REVIEW

Korean J Intern Med 2017;32:974-983
https://doi.org/10.3904/kjim.2017.354

Combination therapy of oral hypoglycemic agents in patients with type 2 diabetes mellitus

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The Korean Diabetes Association (KDA) recently updated the Clinical Practice Guidelines on antihyperglycemic agent therapy for adult patients with type 2 diabetes mellitus (T2DM). In combination therapy of oral hypoglycemic agents (OHAs), general recommendations were not changed from those of the 2015 KDA guidelines. The Committee on Clinical Practice Guidelines of the KDA has extensively reviewed and discussed the results of meta-analyses and systematic reviews of effectiveness and safety of OHAs and many clinical trials on Korean patients with T2DM for the update of guidelines. All OHAs were effective when added to metformin or metformin and sulfonylurea, although the effects of each agent on body weight and hypoglycemia were different. Therefore, selection of a second agent as a metformin add-on therapy or third agent as a metformin and sulfonylurea add-on therapy should be based on the patient's clinical characteristics and the efficacy, side effects, mechanism of action, risk of hypoglycemia, effect on body weight, patient preference, and combined comorbidity. In this review, we address the results of meta-analyses and systematic reviews, comparing the effectiveness and safety among OHAs. It will help to choose the appropriate drug for an individual patient with T2DM.

Keywords: Diabetes mellitus, type 2; Efficacy; Oral hypoglycemic agents; Practice guideline

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This manuscript is simultaneously published in the *Diabetes Metabolism Journal* and the *Korean Journal of Internal Medicine* by the Korean Diabetes Association and the Korean Association of Internal Medicine.

Received: September 28, 2017
Accepted: October 20, 2017

pISSN 1226-3303
eISSN 2005-6648
http://www.kjim.org

INTRODUCTION

The Korean Diabetes Association (KDA) has stated that the prevalence of diabetes among adults 30 years or older was about 13.7% in 2014 [1]. Good glycemic control is well known to be the best way to prevent chronic complications of diabetes [2], but the control rate of glycemia among those with diagnosed diabetes is only 23.3% for a target goal of glycosylated hemoglobin (HbA1c) < 6.5% or 43.5% for < 7.0% [1,3]. Because about 80% of people with diabetes are treated with oral hypoglycemic agents (OHAs) [1,3], it is very important to establish appropriate guidelines for the selection of OHAs. Moreover, most OHAs were developed in Western countries, so the efficacy and safety data of OHAs were provided from the clinical studies performed on Caucasians. The pharmacodynamics and pharmacokinetics of specific OHAs can be different among ethnicities. Therefore, it is very important to get specifically Korean data. Fortunately, many clinical trials on Korean patients with diabetes have been conducted, and the results have been published in the past few years. For this 2017 position statement regarding pharmacological therapies for non-pregnant adult patients with type 2 diabetes mellitus (T2DM), extensive review of scientific evidence, including the results of clinical trials of OHAs for Koreans was performed by the Committee on Clinical Practice Guidelines of the KDA. In this review, we describe the results of systematic reviews and the considerations during the process and propose appropriate combination therapy of OHAs for Korean patients with T2DM.

RECOMMENDATIONS

Principles of treatment with antihyperglycemic agents

1. Metformin is the preferred initial oral antihyperglycemic agent [A].
2. If metformin is contraindicated or intolerable as the initial treatment, then another class of antihyperglycemic agent can be used, depending on the clinical situation [E].
3. If monotherapy fails to achieve the glycemic goal, then combination therapy using a second agent with a different mechanism of action should be initiated [A].
4. Dual combination therapy can be used as the initial management strategy, depending on the patient [B].
5. Although the maximal dosage of a single oral agent may be prescribed, early initiation of combination therapy is suitable after considering the glucose-lowering efficacy and side-effects of the drug [B].
6. When selecting a class of antihyperglycemic agents for combination therapy, the glucose-lowering efficacy, risk of hypoglycemia, body weight gain, and cardiovascular benefits associated with the drugs are preferentially considered [E].
7. The different mechanisms of action, drug interactions, and patient preferences for combination therapy with more than two classes of antihyperglycemic agents should be considered [C].

