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Long-term efficacy and safety of sodium-glucose cotransporter-2 inhibitors as add-on to metformin treatment in the management of type 2 diabetes mellitus

A meta-analysis

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Abstract

Background: Drug intensification is often required for patients with type 2 diabetes mellitus on stable metformin therapy. Among the potential candidates for a combination therapy, sodium-glucose transporter-2 (SGLT2) inhibitors have shown promising outcomes. This meta-analysis was performed to compare the efficacy and safety of SGLT2 inhibitors with non-SGLT2 combinations as add-on treatment to metformin.

Methods: Literature search was carried out in multiple electronic databases for the acquisition of relevant randomized controlled trials (RCTs) by following *a priori* eligibility criteria. After the assessment of quality of the included RCTs, meta-analyses of mean differences or odds ratios (OR) were performed to achieve overall effect sizes of the changes from baseline in selected efficacy and safety endpoints reported in the individual studies. Between-studies heterogeneity was estimated with between-studies statistical heterogeneity (I^2) index.

Results: Six RCTs fulfilled the eligibility criteria. SGLT2 inhibitors as add-on to metformin treatment reduced % HbA1c significantly more than non-SGLT2 combinations after 52 weeks ($P = .002$) as well as after 104 weeks ($P < .00001$). Among other endpoints, SGLT2 inhibitors also reduced fasting plasma glucose levels, body weight, systolic, and diastolic blood pressures after 52 weeks and 104 weeks significantly ($P < .00001$) more than non-SGLT2 combinations. Incidence of hypoglycemia was significantly lower ($P = .02$) but incidence of suspected or confirmed genital tract infections was significantly higher ($P < .00001$) in SGLT2 inhibitors treated in comparison with non-SGLT2 combinations.

Conclusion: As add-on to metformin treatment, SGLT2 inhibitors are found significantly more efficacious than non-SGLT2 inhibitor combinations in the management of type 2 diabetes mellitus, although, SGLT2 inhibitor therapy is associated with significantly higher incidence of suspected or confirmed genital tract infections.

Abbreviations: AE = adverse effect, BW = body weight, CANA = canagliflozin, chol = cholesterol, DAPA = dapagliflozin, DBP = diastolic blood pressure, DPP-4 = dipeptidyl peptidase-4, eGFR = estimated glomerular filtration rate, EMPA = FDA = Federal Drug Agency, empagliflozin, FPG = fasting plasma glucose, GLP-1 = glucagon-like peptide 1, HbA1c = glycosylated hemoglobin-A1c, HDL = high density lipoprotein, I^2 = between-studies statistical heterogeneity, IPRA = ipragliflozin, kcal = kilocalories, LDL = low-density lipoprotein, MeSH = medical subject headings, mg = milligram, OR = odds ratio, PPG = postprandial glucose, PRISMA = preferred reporting items for systematic reviews and meta-analyses, RCT = randomized controlled trial, SAT = subcutaneous adipose tissue, SBP = systolic blood pressure, SGLT = sodium-glucose cotransporter, TOFO = tofogliflozin, VAT = visceral adipose tissue.

Keywords: meta-analysis, metformin, SGLT2 inhibitor, sodium-glucose cotransporter-2 inhibitor, type 2 diabetes

1. Introduction

Type 2 diabetes mellitus is one of the most prevalent and devastating diseases with a global incidence estimate of about 9% of adult population. According to an estimate, in the year 2012 alone, this disease caused 1.5 million deaths.[1] This form of metabolic disorder poses increased risk of morbidity and mortality attributable to a reduced life expectancy of up to 13 years.[2] Among several pathologies associated with type 2 diabetes mellitus, microvascular complications can cause blindness, renal failure, and the loss of function of other important organs.[3] Cerebrovascular and cardiovascular comorbidity related mortality risk is 2 to 4 times higher in type 2 diabetes mellitus patients than in general population.[4]

Upon diagnosis, if lifestyle interventions remain insufficient to control type 2 diabetes, metformin is the first line drug. Metformin is an efficacious drug because of its glycemic control, insulin sensitizing, and body weight effects.[5] However, with the

passage of time it may not provide adequate glycemic control due to disease progression which necessitates add-on treatments to maintain euglycemia which is necessary for the prevention of glucotoxicity. According to the American Diabetes Association and the American Association of Clinical Endocrinologists guidelines, metformin may be followed by GLP-1 receptor agonists, DPP-4 inhibitors, or SGLT2 inhibitors in preference to sulfonylurea, thiazolidinediones, meglitinides, alpha-glycosidase inhibitors, bile acid sequestrants, dopamine-2 agonists, amylin mimetics, or insulin. However, depending on the level of HbA1c lowering requirements, associated risk of medication and tolerability properties of a particular drug, preferences can be modified.[6,7]

Among the recently developed drugs, SGLT2 inhibitors have also shown promising results for type 2 diabetes patients.[8–10] Selective and reversible inhibition of SGLT2 can lower blood glucose levels independent of insulin status and is also found to manifest favorable effects on hypertension and body weight control, besides maintaining glycemic control. The SGLT2 is a high-capacity and low-affinity protein, which is expressed in abundance in the proximal renal tubules where it reabsorbs 80% to 90% of glucose. It should be distinguished from the SGLT1 which is low-capacity and high-affinity protein expressed mainly in the small intestine and late proximal renal tubules and is more important for intestinal absorption of glucose and galactose.[11–13] Among the notable SGLT2 inhibitor drugs, dapagliflozin, canagliflozin, empagliflozin, tofogliflozin, and luseogliflozin are well-studied for their efficacy, safety, tolerability, bioavailability, pharmacokinetic, and pharmacodynamic properties.[9,10]

