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Empagliflozin versus dapagliflozin in patients with type 2 diabetes inadequately controlled with metformin, glimepiride and dipeptidyl peptide 4 inhibitors: A 52-week prospective observational study

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ABSTRACT

Aims: To directly compare the effectiveness and safety between two distinct sodium-glucose co-transporter 2 (SGLT2) inhibitors, empagliflozin and dapagliflozin, as part of a quadruple oral antidiabetic agents (OADs) in patients with inadequately controlled type 2 diabetes (T2D).

Methods: This study was an open-labeled, prospective, 52-week study conducted in T2D patients with glycated hemoglobin (HbA_{1c}) ranging 7.5–12.0% with metformin, glimepiride and dipeptidyl peptidase-4 inhibitors. Patients were divided into either empagliflozin (25 mg/day) or dapagliflozin (10 mg/day). The outcome measures included changes in HbA_{1c}, fasting plasma glucose (FPG), and cardiometabolic variables and the safety profiles.

Results: In total, 350 patients were enrolled with empagliflozin (n = 176) and dapagliflozin (n = 174), respectively. After 52 weeks, both groups showed significant reductions in HbA_{1c} and FPG, but the reduction was greater in the empagliflozin group ($P < 0.001$). Both groups showed significantly decreased blood pressure and body weight and high-density lipoprotein cholesterol levels were increased in the empagliflozin (between groups, $P = 0.035$). Both groups showed similar safety profiles.

Conclusions: Our study demonstrated that SGLT2 inhibitors can be effectively used as a fourth OAD in T2D patients who are treated with three other OADs. More specifically, empagliflozin was more effective in reducing HbA_{1c} and improving other cardiometabolic parameters than dapagliflozin.

Clinical Trial Number NCT03748810 (ClinicalTrials.gov).

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1. Introduction

Type 2 diabetes (T2D) exhibits insulin resistance in muscle, liver, and adipose tissue, with progressive deterioration of pancreatic beta cell function [1]. Due to the complex pathophysiology of T2D, the ideal combination therapy of oral antidiabetic drugs (OAD) provides distinct, but complementary mechanisms of action that preserves pancreatic beta cell function, improve the insulin resistance observed in peripheral tissues, provide durability, be well tolerated without risk of hypoglycemia or weight gain, as well as provide cardiovascular benefits [2,3].

At present, sodium-glucose co-transporter 2 (SGLT2) inhibitors are recommended as optional add-on treatments from early to advanced stages of diabetes depending upon the patient risk for atherosclerotic cardiovascular diseases and weight gain [3]. Although several years have passed since empagliflozin and dapagliflozin initially became available in the clinics, previous studies have only reported the efficacy and safety of each individual medicines or its network meta-analysis results [4–9]. Our previous studies showed that quadruple combination therapy including SGLT2 inhibitors were at least comparable, if not possibly superior to the use of basal insulin injections as an add-on therapy [10,11].

To date, however, there is no direct clinical studies that have compared the efficacy of empagliflozin and dapagliflozin using a combination drug therapy with other OADs to control blood glucose levels in T2D patients. Moreover, it remains to be determined what benefit these drugs have on the cardiometabolic profiles in this patient population relative to the other OADs.

In this report, we provide new clinical evidence regarding the effectiveness and safety/tolerability of empagliflozin compared to dapagliflozin as a fourth add-on OAD in patients with T2D, who are incapable of adequately controlling their blood glucose despite being treated with 3 other pre-existing 3 distinct classes of OADs.

2. Research design and methods

2.1. Study design

This open-labeled, prospective, observational, 52-week, clinical study was conducted to compare the effectiveness and safety between empagliflozin (25 mg once daily) and dapagliflozin (10 mg once daily) in patients with inadequately controlled T2D with three different OAD combination (Clinical Trial Reg. No. NCT03748810). This study protocol was approved by an ethics committee/institutional review board of Chungbuk National University Hospital (IRB No.2018-10-016). All procedures were conducted in accordance with the Helsinki Declaration and the International Conference of Harmonization/Good Clinical Practice guidelines. All patients provided written informed consent.

Inclusion criteria were adults aged 18–80 years with T2D, who had glycated hemoglobin (HbA_{1c}) $\geq$7.5 to <12.0% at baseline, and were on a stable regimen of a triple combination therapy with metformin (2000 mg/day or maximal tolerated dose), glimepiride (8 mg/day or maximal tolerated dose) and dipeptidyl peptidase 4 (DPP4) inhibitors (maximum dose according to the local label) for >12 weeks before the study enrollment. Patients were excluded for any of the following criteria: (1) type 1 diabetes; (2) gestational diabetes, pregnant, or lactating; (3) diabetes due to secondary causes (e.g., pancreatic cancer, chronic pancreatitis, steroid-induced diabetes mellitus, Cushing's syndrome, or acromegaly); (4) active anticancer treatment; (5) serum creatinine levels >1.5 mg/dl for male or 1.4 mg/dl for female; (6) serum aspartate transaminase (AST) or alanine transaminase (ALT) levels above 3 times the upper limit of normal range; (7) current treatment with any SGLT2 inhibitors more than 7 days within 3 months before enrollment or during the period of this study; (8) existence of severe symptoms reflecting hyperglycemia (polyuria, polydipsia, or polyphagia) or catabolic features including weight loss or ketosis; or (9) patients considered unsuitable for inclusion according to the clinician's judgement.