WHAT IS THE BEST DRUG AS ADD-ON THERAPY TO METFORMIN?

There are six major classes of antidiabetic agents that can be combined with metformin. They are sulfonylurea (SU), thiazolidinediones (TZDs), dipeptidyl peptidase-4 inhibitors (DPP4i), sodium-glucose cotransporter-2 inhibitors (SGLT2i), glucagon-like peptide-1 receptor agonists, and insulin. The American Diabetes Association does not prioritize any specific medication and recommends physicians to choose one based on their efficacy, hypoglycemic risk, weight effects, side-effects, and cost [4]. However, the American Association of Clinical Endocrinologists recommended the SGLT2i first, followed by DPP4i, TZD, α-glucosidase inhibitors, and SU among the OHAs, mainly based on the weight-reducing effect [5]. In this paper, we provide a comparative review among the OHAs based on meta-analyses and suggest a guide to select one as a first-combination medication with metformin.

Comparison of SU and DPP4i as an add-on therapy to metformin

Several meta-analyses compared SU and DPP4i as an add-on therapy to metformin [6-11]. DPP4i lowered HbA1c levels to a similar extent [6,7] or slightly less (HbA1c difference 0.08% to 0.21%) [8,9,11] compared to SU when added to metformin (Table 1). A meta-analysis comparing DPP4i with SU as an add-on therapy to

Table 1. Summary of meta-analyses reviewed for comparison of sulfonylurea and DPP-4 inhibitor as an add-on therapy to metformin

Study	Included trials (*n*)	Results
Palmer et al. (2016) [8]	301 RCTs comparing 2 glucose-lowering drug classes for treatment of T2DM for 24 weeks' or longer duration	No significant differences in the associations between any of 9 available classes of glucose-lowering drugs (alone or in combination) and the risk of cardiovascular or all-cause mortality All drugs were effective when added to metformin.
Mishriky et al. (2015) [7]	16 RCTs comparing DPP4i to SU as add-on therapy to metformin	A significantly greater reduction in HbA1c from baseline to 12 weeks with SU vs. DPP4i (MD, 0.21%; 95% CI, 0.06–0.35) No significant difference at 52 and 104 weeks (MD, 0.06%; 95% CI, 0.03–0.15; and MD, 0.02%; 95% CI, 0.13–0.18, respectively) SU was associated with weight gain and DPP4i with weight loss at all time-points. The incidence of hypoglycemia at 12, 52, and 104 weeks was significantly greater with SU (20%, 24%, and 27% respectively) compared to DPP4i (6%, 3%, and 4% respectively).
Zhou et al. (2016) [9]	14 RCTS comparing DPP4i to SU (5,480 patients randomised to DPP4i and 5,214 patients randomised to SU)	Compared with SU, DPP4i were associated with a smaller decline in HbA1c (WMD, weighted mean differences, 0.08%; 95% CI, 0.03–0.14; $p = 0.001$), and resulted in weight loss of 1.945 kg (95% CI, –2.237 to –1.653; $p < 0.0001$). The effect of DPP4i lowering FPG was inferior to that of SU (WMD, 0.268 mmol/L; 95% CI, 0.151–0.385; $p < 0.0001$), and similar in reducing PPG (WMD, 0.084 mmol/L; 95% CI, –0.701 to 0.869; $p = 0.833$). DPP4i had a favorable insulin resistance and low risk for AE and hypoglycemia.
Foroutan et al. (2016) [10]	10 RCTs comparing DPP4i to SU as add-on therapy to metformin (10,139 subjects)	DPP4i compared to SU produced a non-significant difference in HbA1c% change whereas a significant decrease in the rate of hypoglycemic events was observed in favor of DPP4i. DPP4i was associated with significant weight loss (2.2 kg) compared to SU.