In a number of clinical studies with type 2 diabetes patients, SGLT2 inhibitors are found to decrease HbA1c, fasting plasma glucose (FPG) levels, and body weight by inducing favorable glucosuria (urinary loss of approximately 200–300 kcal/d) in a variety of designs involving monotherapies and combination therapies.[14–19] Whereas, a recent meta-analysis of the placebo-controlled RCTs has found SGLT2 inhibitors efficacious as add-on to metformin treatment,[20] there is no study to systematically review the efficacy and safety of SGLT2 inhibitors against non-SGLT2 combinations investigated in RCTs. Aim of the present study was to evaluate the efficacy and safety of this important therapeutic regimen by performing a meta-analysis of the RCTs which compared the efficacy and safety of SGLT2 inhibitors against non-SGLT2 combinations, as add-on to metformin treatment for more than 1-year.

2. Methods

This meta-analysis was performed by following Cochrane Collaboration guidelines and is reported in accordance with the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement. Ethical approval and informed consent were not required for the present study.

2.1. Literature search

The literature search was carried out in Medline/PubMed, Embase, Scopus, Ovid SP, Google Scholar, and Web of Science databases. The MeSH and keywords used in different combinations were sodium-glucose cotransporter-2 inhibitor, SGLT2 inhibitor, dapagliflozin, DAPA, canagliflozin, CANA, ipragliflozin IPRA, empagliflozin, EMPA, tofogliflozin, TOFO, luseogliflozin, type 2 diabetes mellitus, randomized controlled trial, RCT, efficacy, safety, tolerability, adverse effects, AEs,

metformin, add-on treatment, glycosylated hemoglobin, HbA1c, fasting plasma glucose, FPG, systolic blood pressure, SBP, diastolic blood pressure, DBP, body weight, postprandial glucose, PPG, cholesterol, high density lipoprotein, HDL, low-density lipoprotein, LDL, triglyceride, and estimated glomerular filtration rate, eGFR. Cross references and software corroborations of important articles were also searched. The search encompassed original articles published before September 2016.

2.2. Primary and secondary endpoints

Studies included in the meta-analyses are RCTs which evaluated the efficacy, safety, and tolerability of a SGLT2 inhibitor as add-n to metformin by comparing with a suitable non-SGLT2 combination. Participants were type 2 diabetes patients having inadequate control of disease by diet/exercise and metformin therapy. Primary outcome measures of interest were the changes from baseline in percent HbA1c, FPG levels, and body weight. Secondary endpoints were the changes from baseline in blood pressure (SBP and DBP), lipid profile (HDL-chol, LDL-chol, and triglyceride), and eGFR. Safety endpoints were the incidence of hypoglycemia, incidence of genital tract infections, incidence of urinary tract infections, and incidence of ketoacidosis.

2.3. Inclusion and exclusion criteria

The inclusion criteria were: (a) RCT recruited adult type 2 diabetes patients to evaluate the efficacy and safety of a SGLT2 inhibitor as add-on to metformin treatment by comparing it with a suitable non-SGLT2 combination controlled group; and (b) trial reported at least 1 indicator of disease condition of interest (primary, secondary and/or safety). Exclusion criteria were: Relevant RCTs (a) of less than 52 weeks duration, (b) examined the efficacy of SGLT2 inhibitors as add-on to metformin against a placebo-controlled group or as a single arm study, (c) compared SGLT2 inhibitor monotherapy with metformin either alone or in combination with other antidiabetic drugs, (d) compared SGLT2 inhibitors in combination with other non-SGLT2 drugs with any other combination or monotherapy as add-on to metformin, and (e) report provided inadequate information about quantitative outcome/s.

2.4. Quality assessment of the trials

Quality assessment of the RCTs included in this meta-analysis was carried out by using the Cochrane Collaboration's (St Albans House, London, UK) Tool for Quality Assessment of Randomized Controlled Trials.[21]