All participants in this study were initially recommended to initiate insulin therapy, but rejected the injection treatment and insisted on using another form of OAD. The participants were divided into two groups in which either empagliflozin (25 mg once daily) or dapagliflozin (10 mg once daily) was added to the drug regimen over a 52-week period under the supervision of the attending physician. The doses of metformin and DPP4 inhibitors were maintained during the whole study period, whereas the dose of glimepiride was reduced if patients experienced hypoglycemia. All participants visited the clinic every 12 weeks after initiation of study medication. The medication adherence was assessed at each visit by counting the number of pills remained.

2.2. Endpoints and assessments

The primary and secondary endpoints in this study were calculated by subtracting the 52 week from baseline values between the empagliflozin versus dapagliflozin groups. The primary values were designated as: (1) mean changes in HbA_{1c}; and (2) fasting plasma glucose (FPG) levels. The secondary endpoints were designated as: (1) changes in body weight; (2) systolic (SBP) and diastolic blood pressure (DBP); and (3) lipid profiles. In addition, the occurrence of adverse events (AE), which included hypoglycemia, genitourinary tract infection (GUTI), volume depletion, nocturia, or ketoacidosis, was used as secondary endpoints. The definition of hypoglycemia was blood glucose level under 70 mg/dL or occurrence of hypoglycemia-related symptoms, such as sweating, tremors, palpitation, or confusion. Severe hypoglycemia was defined as hypoglycemia requiring medical assistance.

At baseline, each patient medical history, family history of diabetes, onset age of diabetes, alcohol or smoking habits were noted. Anthropometric data as SBP, DBP and body weight, and laboratory data were measured at baseline, 12, 24, and 52 weeks, respectively. HbA_{1c} was measured by affinity chromatography (Bio-Rad Laboratories, Hercules, CA, USA) in a National Glycated Hemoglobin Standardization Program level II-certified laboratory. The levels of plasma glucose, AST, ALT, and the lipid profile were assessed using an automated chemistry analyzer (Hitachi 7600, Tokyo, Japan). Fast-

ing insulin and C-peptide levels were measured by chemiluminescence enzyme immunoassays (Abbott, Lake Forest, IL, USA). The homeostasis model assessment of insulin resistance (HOMA-IR) and beta cell function (HOMA-beta) were defined as the following equations: [(fasting glucose in mg/dL) × (fasting insulin)/405] and [(360 × fasting insulin)/(fasting glucose in mg/dL) − 63] [12]. The estimated glomerular filtration rate (eGFR) was calculated as the Modification of Diet in Renal Disease formula.

2.3. Statistical analysis

The sample size for this study was calculated based on the anticipated differences in the mean changes HbA_{1c} from baseline to week 52 between empagliflozin versus dapagliflozin. and was also considered to identify the difference between the two groups for adverse events. To detect a difference of 0.4% using a 2-sided significance level of 0.05 (assuming a SD of 1.2%) would require 143 patients per group to achieve 80% power. In previously reported guidelines, 50–100 cases were needed to evaluate the safety and efficacy of the OAD in an open-label method [13]. The planned study cohort was 360 patients (180 cases per study group) to account for any possible withdrawals.

All data are expressed as the mean ± standard deviation or frequencies with percentage. The Kolmogorov-Smirnov test for normality was examined for the appropriate statistical test for continuous variables. Fasting insulin, fasting C-peptide, HOMA-IR, HOMA-beta cell function, triglyceride, high-density lipoprotein (HDL) cholesterol, AST, ALT, and spot urine albumin-to-creatinine ratio (ACR) were analyzed after logarithmic transformation. The last observation-carried-forward approach was used to impute missing continuous effectiveness data. The baseline characteristics were tested using Chi-square test for the categorical variables and independent Student's *t*-test for the continuous variables. Differences in HbA_{1c}, FPG, BP, body weight, lipid profiles, AST, ALT, and eGFR between baseline and 12, 24, and 52 weeks of treatment were analyzed by the paired *t*-test. Adverse events were analyzed using Chi-square test. Statistical analyses were performed using SPSS Statistics for Windows, version 22.0 (IBM Corp., Armonk, NY, USA). $P < 0.05$ was considered significant.

3. Results

3.1. Study subjects and baseline characteristics (Table 1 and Fig. 1)

A total of 393 patients were eligible, but 43 were excluded resulting in a net total of 350 patients in our study (Fig. 1). The rate of premature discontinuation of our drug regimen before week 52 were 9.1% (n = 16) in the empagliflozin and 10.3% (n = 18) in dapagliflozin groups, respectively. Baseline demographic and clinical characteristics were generally similar between both groups (Table 1). All patients had moderate hyperglycemia at baseline (mean HbA_{1c}, 9.1% and 9.0% for empagliflozin and dapagliflozin, respectively). There were no significant differences in age, sex, duration of diabetes, comorbid diseases, BP, body weight, and baseline biochemical data including HbA_{1c}, FPG, PP2, HOMA-IR, HOMA-β cell function, AST, ALT, eGFR, spot urine ACR and lipid profiles between both groups. The baseline doses of metformin, glimepiride and DPP4 inhibitors did not show any significant differences between the two groups.