RCT, randomized controlled trial; T2DM, type 2 diabetes mellitus; DPP4i, dipeptidyl peptidase-4 inhibitor; SU, sulfonylurea; MD, mean difference; CI, confidence interval; HbA1c, glycosylated hemoglobin; WMD, weighed mean difference; FPG, fasting plasma glucose; PPG, postprandial glucose; AE, adverse events.

metformin showed a significantly greater reduction in HbA1c from baseline to 12 weeks with SU versus DPP4i (mean difference, 0.21%) but no significant difference at 52 and 104 weeks [7]. As we expected, DPP4i was associated with a lower risk of hypoglycemia (odds ratio [OR], 0.12) and weight gain (–0.58 kg) compared to SU. In terms of cardiovascular (CV) outcome, there were no significant differences between DPP4i and SU for CV mortality, all-cause mortality, serious adverse events, or myocardial infarction, but DPP4i and metformin exhibited a lower risk of stroke compared with a combination of SU and metformin (OR, 0.47; 95% confidence interval [CI], 0.23 to 0.95) in a meta-analysis of 301 randomized clinical trials involving 118,094 patients published in JAMA in 2016 [8]. In a cohort study of 349,476 patients with T2DM, using the Korean National Health Insurance Service (NHIS) claims database, however, treatment with SU + metformin was associated with increased total cardiovascular disease (CVD) (hazard ratio [HR], 1.20; 95% CI, 1.09 to 1.32), myocardial infarction (HR, 1.41; 95% CI, 1.04 to 1.91), and ischemic stroke risks (HR, 1.51; 95% CI, 1.28 to 1.79) compared with a DPP4i + metformin regimen [12]. Because there is no randomized controlled prospective study for CV outcomes for SU, and all possible confounders could not be adjusted in observational studies, these results should be interpreted with caution. However, DPP4i is at least not inferior to SU in terms of efficacy and superior in terms of safety.

https://doi.org/10.3904/kjim.2017.354

Table 2. Between-group differences in the change in HbA1c for comparison of SU and SGLT2i as an add-on therapy to metformin [13]

Intervention	Trials	Duration, wk	No. of patients	HbA1c SGLT2i	HbA1c control	Change in HbA1c (mean difference)
Metformin + SGLT2i vs. Metformin + SU	Cefalu et al. (2013) [14]	104	1,452	7.8	7.8	−0.19 (−0.29 to −0.09)
	Nauck et al. (2011) [15]	208	814	7.7	7.7	−0.30 (−0.79 to 0.19)
	Ridderstrale et al. (2014) [16]	104	1,549	7.9	7.9	−0.11 (−0.19 to −0.03)
	Total					−0.15 (−0.21 to −0.08)

HbA1c, glycosylated hemoglobin; SU, sulfonylurea; SGLT2i, sodium-glucose cotransporter-2 inhibitor.

Comparison of SU and SGLT2i as an add-on therapy to metformin

Two meta-analyses showed that SGLT2i as an add-on therapy to metformin lowered HbA1c levels more (0.15%) than SU did (Table 2) [6,13-16]. In addition, SGLT2i was associated with a lower risk of hypoglycemia and less body weight gain [6,8,13]. Because these analyses included only three studies, and differences in efficacy among SGLT2i results were reported [17], we need to wait for further studies.

From pooled data from four empagliflozin phase III trials, adjusted mean differences versus placebo in change from baseline in HbA1c were −0.61% (baseline, 7.91%) and −0.75% (baseline, 7.94%) and in weight were −1.4 kg (baseline, 70.3 kg) and −1.5 kg (baseline, 72.1 kg) with empagliflozin 10 and 25 mg, respectively, when combined with metformin in Asian patients with T2DM [18]. These results were consistent with previous empagliflozin phase III trials in which at week 24, adjusted mean ± SE changes from baseline in HbA1c were −0.70% ± 0.05% with empagliflozin 10 mg, and −0.77% ± 0.05% with empagliflozin 25 mg [19]. In terms of ipragliflozin and metformin combination therapy in Korean patients with T2DM inadequately controlled with metformin, adjusted mean differences versus placebo in change from baseline in HbA1c were −0.60% (baseline, 7.67%) and in weight were −1.53 kg (baseline, 68.12 kg) with ipragliflozin [20]. These results suggested that the efficacy of SGLT2i in Korean patients with T2DM as an add-on therapy to metformin would be similar to Caucasian populations.