2.5. Data extraction, synthesis and statistical analysis

Data extraction was carried out by 2 reviewers independently by adapting a standardized procedure. Data pertaining to the participants' demographic and pathological characteristics, intervention design, and trial eligibility criteria, outcome measures, and outcomes were extracted from the selected research articles. From the studies which used multiple doses of a SGLT2 inhibitor drug, dose groups were selected to achieve maximum equivalence between the studies. Changes from baseline in the endpoints were either extracted raw from the respective research articles if provided, or calculated from the baseline values and values noted at weeks 24, 52, and 104 of treatment duration. Data and analyses module of RevMan software (version 5.2; Cochrane Collaboration) was used for the
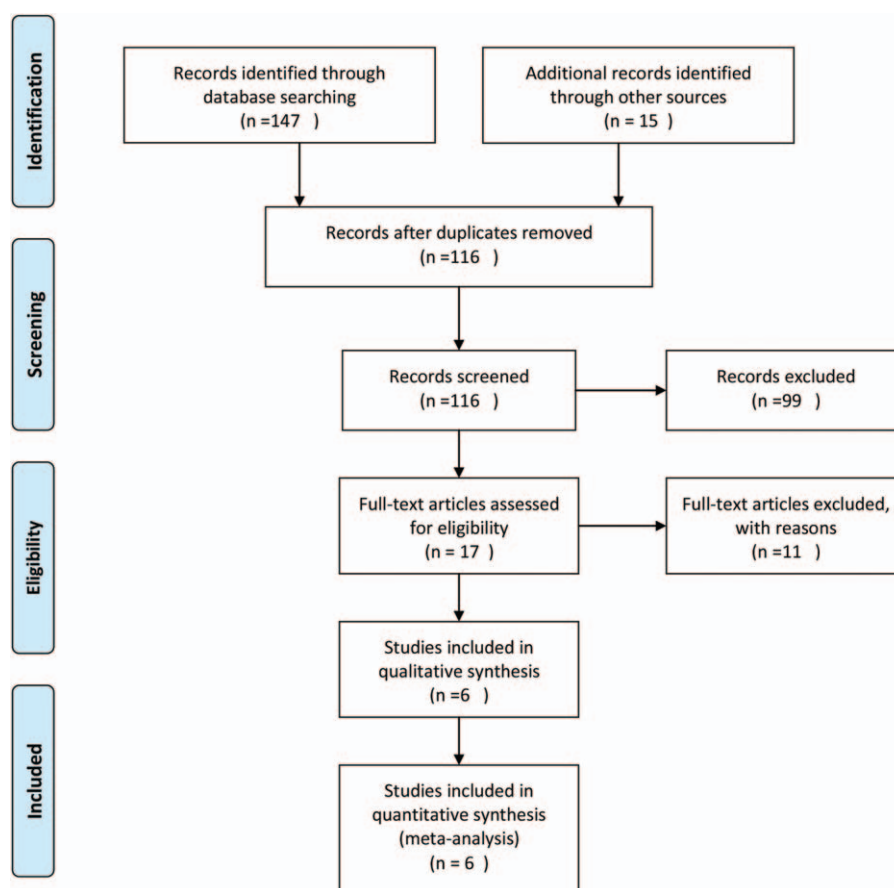
Figure 1. Flow chart of literature search and study selection process.

meta-analyses of weighted mean differences (for efficacy endpoints) or OR (for safety endpoints) between SGLT2 inhibitors and non-SGLT2 combinations. Between-studies inconsistency (heterogeneity) was tested by I^2 statistics.

3. Results

Six RCTs[22–27] out of 17 related trials which were screened from 116 abstracts fulfilled the eligibility criteria (Fig. 1). Placebo-controlled trials, trials investigating SGLT2 inhibitor plus non-SGLT2 inhibitor as add-on to metformin designs, monotherapy in 1 arm (SGLT2 inhibitor as add-on to metformin vs monotherapy) designs, and pharmacokinetic/pharmacodynamics

studies were excluded. Important characteristics of the included studies are presented in Tables 1 and 2. Quality of the included studies was generally high. An assessment summary is presented in Table 3.

Overall, this meta-analysis is based on 4533 type 2 diabetes patients with inadequate control on the disease with lifestyle interventions and metformin despite a daily dose range of 1.5 to 3 g. Of these, 2320 patients were treated with a SGLT2 inhibitor (CANA/DAPA/EMPA) and 2213 were treated with a non-SGLT2 combination (glimepiride/linagliptin/sitagliptin/glipizide), as add-on to metformin. All of these trials used percent change in HbA1c levels from baseline as the primary endpoint. Secondary and exploratory endpoints included changes from baseline in FPG,

Table 1

Study design characteristics of the studies/study arms included in the meta-analysis.

Study	Trial identifier	Trial duration (wk)	Number of patients		Dosage		
			SGLT-Inh	Non-SGLT-Inh	SGLT-Inh	Non-SGLT-Inh	MET
Cefalu et al[22]/Leiter et al (2015)	NCT00968812	104	485 CANA	482 Glimepiride	CANA (300 mg/d)	Glimepiride (up-titrated 6–8 mg/d)	≥1.5 g/d
DeFronzo et al (2014)	NCT01422876	52	140 EMPA	128 LINA	EMPA 25 mg/d	LINA 5 mg/d	≥1.5 g/d
Ferrannini et al[24]	NCT00881530	90+	166 EMPA	56 SITA	EMPA (25 mg/d)	SITA (100 mg/d)	≥1.5 g/d
Lavalle-Gonzalez et al. (2013)	NCT01106677	52	367 CANA	366 SITA	CANA (300 mg/d)	SITA (100 mg/d)	≥2 g/d
Nauck et al[26]/Nauck et al. (2013)	NCT00660907	52	400 DAPA	401 Glipizide	DAPA (up-titrated 2.5–10 mg/d)	Glipizide (up-titrated 5–20 mg/d)	2 g/d
Ridderstrale et al[27]	NCT01167881	104	765 EMPA	780 glimepiride	EMPA (25 mg/d)	Glimepiride (1–4 mg/d)	≥1.5 g/d

CANA = canagliflozin, DAPA = dapagliflozin, EMPA = empagliflozin.

Table 2

Patient characteristics of the included studies.