3.2. Effectiveness outcomes (Table 2 and Fig. 2)

Over the treatment period of 52 weeks, the HbA_{1c} levels were reduced by −1.6 ± 1.4% ($P < 0.001$) and −1.2 ± 1.3% ($P < 0.001$) in the empagliflozin (25 mg/day) and dapagliflozin (10 mg/day) groups, respectively, from baseline levels. More importantly, the HbA_{1c} levels between groups at week 52 was significantly lower ($P = 0.011$) in the empagliflozin versus dapagliflozin groups. Of the study subjects, 35.2% (n = 62) and 18.8% (n = 33) in the empagliflozin group and 24.7% (n = 43) and 9.8% (n = 17) in the dapagliflozin group reached the HbA_{1c} target <7% and ≤6.5%, respectively [(between groups, for HbA_{1c} <7.0% ($P = 0.036$); for HbA_{1c} ≤6.5% ($P = 0.021$)].

A similar trend was determined for FPG levels where empagliflozin and dapagliflozin were reduced by −65.7 ± 53.0 mg/dL ($P < 0.001$) and −53.1 ± 70.6 mg/dL ($P < 0.001$) from baseline levels, respectively. Empagliflozin showed a greater significant reduction of FPG compared to dapagliflozin ($P = 0.007$) at 52 weeks.

SBP and DBP were monitored in each of the patient groups. After drug treatment for 52 weeks, SBP was significantly lower in both treatment groups by −6.0 ± 13.4 mmHg using empagliflozin ($P < 0.001$) and −2.7 ± 16.0 mmHg using dapagliflozin ($P = 0.030$) from baseline. A corresponding significant decrease was also measured in the DBP for patients in both treatment groups (Table 2). At 52 weeks, however, the patients using empagliflozin as part of their drug regimen demonstrated a significantly lower SBP compared to dapagliflozin ($P = 0.045$), but there was no difference in DBP between groups.

Body weight was reduced in both groups whereby the patients in the empagliflozin group was reduced by −3.0 ± 7.5 kg ($P < 0.001$) whereas the dapagliflozin group was reduced by −1.5 ± 2.7 kg ($P < 0.001$) from baseline to the 52-week period. Empagliflozin was calculated to have a greater significant effect on reducing body weight compared to dapagliflozin ($P = 0.016$) at 52 weeks. Moreover, there was a significant difference ($P = 0.035$) in the increase of HDL cholesterol by comparing the two groups at 52 weeks. Empagliflozin was shown to increase HDL cholesterol by 1.9 ± 5.7 mg/dL ($P < 0.001$) with no significant change measured in the dapagliflozin group from baseline to 52 weeks. No significant differences were measured in the other lipid profiles, including total cholesterol, triglycerides, and low-density lipoprotein (LDL) cholesterol (Table 2). In addition, there was no beneficial effect on eGFR regardless of the drug groups. On the other hand, both treatments similarly decreased AST and ALT levels from baseline to 52 weeks, but the effect on ALT by dapagliflozin was more dramatic than empagliflozin ($P = 0.002$). During the study period, antihypertensive medications were discontinued in 62 cases (31 cases in each group). Discontinuation of the statin were observed in 9 cases for empagliflozin and 5 cases for dapagliflozin groups. Changes in antihypertensive medications and statin of both groups

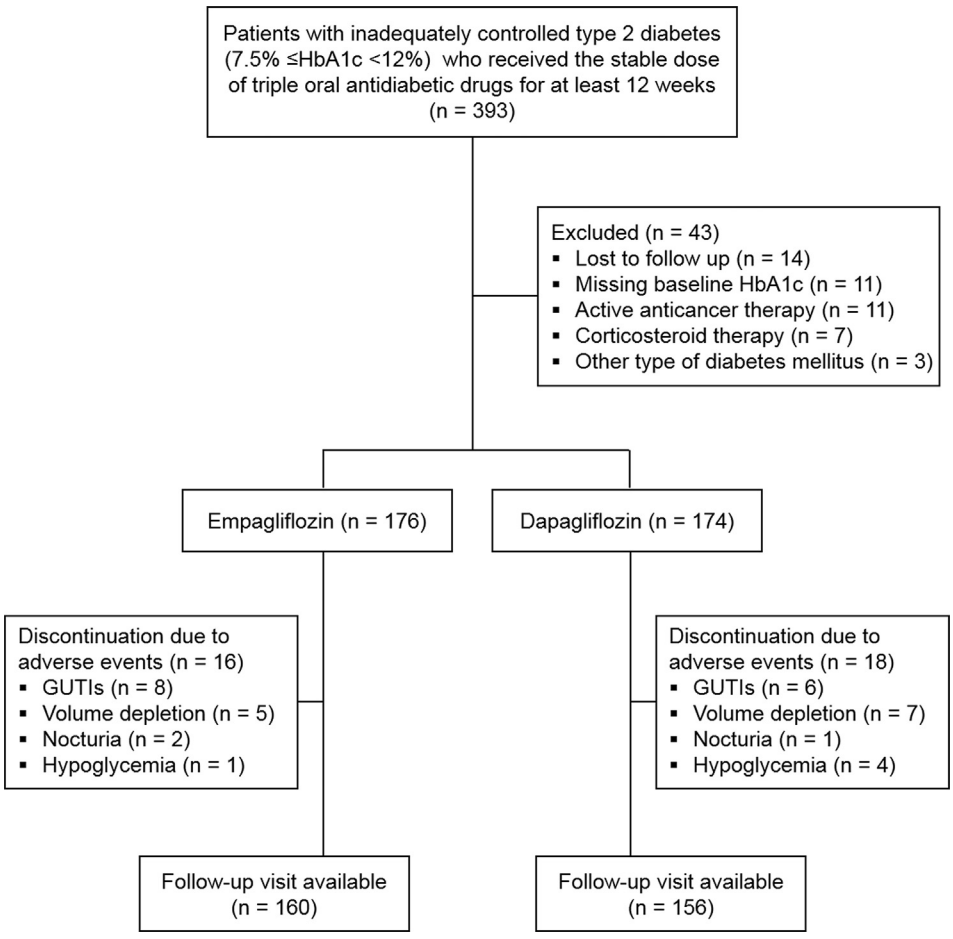

Fig. 1 – Study flowchart.

showed no statistically significant differences (Supplementary Table 1).