Comparison of DPP4i and SGLT2i as an add-on therapy to metformin

A meta-analysis of 4 clinical studies showed that SGLT2i as an add-on therapy to metformin lowered HbA1c levels more (0.17%) and body weight much more than DPP4i (Table 3) [13,21-24]. In a meta-analysis published in JAMA in 2016, the rate of treatment failure was significantly lower with SGLT2i (OR, 0.68; 95% CI, 0.48 to 0.96) and higher with DPP4i (OR, 1.37; 95% CI, 1.07 to 1.76) than with SU [8]. In addition, both DPP4i and SGLT2i were associated with a lower risk of hypoglycemia compared to SU, and the ORs of both drugs were similar to 0.12 [19].

The CV safety of DPP4i has been demonstrated through the Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus–Thrombolysis in Myocardial Infarction 53 (SAVOR-TIMI 53), the Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care (EXAMINE), and the Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS) trials [25-27]. However, these trials failed to show the CV benefits. In contrast, in the Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG) Outcome trial, patients who received empagliflozin rather than a placebo had lower rates of primary composite CV outcome (10.5% vs. 12.1% in the placebo group; 14% relative risk reduction), death from CV causes (3.7%, vs. 5.9%, respectively; 38% relative risk reduction), hospitalization for heart failure (2.7% and 4.1%, respectively; 35% relative risk reduction), and death from any cause (5.7% and 8.3%, respectively; 32% relative risk reduction) [28]. Moreover, empagliflo-

Table 3. Between-group differences in the change in HbA1c for comparison of DPP4i and SGLT2i as an add-on therapy to metformin [13]

Intervention	Trials	Duration, wk	No. of patients	HbA1c SGLT2i	HbA1c control	Change of HbA1c (mean difference)
Metformin + SGLT2i vs. Metformin + DPP4i	Lavalle-Gonzalez et al. (2013) [21]	26	1,284	7.9	7.9	−0.12 (−0.23 to −0.01)
	Rosenstock et al. (2012) [22]	12	451	7.7	7.6	−0.18 (−0.40 to 0.04)
	Rosenstock et al. (2015) [23]	24	534	8.9	9.0	−0.32 (−0.53 to −0.11)
	DeFronzo et al. (2015) [24]	52	899	8.0	8.0	−0.16 (−0.33 to 0.01)

HbA1c, glycosylated hemoglobin; DPP4i, dipeptidyl peptidase-4 inhibitor; SGLT2i, sodium-glucose cotransporter-2 inhibitor.

in was associated with slower progression of kidney disease and lower rates of clinically relevant renal events [29]. In subsequent the Canagliflozin Cardiovascular Assessment Study (CANVAS) and CANVAS–Renal trials, canagliflozin was also associated with lower rates of CVD and renal outcome [30].

From these results, it appears that SGLT2i can be superior to DPP4i. However, there are a few things to consider before deciding which drug is better. First, adverse reactions of SGLT2i such as urogenital infection, euglycemic diabetic ketoacidosis, or dehydration may limit the use of SGLT2i. Second, DPP4i have been reported to be more effective in lowering blood glucose levels in Asians, including Koreans, than in Caucasian [31]. A meta-analysis revealed that DPP4i lowered HbA1c to a greater extent in studies with ≥ 50% of Asian participants (weighted mean difference [WMD], −0.92%; 95% CI, −1.03 to −0.82) than in studies with < 50% Asian participants (WMD, −0.65%; 95% CI, −0.69 to −0.60). The between-group difference was −0.26% (95% CI, −0.36 to −0.17; $p < 0.001$) [11]. In trials with oral combination therapy, HbA1c decreased by 0.66% in the non-Asian dominant studies, whereas it decreased by 0.85% in the Asian-dominant studies. In fact, in clinical studies conducted in Korea, the HbA1c-lowering effect of DPP4i was 0.8% to 1.2% after 24 weeks of treatment with around 8% of baseline HbA1c [32-34]. These results are comparable to the efficacy of the SGLT2i [20].