	Age (y)	Males	BMI (kg/m²)	Disease length (y)	HbA1c (%)	FPG (mM/L)	SBP (mm Hg)	DBP (mm Hg)	TG (mmol/L)	LDL-chol (mmol/L)	HDL-chol (mmol/L)	eGFR (mL/ min /1.73 m²)
Cefalu et al[22]/Leiter et al (2015)	56.2 ± 9.2	52%	31 ± 5.4	6.6 ± 5.3	7.8 ± 0.8	9.2 ± 2.1	130 ± 13.1	79 ± 8.2	2 ± 1.6	2.8 ± 0.9	1.2 ± 0.3	–
DeFronzo et al (2014)	55.8 ± 10.2	50%	30.2 ± 5.3	0–5 y 43.8%, over 5 y 55.9%	8.02 ± 0.83	8.8 ± 2.1	129.2 ± 13.4	79.9 ± 8.7	2 ± 0.15	2.7 ± 0.1	1.2 ± 0	90.2 ± 19
Ferrannini et al[24]	56.2 ± 9.2	52%	30.2 (20–40)	1–5 y 38% and >5 y 54%	7.94 ± 0.8	9.9 ± 2.2	136.5 ± 14.6	80.9 ± 9.4	2.2 ± 22.3	2.7 ± 0.9	1.3 ± 0.3	92.2 ± 19.4
Lavalle-Gonzalez et al (2013)	55.4 ± 9.4	47.1%			7.9 ± 0.9	10.7 ± 3.2			2.1 ± 1.3	2.8 ± 0.9	1.2 ± 0.3	89.4
Nauck et al[26]/ Nauck et al (2013)	58.5 ± 9.5	55.1%	31.5 ± 5	6.5 ± 5.5	7.7 ± 0.9	9.05 ± 2.2			1.94	2.68	1.19	90 ± 22
Ridderstrale et al[27]	55.9 ± 10.4	55.2%	25–35: 66%	6.5 ± 5.5	7.92 ± 0.83	8.32 ± 1.87	133.5 ± 16	79.5 ± 9.4	1.85 ± 1.28	2.42 ± 0.87	1.25 ± 0.3	85.5 ± 16.4

BMI = body mass index, chol = cholesterol, eGFR = estimated glomerular filtration rate, FPG = fasting plasma glucose, HbA1c = glycosylated hemoglobin A1c, HDL/L = high/low-density lipoprotein, S/DBP = systolic/diastolic blood pressure, TG = triglycerides.

Table 3

Risk of bias assessment in the included studies.

	Other bias	Selective reporting	Incomplete outcome data	Blinding of outcome assessment	Blinding of participants/ personnel	Allocation concealment	Random sequence generator
Cefalu et al[22]/Leiter et al (2015)[23]	L	L	L	L	L	L	L
DeFronzo et al (2014)[24]	L	L	L	L	L	L	L
Ferrannini et al[25]	L	L	L	L	L	L	L
Lavalle-Gonzalez et al (2013)[26]	L	L	L	L	L	L	L
Nauck et al[27]/Nauck et al (2013)[28]	L	L	L	L	L	L	L
Ridderstrale et al[29]	L	L	L	L	L	L	L

H = high risk, L = low risk, U = unclear risk.

PPG, BW, SBP, DBP, percent patients with HbA1c < 7%, and hypoglycemia incidence.

Major findings of this meta-analysis are given in Table 4. The SGLT2 inhibitors as add-on to metformin treatment were found to be associated with significantly better efficacy in comparison with non-SGLT2 combinations for at least up to 2 years of treatment. Improvement in the change from baseline in %HbA1c was significantly more in SGLT2 inhibitors than in non-SGLT2

Table 4

Major findings of the meta-analysis of 52-week trials with findings of 1 104-week trials.

Parameter/Duration	No. of RCTs	No. of participants	Mean difference [95% CI]	Significance level	Heterogeneity (I^2)
HbA1c (%)					
After 24 weeks	6	4489	−0.00 [−0.02, 0.11]	P = .22	90%
After 52 weeks	6	4507	−0.11 [−0.18, −0.04]	P < .00001	54%
After 104 weeks	3	2707	−0.16 [−0.21, −0.08]	P < .00001	22%
FPG					
After 24 weeks	2	1142	−0.65 [−1.34, 0.04]	P = .06	80%
After 52 weeks	5	4188	−0.65 [−0.94, −0.35]	P < .0001	84%
After 104 weeks	3	2707	−0.72 [−0.86, −0.58]	P < .00001	0%
Body weight					
After 24 weeks	5	3274	−3.98 [−4.68, −3.28]	P < .00001	82%
After 52 weeks	6	4147	−3.87 [−4.94, −2.80]	P < .00001	95%
After 104 weeks	3	2707	−3.53 [−4.86, −2.21]	P < .00001	92%
SBP					
After 24 weeks	1	1545	−5.60 [−6.91, −4.29]	P < .0001	–
After 52 weeks	5	4276	−4.88 [−5.66, −4.10]	P < .00001	23%
After 104 weeks	3	2707	−5.33 [−6.29, −4.36]	P < .00001	0%
DBP					
After 24 weeks	1	1545	−2.40 [−3.50, −1.30]	P < .00001	0%
After 52 weeks	4	4008	−2.38 [−2.93, −1.84]	P < .00001	62%
After 104 weeks	3	2707	−2.55 [−3.19, −1.91]	P < .00001	0%
eGFR					
After 24 weeks	2	1064	2.32 [−0.14, 4.78]	P = .06	34%
After 52 weeks	4	2139	3.43 [1.65, 5.21]	P = .00002	77%
After 104 weeks	2	1051	0.26 [−6.12, 6.63]	P = .94	80%
LDL-cholesterol (% change)					
After 24 weeks	1	970	9.00 [3.47, 14.53]	P = .001	–
After 52 weeks	3	2449	2.47 [0.25, 4.68]	P = .03	99%
After 104 weeks	1	967	8.00 [2.07, 13.93]	P = .008	–
HDL-cholesterol (% change)					
After 24 weeks	1	967	7.50 [4.87, 10.13]	P < .00001	–
After 52 weeks	3	2449	6.89 [5.82, 7.96]	P < .00001	97%
After 104 weeks	1	1067	9.30 [6.65, 11.95]	P < .00001	–

Dose regimens: EMPA (25 mg/d), CANA (300 mg/d), and DAPA (up-titrated 2.5 to 10 mg/day).

