Original Article
Yonsei Med J 2022 Sep;63(9):825-833
https://doi.org/10.3349/ymj.2022.63.9.825
Yonsei Medical Journal
YMJ
pISSN: 0513-5796 · eISSN: 1976-2437

Effect of Dapagliflozin in Combination with Lobeglitazone and Metformin in Korean Patients with Type 2 Diabetes in Real-World Clinical Practice

Da Hea Seo[1], Young Ju Suh[2], Yongin Cho[1], Seong Hee Ahn[1], Seongha Seo[1], Seongbin Hong[1], Yong-ho Lee[3], Young Ju Choi[4], Eunjig Lee[3], and So Hun Kim[1]

[1]Division of Endocrinology and Metabolism, Department of Internal Medicine, Inha University College of Medicine, Incheon;
[2]Department of Biomedical Sciences, Inha University College of Medicine, Incheon;
[3]Division of Endocrinology and Metabolism, Department of Internal Medicine, Yonsei University College of Medicine, Seoul;
[4]Huh's Diabetes Center, Seoul, Korea.

Purpose: This study aimed to evaluate the efficacy and tolerability of dapagliflozin as an add-on or a switch therapy to lobeglitazone plus metformin (MFM) in Korean patients with inadequately controlled type 2 diabetes mellitus (T2DM) in real-world clinical practice.

Materials and Methods: The study included 109 patients who started dapagliflozin as add-on or switch therapy to lobeglitazone plus MFM. The primary outcome was a change in glycated hemoglobin (HbA1c) level from baseline after 12 months of treatment. Secondary outcomes included changes in fasting plasma glucose (FPG), lipid profiles, body weight, visceral fat area (VFA), and blood pressure after 12 months of treatment.

Results: The baseline HbA1c was 8.3±1.3% (8.7±1.5% in the add-on group and 8.1±1.0% in the switch group). After 12 months, mean HbA1c decreased (-0.91%) in all patients (p<0.05) (-1.39% in the add-on group and -0.63% in the switch group). Significant reductions in FPG were also observed in both the add-on and switch groups (-54.37 mg/dL and -24.68 mg/dL, respectively). Overall, there was a significant improvement in serum triglyceride (-24.74 mg/dL), low density lipoprotein cholesterol (-7.92 mg/dL), body weight (-2.98 kg), VFA (-9.00 cm^2), and systolic blood pressure (-8.67 mm Hg). Approximately 35.8% of patients achieved HbA1c <7.0% after 12 months.

Conclusion: Dapagliflozin, as an add-on or a switch therapy to lobeglitazone plus MFM, can be a suitable alternative for Korean patients with inadequately controlled T2DM. The combination therapy resulted in significant reductions in HbA1c levels, body weight, and blood pressure.

Key Words: Diabetes mellitus, type 2; thiozolidinediones; sodium-glucose transporter 2 inhibitors

Received: March 14, 2022 **Revised:** June 21, 2022
Accepted: June 21, 2022 **Published online:** August 18, 2022
Corresponding author: So Hun Kim, MD, PhD, Division of Endocrinology and Metabolism, Department of Internal Medicine, Inha University College of Medicine, 27 Inhang-ro, Jung-gu, Incheon 22332, Korea.
Tel: 82-32-890-3573, Fax: 82-32-890-3098, E-mail: shoney@inha.ac.kr

This study was presented during the 2021 Korean Diabetes Association 34th Spring Meeting.
•The authors have no potential conflicts of interest to disclose.

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a progressive disorder that frequently requires combination therapy to achieve and maintain target glycated hemoglobin (HbA1c) levels to reduce the risk of diabetic complications. Clinical guidelines, including the consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD), recommend advancing to dual or triple combination therapy in those who do not meet their glycemic target.[1] Since modes of action, safety profiles, and cardiovascular-renal effects can differ among antidiabetic agents, it would be appropriate to

find a combination with an additive or synergistic effect to maximize the treatment outcome.