Therefore, it is difficult to give a comprehensive answer about whether SGLT2i or DPP4i should be preferable in combination therapy with metformin. The choice of an adequate drug should be decided in consideration of the individual characteristics of the patient and the response to the drug.

Comparison of TZD and SU or DPP4i as an add-on therapy to metformin

A meta-analysis showed that TZD lowered HbA1c levels to similarly to SU and slightly more (0.12%) than DPP4i when added to metformin [6]. TZD significantly increased body weight compared to SU and DPP4i [6]. This meta-analysis included only four randomized clinical trials and 674 participants, so the strength of evidence was moderate. In addition, as previously commented, it should be considered that the glucose-lowering efficacy of DPP4i can be higher in Asians than in Caucasians. In the study comparing the efficacy of vildagliptin (50 mg twice daily) to that of pioglitazone (15 mg once daily) as an add-on treatment to metformin in Korean patients with T2DM, the efficacy of vildagliptin to lower the HbA1c level was not inferior to that of pioglitazone, and vildagliptin had beneficial effects on postprandial glucose levels compared to pioglitazone [35]. On the other hand, in the study comparing the efficacy of lobeglitazone and pioglitazone as add-ons to metformin, both of them decreased HbA1c by 0.74% at week 24 [36]. Therefore, the efficacy difference between DPP4i and TZD might be less significant in Koreans.

In the PROspective pioglitAzone Clinical Trial In macroVascular Events (PROactive Study), pioglitazone

https://doi.org/10.3904/kjim.2017.354

reduced the composite of all-cause mortality, non-fatal myocardial infarction, and stroke in patients with T2DM who have a high risk of macrovascular events [37]. In addition, in a cohort study of 349,476 patients with T2DM, using the Korean NHIS claims database, treatment with pioglitazone + metformin was associated with decreased total CVD (HR, 0.89; 95% CI, 0.81 to 0.99), ischemic stroke risks (HR, 0.81; 95% CI, 0.67 to 0.99), and increased heart failure risks (HR, 4.81; 95% CI, 3.53 to 6.56) compared with a DPP4i + metformin combination [12]. It has been reported that TZDs have long-term benefits in glycemic control by augmenting insulin sensitivity and preserving β-cell function [38-40]. In the study that compared the efficacy of TZDs to other oral glucose-lowering medications in maintaining long-term glycemic control in T2DM, the cumulative incidence of monotherapy failure at 5 years was 15% with rosiglitazone, 21% with metformin, and 34% with glyburide [38]. Therefore, it is difficult to say that either DPP4i or TZD is superior, and appropriate drugs should be selected after consideration of individual status.