DBP = diastolic blood pressure, eGFR = estimated glomerular filtration rate, FPG = fasting plasma glucose, HbA1c = glycosylated hemoglobin-A1c, HDL = high density lipoprotein, LDL = low-density lipoprotein, SBP = systolic blood pressure.
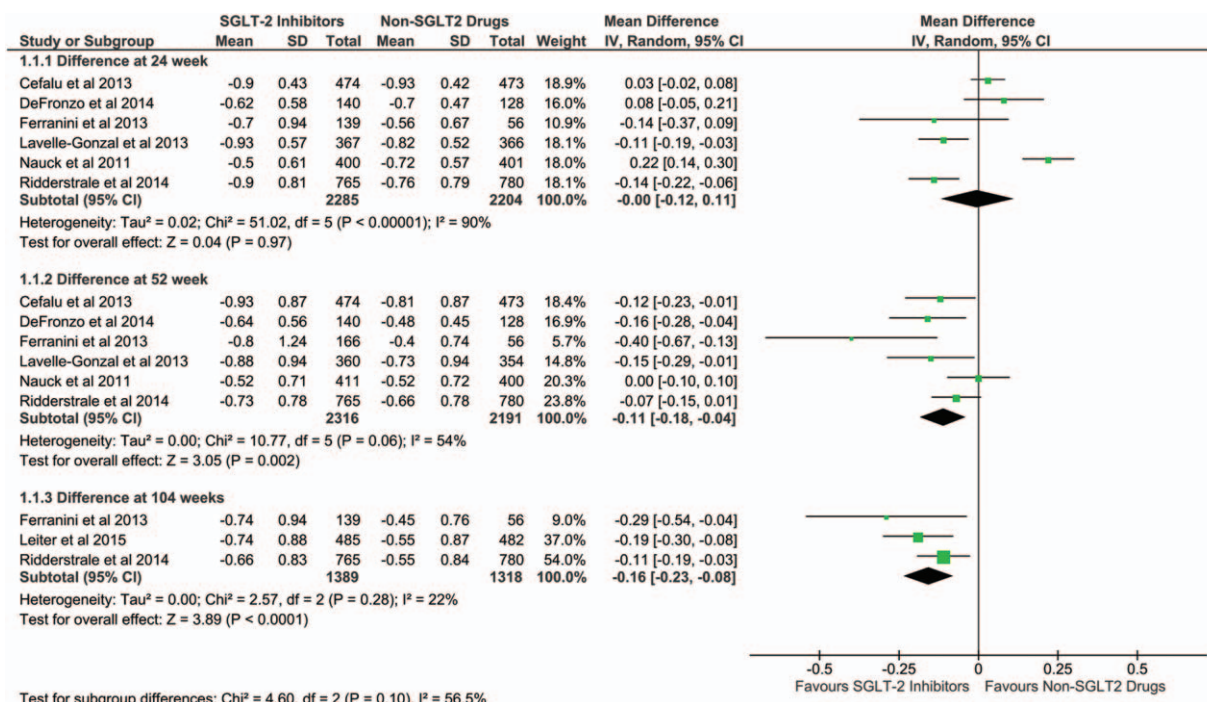
Figure 2. Forest plot showing the effect of SGLT2 inhibitors in comparison with non-SGLT2 combinations as add-on treatment to metformin in changing %HbA1c from baseline. %HbA1c = glycosylated hemoglobin-A1c, SGLT2 = sodium-glucose transporter-2.

combinations after 52 weeks (−0.11 [−0.18, −0.04]; $P < .00001$) and after 104 weeks (−0.16 [−0.21, −0.08]; $P < .00001$) of treatment. However, there was no significant difference between the groups in reducing percent HbA1c at week 24 of treatment period (Fig. 2; Table 4).