Thiazolidinediones (TZD) are peroxisome proliferator-activated receptor-γ agonists known to improve insulin sensitivity and preserve pancreatic β-cell function in patients with T2DM.[2] TZD have been shown to be effective in lowering glucose concentration, maintaining glycemic control, and improving cardiovascular risk factors.[2,3] Lobeglitazone, a new addition to the TZD class, was approved for the treatment of T2DM in Korea in 2013 with a comparable safety and efficacy profile to pioglitazone.[4,5]

Sodium-glucose cotransporter-2 (SGLT2) inhibitors are new glucose-lowering drugs with a novel insulin-independent mechanism with favorable glucose lowering effects.[3] Moreover, marked benefits on cardiovascular-renal outcomes in patients with T2DM prompted an update to relevant guidelines.[6,7] Clinical trials of combination therapies with SGLT2 inhibitors and other oral hypoglycemic agents, in addition to metformin (MFM), have documented clinically meaningful reductions in HbA1c levels.[3] Among these combinations, a combination of SGLT2 inhibitors and TZD, in addition to MFM, has been found to have an additive or synergistic effect along with glycemic control, owing to complementary modes of action.[3,8,9]

Dapagliflozin is an SGLT2 inhibitor that has been approved for the treatment of patients with T2DM. To date, few studies have demonstrated the efficacy of combination therapy with SGLT2 inhibitors and TZD plus MFM in a real-world setting.[10] Therefore, we aimed to evaluate the efficacy of switching or add-on of dapagliflozin among Korean patients with T2DM who had inadequate glycemic control on background lobeglitazone and MFM in a real-world clinical setting.

MATERIALS AND METHODS

Study population

This was a single-center retrospective study conducted at the Huh Diabetes Center in Seoul, Republic of Korea. The eligible study participants were patients with T2DM who had inadequate glycemic control (HbA1c ≥7.0%), while receiving background standard combination therapy with MFM plus lobeglitazone with or without a dipeptidyl peptidase 4 (DPP4) inhibitor for at least 8 weeks between June 2019 and June 2020. We excluded patients with a diagnosis of type 1 diabetes, of age <19 years, with baseline HbA1c <7.0%, or who were receiving insulin or had previously used SGLT2 inhibitors. The patients were divided into two groups according to their use of dapagliflozin: the add-on group and the switch group. The add-on group was further stratified according to background therapy: add-on to MFM+lobeglitazone and MFM+lobeglitazone+DPP4 inhibitor. The switch group included those who were taking MFM, lobeglitazone, and a DPP4 inhibitor, and the DPP4 inhibitor was switched to dapagliflozin. Finally, 109 patients were included in the analysis (41 patients in the add-on group and 68 patients in the switch group) (Fig. 1). The present study protocol was reviewed and approved by the ethics committee of Inha University Hospital (no. 2020-12-029), and the requirement for informed consent was waived by the board.

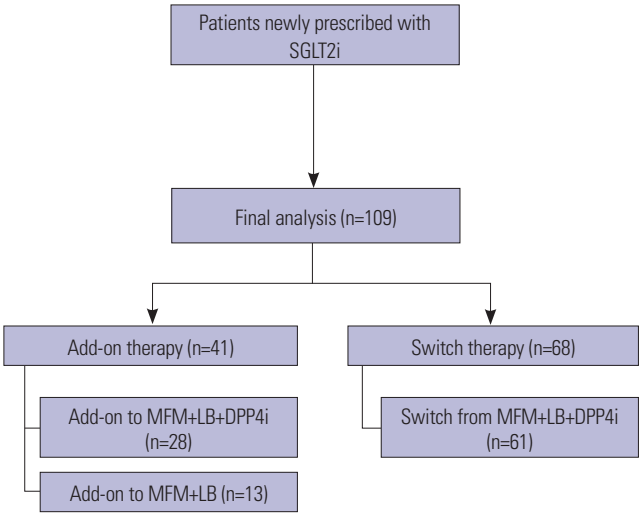

Fig. 1. Study flow diagram. SGLT2i, sodium-glucose cotransporter-2 inhibitor; MFM, metformin; LB, lobeglitazone; DPP4i, dipeptidyl peptidase 4 inhibitor.