TRIPLE ORAL AGENT COMBINATION THERAPY

Five meta-analyses were performed to evaluate the comparative effectiveness and safety of triple combination therapy (drugs added to metformin + SU) (Table 4) [8,41-44]. The addition of a third drug to metformin + SU therapy was statistically and clinically more effective at reducing HbA1c than dual therapy with metformin + SU. In these analyses, the HbA1c-lowering effect was consistently better when combined with TZD (–0.93%) and SGLT2i (–0.86%) than with DPP4i (–0.68%) or acarbose (–0.60%). When triple therapies are compared with each other; however, there are no statistically significant differences with regard to change in HbA1c for any of the comparisons. In a network meta-analysis including 20 randomized controlled trials, canagliflozin and TZDs reduced HbA1c by ~1% (range, 0.98% to 1.2%), whereas acarbose, dapagliflozin, empagliflozin, and DPP4i reduced HbA1c by 0.60% to 0.76% when compared to placebo/control [44]. Interestingly, a triple combination of metformin + TZD + DPP4i showed no improvement in HbA1c compared to metformin + SU [41]. In terms of weight, as we can expect, the SGLT2i was associated with significant weight loss, and the TZDs and DPP4i resulted in significant weight gain compared with placebo/control. In terms of hypoglycemia, although the results are different among the analyses, TZDs as add-on therapy to metformin + SU were associated with significantly higher rates of hypoglycemia [8,44]. It seems there are no statistically significant differences in the risks of hypoglycemia among most triple therapies [41]. In terms of CV safety, there was no evidence of significantly different associations with CV mortality, all-cause mortality, or serious adverse events between any of the drug classes given as triple therapy [8]. From these analyses, the combination of metformin + SU + TZD is the best in lowering HbA1c, but it is the worst in weight gain and hypoglycemia. The combination of metformin + SU + SGLT2i is the second-best in lowering HbA1c, but it is the best in weight loss. The combination of metformin + SU + DPP4i is relatively weak in lowering HbA1c compared to metformin + SU + SGLT2i or metformin + SU + TZD. Therefore, SGLT2i is a reasonable option as a third agent added to metformin + SU. At this point, we have to consider that the efficacy of DPP4i can be higher in Asians. Actually, the addition of gemigliptin significantly reduced HbA1c levels (0.87% at week 24) compared with placebo in 219 Korean patients inadequately controlled with metformin and glimepiride [45]. In the other study, the addition of vildagliptin to metformin and SU decreased the adjusted mean HbA1c levels by 1.19% at week 24 [32], and this reduction seems to be comparable to that of TZD or SGLT2i.

Because there were only limited data about the comparison of other triple combination therapies other than the addition of a third drug to metformin + SU, the preceding descriptions about triple combination therapy need to be interpreted with care.

CONCLUSIONS

Both in metformin add-on and in metformin + SU add-on, SGLT2i and TZD showed more efficacy than DPP4i or acarbose, but the actual difference was as small as 0.1% to 0.2% of HbA1c. Although the difference is statistically significant, it does not seem to be clinically meaningful because usually the difference in HbA1c of ≥ 0.3% is regarded as meaningful. In addition, dif-

Table 4. Summary of meta-analyses reviewed for comparison of triple oral agent combination therapy