The SGLT2 inhibitors as add-on to metformin treatment were also found significantly ($P < .00001$) better in comparison with non-SGLT2 combinations in reducing FPG levels (−0.65 [−0.94, −0.35] after 52 weeks and −0.72 [−0.86, −0.58] after 104 weeks) as well as blood pressure (SBP: −4.88 [−5.66, −4.10]
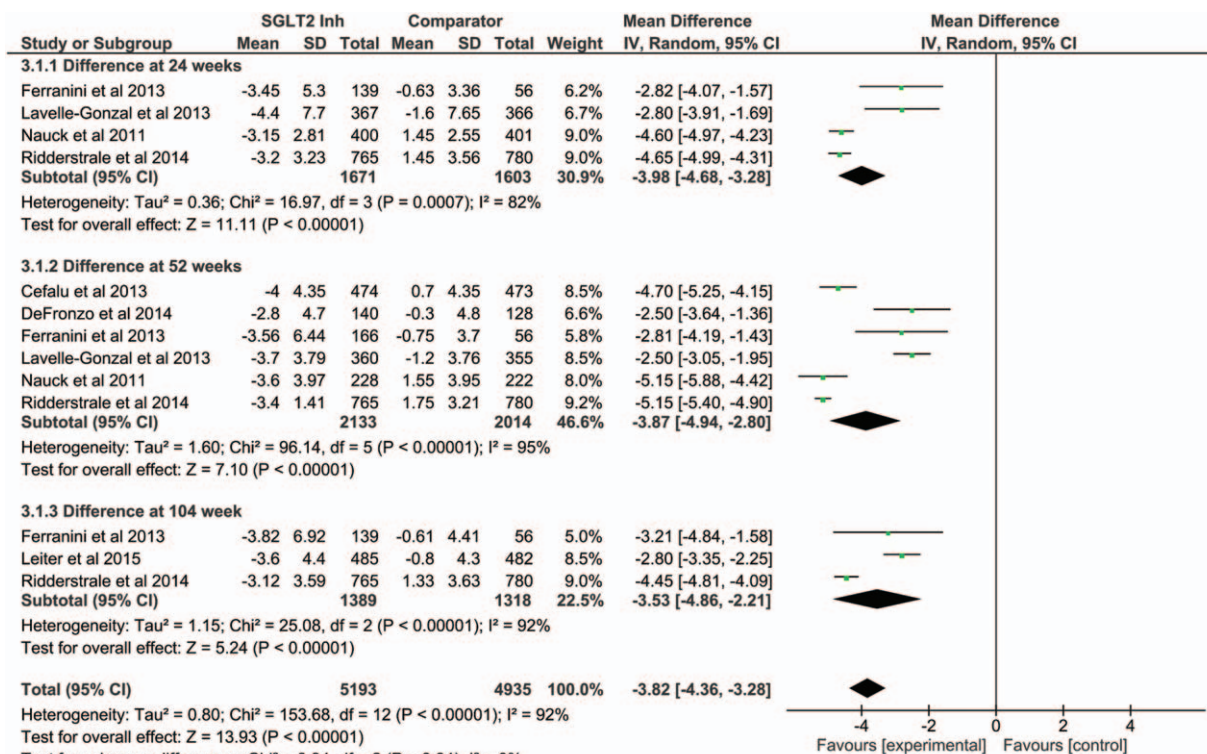

Figure 3. Forest plot showing the effect of SGLT2 inhibitors in comparison with non-SGLT2 combinations as add-on treatment to metformin in changing body weight from baseline. SGLT2 = sodium-glucose transporter-2.
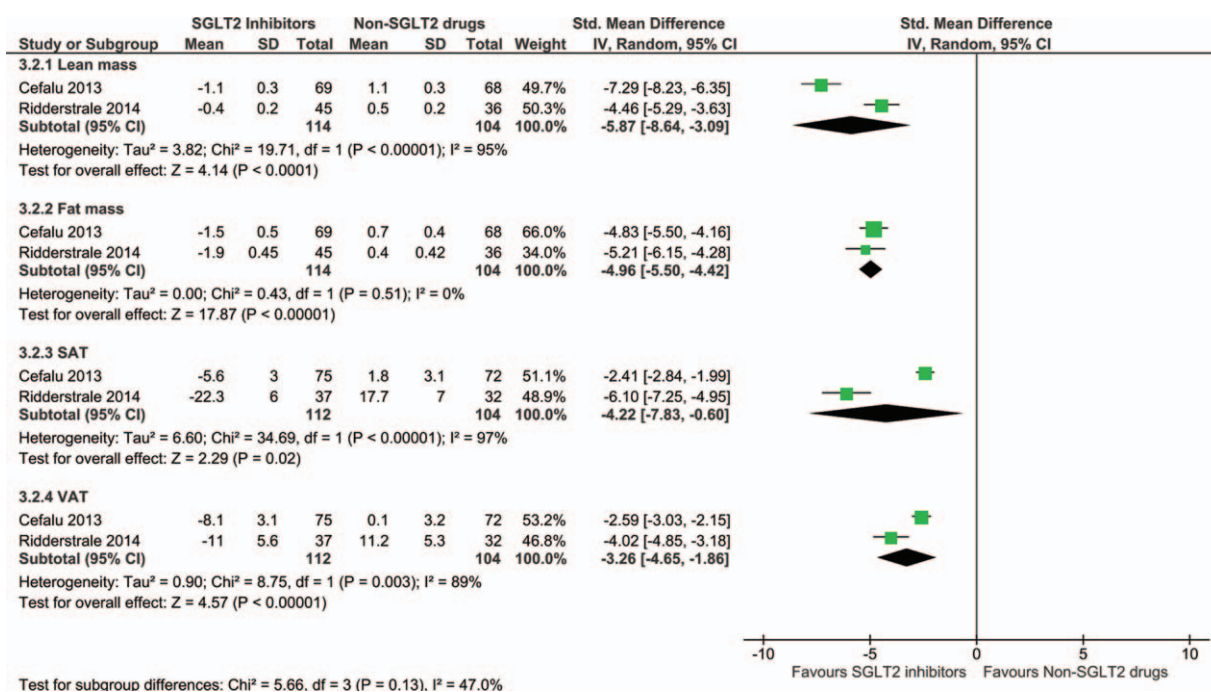
Figure 4. Forest plot showing the effect of SGLT2 inhibitors in comparison with non-SGLT2 combinations as add-on treatment to metformin in changing lean and fat body mass from baseline. SGLT2 = sodium-glucose transporter-2.

after 52 weeks and -5.33 [-6.29, -4.36] after 104 weeks; DBP: -2.38 [-2.93, -1.84] after 52 weeks and -2.55 [-3.19, -1.91] after 104 weeks). These improvements were also associated with significantly higher eGFR with the SGLT2 inhibitor treatment at weeks 24 and 52 but not at week 104 (Table 4).