3.3. *Safety and tolerability (Table 3)*

The drug compliance of SGLT2 inhibitors showed no significant difference between the two groups (95.8 ± 8.6% and 94.9 ± 8.2% in empagliflozin and dapagliflozin group, respectively, P = 0.339). During follow up visits with the patients during the 52-week study period, 46 cases (26.1%) in empagliflozin group and 55 cases (31.6%) in dapagliflozin group developed AEs. The AEs that led to discontinuation of the medication in each group were similar in number where 16 (9.1%) and 18 cases (10.3%) occurred in empagliflozin and dapagliflozin groups, respectively. The most common AEs were mild hypoglycemia in both groups, which was not statistically different between empagliflozin (10.8%) versus dapagliflozin (12.6%; P = 0.621). One patient in each group experienced severe hypoglycemia and required medical support. The doses of metformin and DPP4 inhibitors were maintained during the whole study period, whereas the dose of glimepiride was reduced if patients experienced hypoglycemia (9 in the empagliflozin group and 11 in the dapagliflozin group). Finally, the dose reduction of the glimepiride was not different between two groups (empagliflozin group, −3.0 ± 1.3 mg/day; dapagliflozin group, −3.3 ± 1.5 mg/day, P = 0.276) (Supplementary Table 1).

A small number of patients, 12 (6.8%) and 14 (8.0%) in the empagliflozin and dapagliflozin groups, respectively, complained of at least one episode of GUTI during follow-up. GUTIs were resolved with short-term oral antidiabetics or topical antifungal agents. There were no reports of diabetic ketoacidosis or death for 52 weeks.

4. Discussion

This is the first study that has exhibited the effectiveness and the safety of SGLT2 inhibitors with either empagliflozin or dapagliflozin as part of an add-on drug therapy combination using multiple OAD to treat T2D patients with inadequate blood glucose control. In our study, we selected patients that were already used 3 distinct OADs, including metformin, glimepiride and DPP4 inhibitors, to control their blood glucose for at least 52 weeks. Although both of the drugs tested in this study demonstrated their beneficial effects to improve blood glucose control with minor, we did observe that empagliflozin was relatively superior to dapagliflozin with respect to glycemic control and also some of the cardiometabolic component regulation, such as body weight, blood pressure and other lipid profiles.

Table 1 – Baseline demographics and clinical parameters of study participants.

Variables	Empagliflozin (*n* = 176)	Dapagliflozin (*n* = 174)	P value
Age, years	57.0 ± 11.3	57.2 ± 9.9	0.844
Male, n (%)	91 (48.1)	98 (51.9)	0.393
SBP, mmHg	130.2 ± 16.4	131.4 ± 15.7	0.497
DBP, mmHg	75.1 ± 11.4	76.8 ± 11.1	0.178
Body weight, kg	72.0 ± 15.0	71.6 ± 14.0	0.792
Body mass index, kg/m^2	26.9 ± 4.0	26.3 ± 3.8	0.117
Duration of diabetes, years	11.6 ± 6.0	11.1 ± 6.8	0.545
Family history of diabetes, n (%)	73 (41.5)	72 (41.4)	0.505
Comorbid disease, n (%)			
Coronary heart disease	43 (24.4)	40 (23.0)	0.265
Cerebrovascular disease	16 (9.1)	12 (6.9)	0.556
Hypertension	89 (50.6)	88 (50.6)	0.915
Concomitant OAD			
Metformin, mg/day	1973.0 ± 478.1	1916.6 ± 318.4	0.203
Glimepiride, mg/day	7.2 ± 1.4	7.1 ± 1.6	0.323
DPP4 inhibitors, n (%)			0.527
Sitagliptin	91 (51.7)	81 (46.6)	
Vildagliptin	82 (46.6)	88 (50.6)	
Teneligliptin	3 (1.7)	5 (2.9)	
Sitagliptin, mg/day	100.0 ± 0.0	100.0 ± 0.0	NA
Vildagliptin, mg/day	100.0 ± 0.0	100.0 ± 0.0	NA
Teneligliptin, mg/day	16.7 ± 5.8	20.0 ± 0.0	0.423
Concomitant medication, n (%)			
Statin	115 (65.3)	113 (64.9)	1.000
ACEi or ARB	87 (49.4)	86 (49.4)	1.000
β-blocker	41 (23.3)	48 (27.6)	0.390
Calcium channel blocker	57 (32.4)	59 (33.9)	0.820
Diuretics	22 (12.5)	26 (14.9)	0.536
Smoking status, n (%)			0.253
Never smoker	124 (70.5)	124 (71.3)	
Ever smoker	52 (29.5)	50 (28.7)	
HbA_{1c}, %	9.1 ± 1.3	9.0 ± 1.3	0.850
Fasting plasma glucose, mg/dL	187.5 ± 54.2	191.2 ± 67.8	0.577
PP2, mg/dL	332.4 ± 93.4	338.3 ± 79.2	0.842
Fasting insulin*, μIU/mL	7.0 ± 3.5	7.1 ± 3.4	0.692
Fasting C-peptide*, ng/mL	2.0 ± 0.8	2.0 ± 0.7	0.622
HOMA-IR*	3.0 ± 1.8	2.9 ± 1.5	0.983
HOMA-β*, %	23.5 ± 14.2	27.9 ± 26.3	0.440
Total cholesterol, mg/dL	163.1 ± 40.5	163.2 ± 32.5	0.992
Triglyceride*, mg/dL	163.3 ± 81.1	160.4 ± 83.6	0.790
HDL cholesterol*, mg/dL	42.2 ± 8.3	42.9 ± 8.7	0.523
LDL cholesterol, mg/dL	90.1 ± 28.0	95.2 ± 27.6	0.171
Aspartate aminotransferase*, IU/L	26.8 ± 13.7	26.8 ± 13.0	0.995
Alanine aminotransferase*, IU/L	28.7 ± 15.9	30.7 ± 16.4	0.619
Spot urine ACR*, mg/g	95.8 ± 187.4	70.7 ± 150.0	0.186
eGFR, ml/min/1.73 m^2	107.7 ± 30.1	104.4 ± 27.4	0.351