Study	Included trials (*n*)	Results
Palmer et al. (2016) [8]	301 RCTs comparing 2 glucose-lowering drug classes for treatment of T2DM for 24 weeks' or longer duration	No significant differences in the associations between any of 9 available classes of glucose-lowering drugs (alone or in combination) and the risk of cardiovascular or all-cause mortality All drugs were effective when added to metformin.
Mearns et al. (2015) [44]	20 RCTs evaluating 13 antihyperglycaemic agents in adults with T2DM experiencing poor glycemic control despite optimized metformin and SU therapy	Compared with placebo/control, all antihyperglycemic agents reduced HbA1c levels, albeit by differing magnitudes (0.6% for acarbose to 1.20% for liraglutide) SGLT2i reduced weight (1.43–2.07 kg), whereas TZDs, glargine and sitagliptin caused weight gain (1.48–3.62 kg) compared with placebo/control. SGLT2i, rosiglitazone and liraglutide decreased SBP compared with placebo/control, pioglitazone, glargine and sitagliptin (2.41–8.88 mmHg) Glargine, TZDs, liraglutide, sitagliptin, and canagliflozin increased hypoglycemia risk compared with placebo/control (relative risk, 1.92–7.47), while glargine and rosiglitazone increased hypoglycemia compared with most antihyperglycemic agents (relative risk, 2.81–7.47). Canagliflozin increased the risk of genital tract infection by 3.9-fold compared with placebo/control.
Downes et al. (2015) [41]	27 RCTs comparing metformin + SU dual therapy to other triple therapy combinations	For HbA1c reduction, all triple therapies were statistically superior to metformin + SU dual therapy, except for metformin + TZD + DPP4i. None of the triple therapy combinations demonstrated differences in HbA1c compared with other triple therapies. Metformin + SU + SGLT2i and metformin + SU + GLP-1RA resulted in significantly lower body weight than metformin + SU + DPP4i, metformin + SU + insulin and metformin + SU + TZDs; metformin + SU + DPP4i resulted in significantly lower body weight than metformin + SU + insulin and metformin + SU + TZD. Metformin + SU + insulin, metformin + SU + TZD and metformin + SU + DPP4i increased the odds of hypoglycaemia when compared to metformin + SU. Metformin + SU + GLP-1RA reduced the odds of hypoglycemia compared to metformin + SU + insulin.
Lee et al. (2016) [42]	40 RCTS comparing dual therapy to any triple combinations (15,182 participants)	Compared with none/placebo added to dual therapy, triple combination therapy resulted in significant additional mean reductions in HbA1c from −0.56% (DPP4i) to −0.94% (TZDs). Insulin, TZD and SU were associated with less favourable weight change and GLP-1RA and SGLT2i were associated with more favourable weight change when compared with none/placebo added to dual therapy. Compared with none/placebo added to dual therapy, the odds of hypoglycemia were higher for DPP4i (1.95), SGLT2i (2.27), GLP-1RA (2.61), TZD (2.83), and insulin (5.94).
Lozano-Ortega et al. (2016) [43]	30 RCTs comparing SGLT2i to other drugs as add-on therapy to metformin and SU	The mean change (%) in HbA1c levels compared to placebo was −0.86 for SGLT2i, −0.68 for DPP4i, −0.93 for TZDs, and −1.07 for GLP-1RA, respectively. Only SGLT2i and GLP-1RA led to a weight loss (−1.71 and −1.14 kg, respectively) and decrease in SBP (−3.73 and −2.90 mmHg, respectively), while all other treatments showed either an increase or no changes in weight or SBP.

RCT, randomized controlled trial; T2DM, type 2 diabetes mellitus; SU, sulfonylurea; HbA1c, glycosylated hemoglobin; SGLT2i, sodium-glucose cotransporter-2 inhibitor; TZD, thiazolidinedione; SBP, systolic blood pressure; DPP4i, dipeptidyl peptidase-4 inhibitor; GLP-1RA, glucagon-like peptide-1 receptor agonist.

https://doi.org/10.3904/kjim.2017.354

ferences in efficacy or safety of each drug even in the same class have been reported, and the response to individual drugs can be different, depending on ethnicities and/or individual characteristics. Therefore, the choice of drug requires many aspects of consideration, such as patient preferences, patient characteristics, comorbidity, and drug characteristics, with the goal of reducing blood glucose levels and side effects, including weight gain and hypoglycemia.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

Acknowledgments

Financial support for the development of these guidelines was provided by the Korean Diabetes Association (KDA) operating budget; there was no support or involvement from industry sources.

This position statement on antihyperglycemic agent therapy was written by the KDA Committee of Clinical Practice Guidelines. We gratefully acknowledge the following experts who provided a critical review and discussion of this update: Tae-Nyun Kim, Inje University College of Medicine, Busan; Yong-ho Lee, Severance Hospital, Yonsei University College of Medicine, Seoul; Jin-Hwa Kim, Chosun University Hospital, Chosun University College of Medicine, Gwangju; Eun-Gyoung Hong, Hallym University Dongtan Sacred Heart Hospital, Hwaseong; Jaetaek Kim, Chung-Ang University College of Medicine, Seoul; Won-Young Lee, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul; Bokrye Song, College of Medicine, Seoul St. Mary's Hospital, The Catholic University of Korea, Seoul; Ji Young Kim, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul; Dong Hee Yang, Inje University Ilsan Paik Hospital, Goyang; Taeyoung Yang, Taeyoung 21 Hospital, Gwangju; and Hyeongjin Kim, Kim HJ Medical Clinic, Paju, Korea.

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