The SGLT2 inhibitors as add-on to metformin treatment significantly ($P < .00001$) reduced body weight in comparison with non-SGLT2 combinations after 52 weeks (-3.87 [-4.94, -2.80]) and after 104 weeks (-3.53 [-4.86, -2.21]; Fig. 3). This reduction in body weight by the SGLT2 inhibitors was associated with significant reductions in fat mass (both SAT and VAT) as well as lean mass (Fig. 4).

The safety profile of the SGLT2 inhibitors and non-SGLT2 combinations differed with respect to the incidence of genital tract infections and hypoglycemic events. The incidence of suspected or confirmed genital tract infection was significantly ($P < .00001$) higher in SGLT2 inhibitors treated patients (OR 6.41 [3.58, 11.45] for men and 5.12 [3.48, 7.54] for women; Fig. 5A) whereas the incidence of hypoglycemic events was significantly lower in the SGLT2 inhibitor group than in non-SGLT2 combination group (OR 0.27 [0.09, 0.78]; $P = .02$; Fig. 5B). There was no significant difference in the incidence of urinary tract infections between both the groups (OR 1.13 [0.92, 1.39]; $P = .25$).

There was also no significant difference in the incidence of adverse effects in categorical measures including "at least 1 AE" (OR 1.01 [0.87, 1.16]; $P = .94$), "at least 1 drug-related AE" (OR 1.09 [0.81, 1.47]; $P = .58$), "at least 1 serious AE" (OR 0.82 [0.55, 1.22]; $P = .33$), or "at least 1 AE causing discontinuation" (OR 1.19 [0.91, 1.55]; $P = .71$). There were also no significant differences between the groups in the incidence of individual adverse effects including back pain, influenza, nausea, diarrhea, arthralgia, postural dizziness, bronchitis, gastroenteritis, constipation, nasopharyngitis, respiratory tract infection, hyperglyce-

mia, hypertension, pollakiuria, polyuria, and orthostatic hypotension. No AE related to ketoacidosis was reported by any of the included studies.

4. Discussion

This systematic review was conducted with the aim to evaluate the long-term efficacy and safety of SGLT2 inhibitors as add-on to metformin treatment in type 2 diabetes patients. As add-on to metformin, SGLT2 inhibitor treatment was significantly better than non-SGLT2 combinations in reducing percent % HbA1c, FPG levels, body weight, and blood pressure for more than 2 years. Whereas, the incidence of hypoglycemic events was significantly lower, the incidence of suspected or confirmed genital tract infections was significantly higher in the SGLT2 inhibitor group.

Placebo-controlled trials evaluating the efficacy and safety of SGLT2 inhibitors as add-on to metformin in 52- and 104-week trials have also reported SGLT2 inhibitors to be significantly more efficacious.[20,30] Other related studies also support these findings, for example, Schernthaner et al[17] who compared CANA (300 mg) with sitagliptin (100 mg) as add-on to metformin plus sulfonylurea treatment in type 2 diabetes patients in 1-year duration trial, found CANA similar to sitagliptin in reducing HbA1c but CANA-treated group exhibited greater reductions in FPG, BW, and SBP. Tolerability profile of both the arms was also much similar.

These results suggest that combination therapies with metformin and SGLT2 inhibitors can provide long-term benefits to patients having inadequate control on disease with metformin. Management of type 2 diabetes with SGLT2 inhibitors is a therapeutic option which offers multiple benefits including insulin-independent mechanism of action, significant weight reduction, and blood pressure improvement besides glycemic
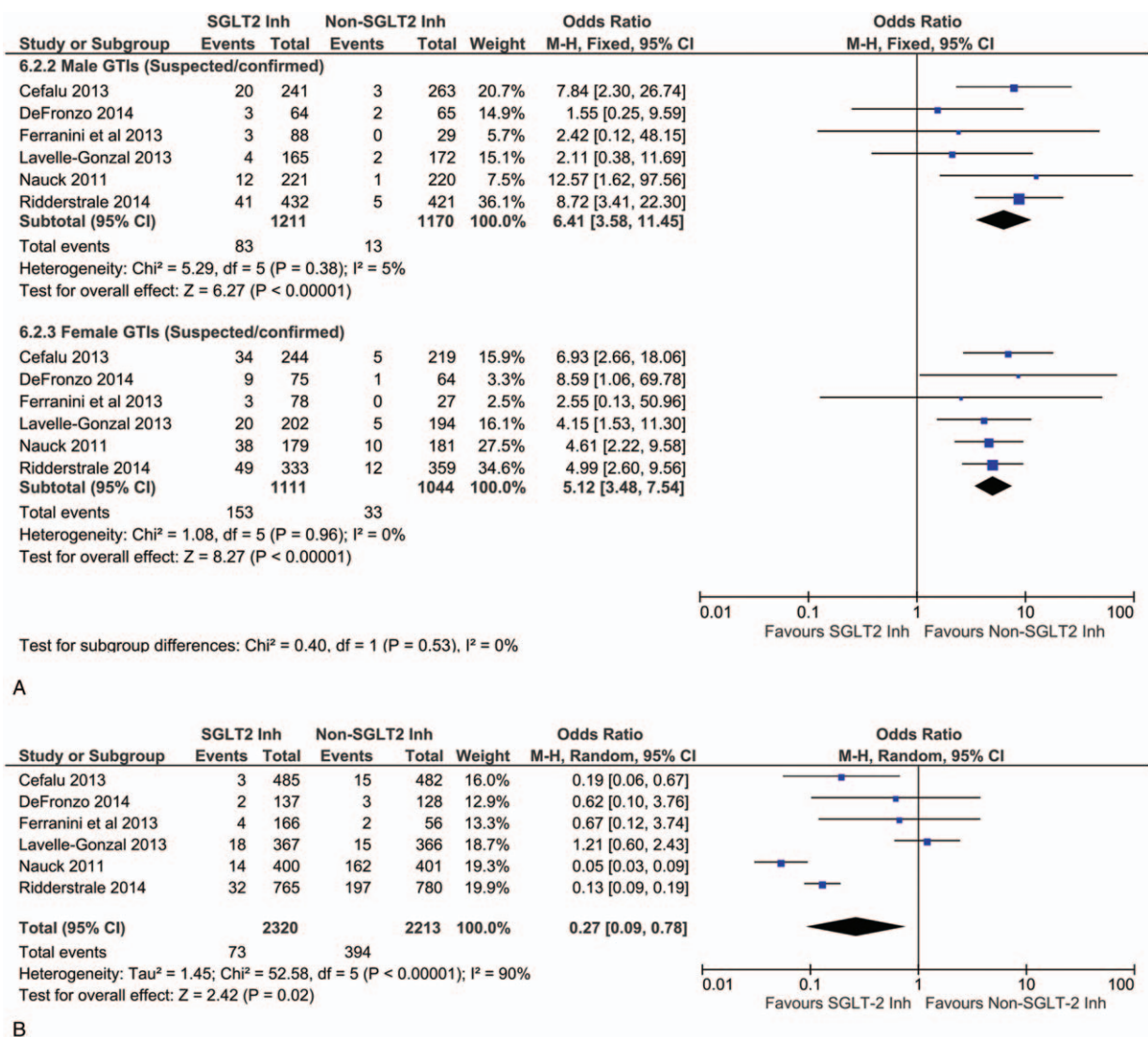
Figure 5. Forest plots showing the incidence of adverse effects in comparison between SGLT2 inhibitors and non-SGLT2 combinations as add-on treatment to metformin; (A) suspected genital tract infections, and (B) incidence of hypoglycemic events. SGLT2 = sodium-glucose transporter-2.