Data are shown as mean ± SD. Numbers in parentheses indicates the calculated percentage of patients in each group. ACEi, angiotensin converting enzyme inhibitor; ACR, albumin-to-creatinine ratio; ARB, angiotensin receptor blocker; DBP, diastolic blood pressure; DPP4 inhibitors, dipeptidyl peptidase 4 inhibitors; eGFR, estimated glomerular filtration rate; HbA_{1c}, glycated hemoglobin; HDL cholesterol, high-density lipoprotein cholesterol; LDL cholesterol, low-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment-insulin resistance; HOMA-β, HOMA-β cell function; OAD, oral antidiabetic agent; PP2, postprandial 2 h glucose; SBP, systolic blood pressure.

* Analysis after logarithmic transformation. Continuous variables were analyzed using *t* tests and categorical variables were analyzed using chi-square tests.

Over the last decade, management guidelines for T2D have started to change towards a patient-centered treatment strategy [3,14,15]. Due to the progressive and complex nature of T2D, many diabetic patients have difficulty to achieve efficient control of their glycemic index using monotherapy alone. Consequently, this leads to the recommended use of a combination therapy of either two or even three different classes of OADs [16]. According to the recent consensus guideline by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD), patients with inadequate blood glucose control using multiple OADs are suggested by their physicians to use injection ther-

Table 2 – Changes in clinical parameters from baseline with empagliflozin or dapagliflozin.

	Empagliflozin (n = 176)			Dapagliflozin (n = 174)			P value[‡]
	Baseline	52 weeks	P value[†]	Baseline	52 weeks	P value[†]	
HbA_{1c}, %	9.1 ± 1.3	7.5 ± 1.1	<0.001	9.0 ± 1.3	7.8 ± 1.2	<0.001	0.011
FPG, mg/dL	187.5 ± 54.2	121.8 ± 51.6	<0.001	191.2 ± 67.8	138.1 ± 68.2	<0.001	0.007
SBP, mmHg	130.2 ± 16.4	124.2 ± 13.4	<0.001	131.4 ± 15.7	128.7 ± 16.0	0.030	0.045
DBP, mmHg	75.1 ± 11.4	72.0 ± 10.1	<0.001	76.8 ± 11.1	74.8 ± 10.2	0.012	0.330
Body weight, kg	72.0 ± 15.0	69.0 ± 7.5	<0.001	71.6 ± 14.0	70.1 ± 6.6	<0.001	0.016
BMI, kg/m^2	26.9 ± 4.0	25.8 ± 2.7	<0.001	26.3 ± 3.8	25.7 ± 1.0	<0.001	0.012
TC, mg/dL	163.1 ± 40.5	158.4 ± 25.8	0.018	163.2 ± 32.5	160.5 ± 33.1	0.296	0.529
TG[*], mg/dL	163.3 ± 81.1	158.6 ± 59.5	0.100	160.4 ± 83.6	157.7 ± 61.5	0.732	0.529
HDL-C, mg/dL	42.2 ± 8.3	44.1 ± 5.7	<0.001	42.9 ± 8.7	43.5 ± 4.5	0.157	0.035
LDL-C, mg/dL	90.1 ± 28.0	88.8 ± 16.9	0.342	95.2 ± 27.6	94.4 ± 16.3	0.552	0.804
AST[*], IU/L	26.8 ± 13.7	24.9 ± 12.9	0.001	26.8 ± 13.0	23.5 ± 11.3	<0.001	0.136
ALT[*], IU/L	28.7 ± 15.9	25.8 ± 15.2	<0.001	30.7 ± 16.4	24.3 ± 13.2	<0.001	0.002
eGFR, ml/min/1.73 m^2	107.7 ± 30.1	106.5 ± 30.7	0.349	104.4 ± 27.4	103.1 ± 27.9	0.170	0.794

Data are shown as mean ± SD. BMI, body mass index; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HbA_{1c}, glycated hemoglobin; HDL cholesterol, high-density lipoprotein cholesterol; LDL cholesterol, low-density lipoprotein cholesterol; SBP, systolic blood pressure.

[*] Analysis after logarithmic transformation.

[†] Differences within groups measured at baseline and week 52.

[‡] Differences within group measured at baseline and week 52.

Table 3 – Adverse events during study period.