Efficacy and safety assessment

The primary outcome was a change in HbA1c levels from baseline after 12 months of treatment. The secondary outcomes were changes in fasting plasma glucose (FPG), lipid profile, blood pressure (BP), body weight, fasting C-peptide, rate constant for plasma glucose disappearance (KITT), visceral fat area (VFA), and spot urine albumin-to-creatinine ratio (ACR) after 12 months of treatment. The proportion of patients who achieved their glycemic target (HbA1c: <7.0% and <6.5%) was also evaluated.

The safety evaluations included self-monitored edema and hypoglycemia, severe hypoglycemia, dyspnea, genital infection, general weakness, increased appetite, and hepatic and renal adverse events based on medical records during treatment with dapagliflozin. Self-monitored hypoglycemia was defined as a condition with blood glucose <70 mg/dL accompanied by typical adrenergic symptoms (e.g., sweating, palpitations, trembling, tingling) and severe hypoglycemia as severe cognitive impairment requiring external assistance for recovery. Hepatic adverse events were defined as a >3-fold increase in alanine aminotransferase (ALT) or aspartate aminotransferase (AST) levels from baseline. Renal adverse events were defined as ≥30% decline in estimated glomerular filtration rate (eGFR) from baseline, as calculated using the Chronic Kidney Disease Epidemiology Collaboration creatinine equation.[11]

Measurement of clinical and laboratory indices

Anthropometric indices, including weight and height, were

https://doi.org/10.3349/ymj.2022.63.9.825

measured in all subjects by a well-trained nurse who was blinded to the patients' clinical and laboratory data. All patients underwent blood tests for determination of metabolic parameters at baseline, including FPG, HbA1c, C-peptide, insulin, total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglyceride (TG), renal and liver function tests, including plasma ALT and AST levels, and urine assessment for ACR after an overnight (≥8 h) fasting period. During the 12-month treatment period, patients visited the clinic at baseline and months 3, 6, and 12 at which fasting blood samples were taken for assessment of FPG and HbA1c. Blood tests for lipid panel and liver function were repeated at months 6 and 12 and renal function test and urine ACR was repeated at month 12.

Each patient's body composition was assessed using a segmental multifrequency bioelectrical impedance analysis system (InBody 4.0; Biospace, Cheonan, Korea) at baseline and at month 12. Measurements were performed with the participants barefoot and wearing minimal clothing. Body weight, VFA, and skeletal muscle mass (SMM) were measured before and after treatment with dapagliflozin. SMM was recorded in kilograms, and skeletal muscle mass index (SMI, %) values were calculated by dividing SMM (kg) by the total body weight (kg)×100.[12]

A short insulin tolerance test was performed to assess insulin sensitivity at baseline and at month 12. The KITT (%/min) was used as a marker of insulin sensitivity.[13] As previously described,[14] the test was performed at 8:00 AM after an 8-hour fast. Venous blood samples were collected at 0, 3, 6, 9, 12, and 15 min after regular intravenous bolus injection of insulin (Humulin; Eli Lilly, Indianapolis, IN, USA) at a dose of 0.1 U/kg. Plasma glucose concentrations were measured immediately after sampling using Beckman Glucose Analyzer II (Beckman Instruments, Fullerton, CA, USA). After the test, 100 mL of 20% dextrose solution was immediately administered intravenously to prevent potential hypoglycemia. The KITT value was calculated as the proportion of the slope of the log-transformed plasma glucose from 3 to 15 min ($t_{1/2}$) using the formula KITT= $0.693/t_{1/2}\times100$ (%/min). Higher KITT values indicate higher insulin sensitivity.