control. Insulin independent mechanism of action of the SGLT2 inhibitors also makes them an attractive option in clinical practice because of their low risk of the incidence of hypoglycemia which makes it feasible to use with insulin secretagouges or early insulin therapy.

Weight loss is an important effect of the SGLT2 inhibitor therapy. Although, SGLT2 inhibitor-metformin fixed-dose bitherapeutic regimens are already in use,[31,32] future studies are needed to evaluate the evidence of efficacy and safety of these fixed-dose therapies in the longer run. The SGLT2 inhibitors are potentially better in declining body weight in comparison with its contemporary drugs. One gram of urinary glucose loss means a loss of 4 kcal energy which can lead to significant weight loss in the long run,[33] especially if lifestyle interventions are observed optimally by the patient. However, future research designs should make provisions for food and fluid intake control along with 24-hour measurement of urinary glucose excretion in the clinical trials in order to understand the mechanism of weight loss by SGLT inhibitors.[9]

Although, none of the included studies of this meta-analysis reported any case of ketoacidosis, recently FDA has warned about the production of excessive ketoacids in some diabetes patients taking SGLT2 inhibitors when it was noted that 20 cases required hospitalization owing to the acidosis with SGLT2 treatment.[34] In the present meta-analysis, SGLT2 as add-on to metformin treatment has also been found to be associated with decrease in lean mass along with fat mass. Whether the decrease in lean mass will have a significant association with ketoacidosis remains to be further researched.

The slightly higher incidence of urogenital infections in SGLT2 inhibitor treated type 2 diabetes patients has been reported after analysis of pooled data from phase III trials of over 52 weeks' duration[35] which is thought to be due to increased urinary glucose which may act as a potential fungal growth factor in SGLT2 inhibitor treated patients.[36] In the present study, we have noted a significantly higher incidence of suspected or confirmed genital infections with almost double incidence in women than in men. Such observations have raised concerns

about the safety testing of SGLT2 inhibitors with regards to the higher incidence of genital infections.[37,38]

One important limitation of this meta-analysis is that trials evaluating the efficacy of SGLT2 inhibitors beyond 2 years are not yet available. Parallel to efficacy, safety analysis in longer-term trials is also necessary. Another constraint was related to statistical heterogeneity (I^2) which was high in many analyses. Although, I^2 does not indicate variation in the effect size, nevertheless it pertains to the extent of inconsistency of findings across studies meta-analyzed in terms of the extent to which confidence intervals of the effect size of included studies overlap. To which this heterogeneity can be attributed to clinical and/or methodological heterogeneity could be clarified in future trials.

Nevertheless, despite some limitations, the present analysis provides reliable summary estimates of the interventions of 6 important RCTs. As Bailey[39] postulated that keeping in mind that type 2 diabetes is a progressive disease, the need for additional therapeutic agents over time is normative and clinical experience and pertinent clinical trial outcomes can help in individualizing the therapy by patient and medication characteristics.

5. Conclusion

Sodium-glucose cotransporter-2 inhibitors as add-on to metformin treatment for type 2 diabetes mellitus patients are found significantly more efficacious than non-SGLT2 combinations in the long-term treatment duration trials by virtue of their effects in improving disease markers (% HbA1c and FPG levels), blood pressure, and body weight. Incidence of hypoglycemic events was significantly lower but incidence of genital tract infections was significantly higher in patients treated with SGLT2 inhibitors. However, more trials are required to assess the efficacy and safety of SGLT2 inhibitors beyond 2 years.

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