	Empagliflozin (n = 176)	Dapagliflozin (n = 174)	P value[*]
Total AEs	46 (26.1)	55 (31.6)	0.280
AEs leading to discontinuation	16 (9.1)	18 (10.3)	0.721
Serious AEs	1 (0.6)	1 (0.6)	1.000
Deaths	0	0	
Special interest categories			
Severe hypoglycemia[†]	1 (0.6)	1 (0.6)	1.000
Mild hypoglycemia	19 (10.8)	22 (12.6)	0.621
Genitourinary tract infection	12 (6.8)	14 (8.0)	0.689
Volume depletion	8 (4.5)	13 (7.5)	0.269
Nocturia (>3times/night)	6 (3.4)	5 (2.9)	1.000
Ketoacidosis	0	0	

Data converted as a percentage in parentheses (%).

[*] Chi-square test was performed for comparison between groups. AE, adverse events.

[†] Severe hypoglycemia where plasma glucose ≤ 70 mg/dl and required assistance by a healthcare provider.

apy with either insulin or GLP-1 receptor agonist [3]. In practice, however, physicians often face the situation where patients insist on the use of alternative OAD instead of the injectable therapies due to various reasons, such as pain from the needle stick, fear of becoming hypoglycemia and unexpected weight gain [17]. Due to the lack of data on the use of 4 or more OAD to treat T2D patients, our research group focused on designing clinical trials to examine the potential for alternate OAD to be safely and effectively used to treat these T2D patients that are requesting another treatment modality rather than injectable drugs. Our previous study was designed to compare the safety and effectiveness in using a SGLT2 inhibitor instead of injectable insulin as a 4th add-on treatment option in T2D patients who were already administered metformin, glimepiride and DPP4 inhibitors for at least 24 weeks. In these studies, we definitively showed that quadruple combination therapy with SGLT2 inhibitors could be a viable therapeutic regiment as it resulted in comparable or even more effective glucose lowering effects in T2D patients. Moreover, our results showed that the use of SGLT2 inhibitors had a beneficial effects on reducing blood pressure and body weight without any serious AEs [10,11]. This present study was designed to further extend our previous results by examining whether there was any difference in the efficacy of distinct SGLT2, specifically empagliflozin and dapagliflozin, to control blood glucose levels and also improve the cardiometabolic components of the patients.

In terms of the glucose lowering effect, HbA_{1c} was maximally reduced by 24 weeks and consistently maintained through the end of study (Fig. 2A) using either empagliflozin and dapagliflozin. However, empagliflozin demonstrated superior reduction in HbA_{1c} levels compared to dapagliflozin at both 24 weeks and 52 weeks. In a recent meta-analysis, SGLT2 inhibitors were shown to exert moderate glucose-lowering efficacy as either a monotherapy (ΔHbA_{1c} −0.79%) or as an add-on therapy (ΔHbA_{1c} −0.61%) [18]. In our study,