Statistical analysis

All variables are reported as a mean±SD or as a number and percentage. The participants' baseline characteristics were compared using Student's t-test for continuous variables and the chi-square test for categorical variables, as appropriate. Changes in HbA1c, FPG, lipid profiles, BP, body weight, fasting C-peptide, KITT, VFA, and spot urine ACR from baseline an after 12 months of treatment in each group were analyzed using a paired t-test, and Bonferroni correction was applied to three time points compared to baseline. Family-wise type I error was controlled by 5%. We used linear regression analyses to identify factors responsible for changes in HbA1c. The multivariate model was adjusted for age, sex, duration of diabetes, body mass index (BMI), baseline FPG, HbA1c, KITT, and eGFR level. Statistical significance was set at $p<0.05$. All statistical analyses were performed using SPSS software (version 26.0; IBM Corp., Armonk, NY, USA).

Table 1. Baseline Characteristics of the Study Participants

Characteristics	Overall (n=109)	Add-on therapy (n=41)	Switch therapy (n=68)	*p* value
Age (yr)	54.3±9.7	58.0±8.1	52.1±10.0	0.002
Sex, male	71 (65.1)	23 (56.1)	48 (70.6)	0.183
Height (cm)	166.0±8.4	164.5±9.8	166.9±7.4	0.183
Weight (kg)	73.2±9.8	72.0±11.3	74.0±8.8	0.310
BMI (kg/m^2)	25.4±2.0	26.4±2.3	26.5±1.9	0.943
SBP (mm Hg)	133.7±11.4	133.8±12.8	133.6±10.5	0.924
DBP (mm Hg)	74.8±9.6	72.7±10.7	76.0±8.8	0.085
Duration of diabetes (yr)	11.0±7.8	12.5±8.8	10.1±7.0	0.123
Hypertension	66 (60.6)	28 (68.3)	38 (55.9)	0.279
Hyperlipidemia	75 (68.8)	25 (61.0)	50 (73.5)	0.247
CVD	7 (6.4)	3 (7.3)	4 (5.9)	>0.999
HbA1c (%)	8.3±1.3	8.7±1.5	8.1±1.0	0.029
≥7% and <8%	52 (47.7)	19 (46.3)	33 (48.5)	
≥8% and <9%	27 (24.8)	5 (12.2)	22 (32.4)	0.012
≥9%	30 (27.5)	17 (41.5)	13 (19.1)	
FPG (mg/dL)	187.1±49.1	199.8±58.2	179.4±41.3	0.054
Fasting C-peptide (ng/mL)	2.3±0.7	2.4±0.8	2.2±0.7	0.376
KITT (%/min)	1.6±0.8	1.5±0.5	1.6±0.9	0.303
Total cholesterol (mg/dL)	180.8±27.2	179.1±35.7	181.8±20.8	0.665
TG (mg/dL)	176.6±104.1	172.4±105.0	179.1±104.2	0.746
HDL-C (mg/dL)	48.7±9.3	47.8±7.1	49.2±10.5	0.397
LDL-C (mg/dL)	97.6±17.2	97.4±18.7	97.7±16.4	0.921
AST (IU/L)	32.2±12.1	32.0±12.2	32.4±12.1	0.900
ALT (IU/L)	37.3±17.3	35.8±18.1	38.3±16.8	0.462
eGFR (mL/min/1.73 m^2)	82.1±15.6	79.6±16.3	83.6±15.0	0.199
Urine ACR (mg/L)	79.3±73.8	92.0±77.7	71.7±70.8	0.164
Visceral fat (cm^2)	63.8±15.2	62.6±12.5	64.5±16.7	0.518
SMI (%)	38.5±4.2	37.9±4.5	38.9±4.0	0.235
Medications				
ARB	63 (57.8)	23 (56.1)	40 (58.8)	0.937
Statins	72 (66.1)	25 (61.0)	47 (69.1)	>0.999
Fenofibrate	7 (6.4)	6 (14.6)	1 (1.5)	0.021
Omega-3-fatty acid	4 (3.7)	2 (4.9)	2 (2.9)	>0.999
Antiplatelets	39 (35.8)	15 (36.6)	24 (35.3)	>0.999

ACR, albumin-to-creatinine ratio; ALT, aminotransferase; ARB, angiotensin receptor blocker; AST, aspartate aminotransferase; BMI, body mass index; CVD, cardiovascular disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; KITT, rate constant for plasma glucose disappearance; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; SMI, skeletal muscle mass index; TG, triglyceride.
Data are presented as a mean±standard deviation or number (%). *p*-values were obtained via an unpaired t-test or chi-square test between the add-on group and switch group (for categorical variables).

