −0.85% (9.3 mmol/mol) in patients with baseline $HbA_{1c} \geq 8.5\%$ ($\geq$ 69.4 mmol/mol) and −0.32% (3.5 mmol/mol) in patients with baseline $HbA_{1c} < 8.5\%$ ($<$ 69.4 mmol/mol) [20]. The added benefit of linagliptin 5 mg over empagliflozin 25 mg was −0.62% (6.8 mmol/mol) in patients with baseline $HbA_{1c} \geq 8.5\%$ ($\geq$ 69.4 mmol/mol) and −0.51% (5.6 mmol/mol) in patients with baseline $HbA_{1c} < 8.5\%$ ($<$ 69.4 mmol/mol) [20]. Collectively, these results suggest that the impact of increased baseline HbA_{1c} on the clinical efficacy of SGLT2i is indeed much greater than it is on DPP4i, as previously suggested [16]. In line with this, our present analysis has also demonstrated that baseline HbA_{1c} determines the additional glucose-lowering effect of SGLT2i in combination with DPP4i (Fig. 3A). These effects of SGLT2i may be explained by its mechanism of action, where the amount of urinary glucose excretion is partially dependent on the patient's level of glycaemia [4,37].

In theory, the complementary mechanisms of SGLT2is and DPP4is suggest that they could be used in combination with no significant detrimental effects [2]. Each has a good safety profile, including a low risk of hypoglycaemia when used together with hypoglycaemic agents other than insulin or insulin secretagogues [4]. Consistent with these known safety profiles, our present results have also shown that both DPP4is and SGLT2is rarely cause hypoglycaemia (Fig. S7). Reductions in body weight and SBP are other potential benefits of the combination of SGLT2i/DPP4i [4]. Indeed, our present findings indicate that SGLT2i leads to significant reductions in weight (Fig. S5) and SBP (Fig. S6). Together with low hypoglycaemia risk, these effects again support SGLT2/DPP4i as combination therapy.

Genital infections are the most common adverse events associated with SGLT2i therapy [38] and, recently, it was proposed that DPP4i might moderate this risk [39]. In line with this suggestion, it was observed that SGLT2i/DPP4i resulted in a lower combined RR for genital infection than SGLT2i on its own (Fig. S8). Although the mechanisms whereby DPP4i might reduce this SGLT2i-associated risk are still highly speculative [39], the additional benefit of DPP4i reducing the risk of genital infections in fact strengthens the rationale for SGLT2i/DPP4i combination therapy.

Our present analysis nevertheless has certain limitations. First, our definition of low and moderate-to-high baseline HbA_{1c} was arbitrary [8.0–8.5% (63.9–69.4 mmol/mol) as the cut-off] as the cut-offs among the included studies were inconsistent. However, this limitation has no effect on the implications of our findings. Second, although the cardiovascular benefit of antidiabetic medications is of major importance, it was not possible to evaluate the cardiovascular effects of SGLT2i and DPP4i. Third, the definitions of hypoglycaemia (Table S2) were inconsistent among the included studies and, fourth, the long-term complications of T2D and certain major safety concerns, including euglycaemic ketoacidosis, were not addressed. Finally, our discussion of the minor benefit of DPP4i as an add-on to SGLT2i with respect to HbA_{1c} reduction is highly theoretical.

Despite these limitations, this was the first meta-analysis to demonstrate the efficacy and safety of SGLT2i/DPP4i in combination with a focus on the respective efficacy and safety of each agent on its own. When combined, they are effective and well tolerated. However, when SGLT2i is already being given or is started simultaneously, the additional glucose-lowering effects of DPP4i could be limited. In contrast, the additional glucose-lowering effects of SGLT2i when combined with DPP4i are more clinically meaningful. Therefore, although the combination of DPP4i/SGLT2i has been confirmed as a useful approach in a wide range of cases [2], our present results support the notion that no therapy fits every patient, thus highlighting the need for individualized strategies in the management of patients with T2D.

Conclusion

Combined therapy with SGLT2i/DPP4i is effective and safe. However, interestingly, a marked additional glucose-lowering effect is evident when SGLT2i is combined with or added to DPP4i, but not vice versa. In addition, baseline HbA_{1c} levels significantly influence the glucose-lowering effects of SGLT2i in combination with DPP4i and, thus, further studies are needed to elucidate the underlying mechanism of this effect.

Ethics approval

Not required.

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Availability of data and materials

All data and material are published and available.

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Author contributions

Y.-J.K. and C.H.J. conceived this study. Y.K.C. and C.H.J. contributed to the design of the study. Y.K.C., Y.M.K., S.E.L. and J.L. conducted data collection. J.-Y.P., W.J.L., Y.K.C., Y.-J.K. and C.H.J. conducted the analysis and interpreted the results. Y.K.C. wrote the initial draft of the manuscript, with revisions by all authors. The final manuscript was approved by all authors. Y.K.C., Y-.J.K. and C.H.J. are the guarantors of this work.

Disclosure of interest

The authors declare that they have no competing interest.

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None.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at Supplementary materials (Figs. S1–S8 and Tables S1–S3) associated with this article can be found at http://www.sciencedirect.com at https://doi.org/10.1016/j.diabet.2018.01.011.

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