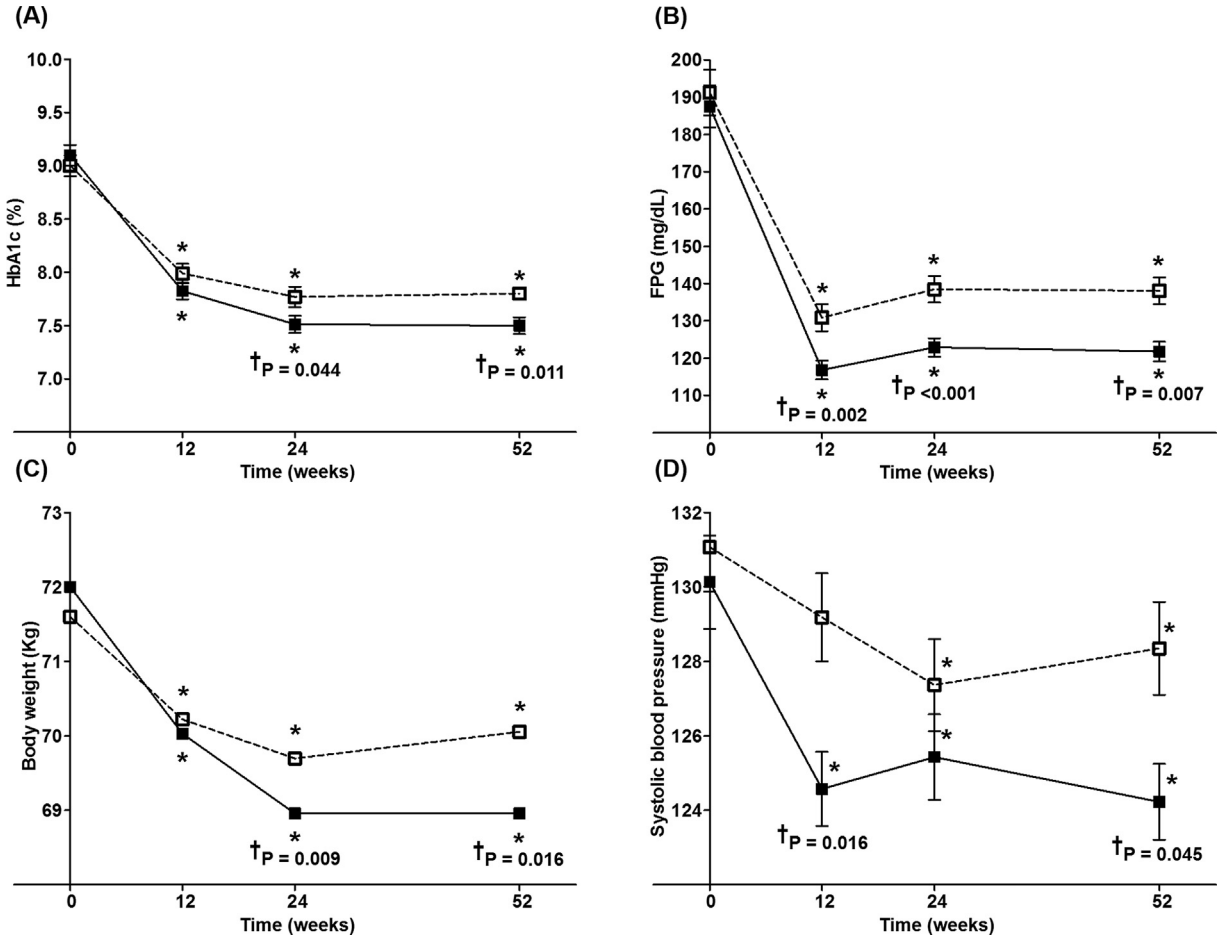

Fig. 2 – Comparison of drug treatment effects on clinical parameters from baseline over 52 weeks. Time = 0 is the baseline time point. □ = Dapagliflozin; ■ = Empagliflozin. (A) glycated hemoglobin (HbA_{1c}), (B) fasting plasma glucose, (C) body weight, and (D) systolic blood pressure. Data are shown as mean ± SE. *P < 0.05, significant difference between baseline to week 12, week 24, or week 52 in each group. †P < 0.05, significance difference between groups.

both empagliflozin (ΔHbA_{1c} −1.6%) and dapagliflozin (ΔHbA_{1c} −1.2%) showed further improvement in reducing HbA_{1c} than these previous studies, which may be due to the complementary interactive effect of the other OADs [19].

In addition to their effective control of blood glucose, SGLT2 inhibitors exert pleiotropic effects on other cardiometabolic parameters, including body weight reduction, antihypertensive effect, and regulation of lipid profiles (decrease of triglycerides and increasing the ratio of HDL: LDL cholesterol) [20–22]. Consistent with these effects, our study demonstrated that body weight and systolic blood pressure was markedly reduced in the T2D patients for both drugs, but that empagliflozin was more effective than dapagliflozin during the course of the study period. Encouragingly, we observed an increase in the HDL cholesterol levels only in the Empagliflozin group, but no changes were detected in other lipids, including serum triglyceride and LDL cholesterol levels. Our findings in our study complements some of the findings in other recent clinical trials where EMPA-REG OUTCOME [23] and DECLARE-TIMI 58 [24] evaluated the effects of empagliflozin and dapagliflozin, respectively, on the safety and biological efficacy on the cardiovascular system. In the EMPA-REG OUTCOME trial, empagliflozin reduced major adverse cardiovascular events (MACE), whereas dapagliflozin was not observed to exert a beneficial effect on the same parameters in the DECLARE-TIMI 58 trial. One reason for the lack of efficacy for dapagliflozin may have been the distinct patient populations where the EMPA-REG OUTCOME included high risk patients compared to the other study. Alternatively, it could be a pharmacodynamic difference in the potency between the two distinct SGLT2 inhibitors to control MACE.

In terms of adverse effects AEs, both empagliflozin and dapagliflozin were generally well tolerated where hypoglycemia was the most common AE. All of the episodes of hypoglycemia were mild regardless of the treatment group, except for two patients (one in each group) who exhibited severe hypoglycemia. Fortunately, both patients recovered with medical assistance without any sequelae and then halted further index medication. Otherwise, the similar AEs were observed in both groups where GUTIs and generalized weakness related to volume depletion were reported, but ultimately resolved by short-term treatment. Some patients, however, were required to discontinue their index medication in the latter situations.

Although this study has limitations as an open-label and single center study, this study does provide new information

about the safe and effective use of SGLT2 inhibitors in T2D patients that decline injection therapy to control their blood glucose regulation. Our study makes the assumption that a single dose of empagliflozin at 25 mg/day is pharmacodynamically equivalent to dapagliflozin at 10 mg/day, but there may need to be dose adjustment studies to fully determine whether there is superiority of empagliflozin versus dapagliflozin at least at the same dose. Regardless, this is a first step in developing larger scale, multi-center trial to support the results of our study and potentially use this drug regimen for specific patient populations who have T2D.

In conclusion, our study was the first to directly compare distinct SGLT2 inhibitors as an add-on therapeutic option in T2D patients who are already on a cocktail of 3 different OAD to control their glycemia. We provided new data that empagliflozin and dapagliflozin were capable of safely controlling blood glucose in T2D patients, but empagliflozin may be slightly more efficacious especially with its ability to beneficially regulate cardiometabolic parameters.

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Conflict of interest statement

The authors have no conflicts of interest to disclose.

Author contributions

T.K.O. and E.J.K conceived and designed the experiments. E.J.K. analyzed the data and wrote the manuscript. E.J.K., D.H.L., H.J.J., and T.K.O. contributed to the review and interpretation of results. All authors approved the final version of the manuscript.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.diabres.2019.04.008.