RESULTS

Baseline characteristics of the study subjects

The baseline demographic and clinical characteristics of the study subjects are presented in Table 1. The mean age was 54.3±9.7 years, and the mean duration of diabetes was 11.0±7.8 years. Approximately 15.6% of patients were older than 65 years. The mean body weight was 73.2±9.8 kg, and the mean BMI was 25.4±2.0 kg/m^2. All patients were treated with oral hypoglycemic agents. All clinical characteristics of the participants were comparable between the add-on group and the switch group except mean age and HbA1c. At baseline, the mean age was 58.0±8.1 years in the add-on group and 52.1±10.0 years in the switch group (p=0.002). Mean HbA1c was significantly higher in the add-on group than that in the switch group (8.7±1.5% vs. 8.1±1.0%, p=0.029); moreover, a higher proportion of patients had HbA1c ≥9% in the add-on group than in the switch group (41.5% vs. 19.1%, p=0.012). Meanwhile, there were no significant differences in the prevalences of other comorbidities and the use of concurrent medications except for fenofibrate, of which use was higher in the add-on group. In a subgroup analysis of individuals in the add-on group, those receiving combination therapy with a DPP4 inhibitor had longer durations of diabetes and higher baseline HbA1c and FPG levels, compared to those not receiving a DPP4 inhibitor (Supplementary Table 1, only online).

Efficacy

Mean HbA1c levels and changes over the 12-month treatment period are shown in Fig. 2A and C. There was a significant reduction in HbA1c at all time-points (3, 6, 9, and 12 months) regardless of the background therapy. HbA1c decreased gradually and progressively over time, and substantial reductions in HbA1c were observed at the end of the study period (-1.39% and -0.63% in the add-on group and the switch group, respectively) (Table 2 and Fig. 2A). After 12 months, 35.8% of all patients achieved HbA1c <7%, with a higher proportion of patients in the add-on group than in the switch group (46.3% vs. 29.4%, respectively) achieving HbA1c <7% (Fig. 3). Changes in FPG from the baseline are shown in Fig. 2B. There was a significant reduction in FPG compared to baseline at all time-points from 3 months to 12 months. After 12 months, the adjusted mean changes in FPG were -54.4 mg/dL and -24.7 mg/dL in the add-on group and the switch group, respectively (Fig. 2D). Overall, there were significant reductions in serum TG and LDL-C levels, systolic BP, and urine ACR of -24.74 mg/dL, -7.92 mg/dL, -8.67 mm Hg, and -30.57 mg/L, respectively, at 12 months (Table 2, Fig. 4B and C). Serum eGFR levels decreased by -2.33 mL/min/1.73 m^2 after administration of dapagliflozin for 12 months.

Significant reductions in body weight from baseline were observed in both groups from the third month onward until the end of the study period. After 12 months, there were significant