REFERENCES

[1] Defronzo RA. Banting Lecture. From the triumvirate to the ominous octet: a new paradigm for the treatment of type 2 diabetes mellitus. Diabetes 2009;58(4):773–95.
[2] Garber AJ, Abrahamson MJ, Barzilay JI, Blonde L, Bloomgarden ZT, Bush MA, et al. Consensus statement by the american association of clinical endocrinologists and american college of endocrinology on the comprehensive Type 2 diabetes management algorithm – 2018 executive summary. Endocr Pract 2018;24(1):91–120.
[3] Davies MJ, D'Alessio DA, Fradkin J, Kernan WN, Mathieu C, Mingrone G, et al. Management of Hyperglycemia in Type 2 Diabetes, 2018. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Dia Care 2018;41(12):2669–701.
[4] Tang H, Li D, Zhang J, Li Y, Wang T, Zhai S, et al. Sodium-glucose co-transporter-2 inhibitors and risk of adverse renal outcomes among patients with type 2 diabetes: a network and cumulative meta-analysis of randomized controlled trials. Diabetes Obes Metab 2017;19(8):1106–15.
[5] Zaccardi F, Webb DR, Htike ZZ, Youssef D, Khunti K, Davies MJ. Efficacy and safety of sodium-glucose co-transporter-2 inhibitors in type 2 diabetes mellitus: systematic review and network meta-analysis. Diabetes Obes Metab 2016;18 (8):783–94.
[6] Araki E, Tanizawa Y, Tanaka Y, Taniguchi A, Koiwai K, Kim G, et al. Long-term treatment with empagliflozin as add-on to oral antidiabetes therapy in Japanese patients with type 2 diabetes mellitus. Diabetes Obes Metab 2015;17(7):665–74.
[7] Ferrannini E, Berk A, Hantel S, Pinnetti S, Hach T, Woerle HJ, et al. Long-term safety and efficacy of empagliflozin, sitagliptin, and metformin: an active-controlled, parallel-group, randomized, 78-week open-label extension study in patients with type 2 diabetes. Diabetes Care 2013;36 (12):4015–21.
[8] Jabbour SA, Hardy E, Sugg J, Parikh S, Study G. Dapagliflozin is effective as add-on therapy to sitagliptin with or without metformin: a 24-week, multicenter, randomized, double-blind, placebo-controlled study. Diabetes Care 2014;37 (3):740–50.
[9] Bailey CJ, Gross JL, Hennicken D, Iqbal N, Mansfield TA, List JF. Dapagliflozin add-on to metformin in type 2 diabetes inadequately controlled with metformin: a randomized, double-blind, placebo-controlled 102-week trial. BMC Med 2013;11:43.
[10] Ku EJ, Lee DH, Jeon HJ, Oh TK. Effectiveness and safety of empagliflozin-based quadruple therapy compared with insulin glargine-based therapy in patients with inadequately controlled type 2 diabetes: An observational study in clinical practice. Diabetes Obes Metab 2019;21(1):173–7.
[11] Jeon HJ, Ku EJ, Oh TK. Dapagliflozin improves blood glucose in diabetes on triple oral hypoglycemic agents having inadequate glucose control. Diabetes Res Clin Pract 2018;142:188–94.
[12] Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 1985;28(7):412–9.
[13] Pharmaceutical and medical devices agency. On release of the guideline for clinical evaluation of oral hypoglycemic agents. PFSB/ELD Notification 2010 No. 0709-1. <http://www.pmda.go.jp/files/000208194.pdf>. [accessed 26 December, 2018].
[14] American Diabetes Association. 8. Pharmacologic approaches to glycemic treatment: standards of Medical Care in Diabetes-2018. Diabetes Care 2018;41(suppl 1):S73–85.
[15] Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M, et al. Management of hyperglycaemia in type 2 diabetes, 2015: a patient-centred approach. Update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetologia 2015;58(3):429–42.
[16] Kahn SE, Haffner SM, Heise MA, Herman WH, Holman RR, Jones NP, et al. Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. N Engl J Med 2006;355 (23):2427–43.
[17] Brod M, Kongso JH, Lessard S, Christensen TL. Psychological insulin resistance: patient beliefs and implications for diabetes management. Qual Life Res 2009;18(1):23–32.
[18] Vasilakou D, Karagiannis T, Athanasiadou E, Mainou M, Liakos A, Bekiari E, et al. Sodium-glucose cotransporter 2

inhibitors for type 2 diabetes: a systematic review and meta-analysis. Ann Intern Med 2013;159(4):262–74.
[19] Polidori D, Capuano G, Qiu R. Apparent subadditivity of the efficacy of initial combination treatments for type 2 diabetes is largely explained by the impact of baseline HbA1c on efficacy. Diabetes Obes Metab 2016;18(4):348–54.
[20] Baker WL, Buckley LF, Kelly MS, Bucheit JD, Parod ED, Brown R, et al. Effects of sodium-glucose cotransporter 2 inhibitors on 24-hour ambulatory blood pressure: a systematic review and meta-analysis. J Am Heart Assoc 2017;6(5). pii: e005686.
[21] van Bommel EJ, Muskiet MH, Tonneijck L, Kramer MH, Nieuwdorp M, van Raalte DH. SGLT2 inhibition in the diabetic kidney-from mechanisms to clinical outcome. Clin J Am Soc Nephrol 2017;12(4):700–10.
[22] Sha S, Polidori D, Heise T, Natarajan J, Farrell K, Wang SS, et al. Effect of the sodium glucose co-transporter 2 inhibitor canagliflozin on plasma volume in patients with type 2 diabetes mellitus. Diabetes Obes Metab 2014;16(11):1087–95.
[23] Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, et al. Empagliflozin, cardiovascular outcomes, and mortality in Type 2 diabetes. N Engl J Med 2015;373(22):2117–28.
[24] Wiviott SD, Raz I, Bonaca MP, Mosenzon O, Kato ET, Cahn A, et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. N Engl J Med 2018. https://doi.org/10.1056/NEJMoa1812389 [Epub ahead of print].