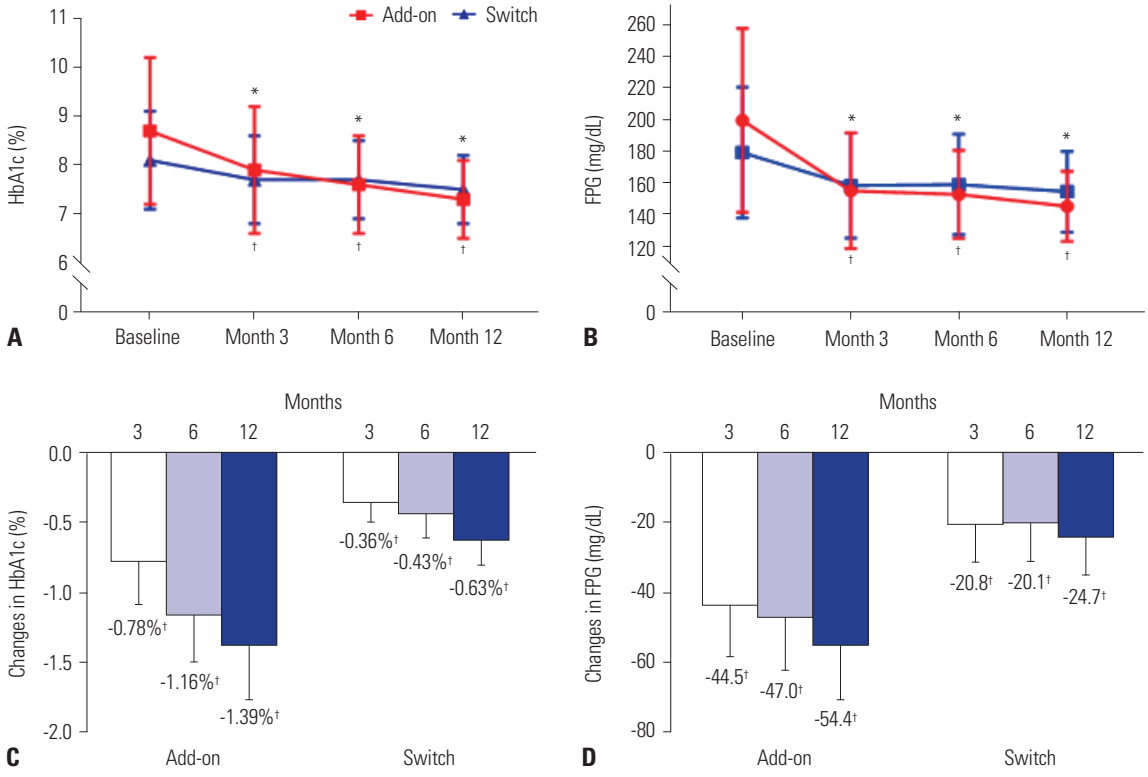

Fig. 2. Mean changes in HbA1c (A) and FPG (B) and changes in HbA1c (C) and FPG (D) at 3, 6, and 12 months from baseline following dapagliflozin treatment for 12 months. Data are expressed as the adjusted mean±standard error. FPG, fasting plasma glucose; HbA1c, glycated hemoglobin. *p<0.05 compared to the baseline in each treatment group; †p<0.05, vs. baseline in the add-on group, by post hoc analyses (Bonferroni tests).

https://doi.org/10.3349/ymj.2022.63.9.825

Table 2. Changes in Clinical Parameters after 12-Month Treatment with Sodium-Glucose Cotransporter-2 Inhibitors

	Baseline	6 months	Mean change from baseline (95% CI) at 6 months	12 months	Mean change from baseline (95% CI) at 12 months
HbA1c (%)					
Overall	8.3±1.3	7.6±0.9	-0.70 (-0.87 to -0.52)*	7.4±0.7	-0.91 (-1.10 to -0.73)*
Add-on	8.7±1.5	7.6±1.0	-1.16 (-1.50 to -0.81)*	7.3±0.8	-1.39 (-1.76 to -1.02)*
Switch	8.1±1.0	7.7±0.8	-0.43 (-0.60 to -0.23)*†	7.5±0.7	-0.63 (-0.80 to -0.45)*†
FPG (mg/dL)					
Overall	187.1±49.1	157.0±30.4	-30.08 (-39.02 to -21.15)*	151.2±24.6	-35.84 (-44.79 to -26.90)*
Add-on	199.8±58.2	153.0±27.9	-47.03 (-62.30 to -31.75)*	145.4±22.2	-54.37 (-70.72 to -38.01)*
Switch	179.4±41.3	159.3±31.8	-20.12 (-30.68 to -9.56)*†	154.7±25.5	-24.68 (-34.48 to -14.88)*†
TG (mg/dL)					
Overall	176.6±104.1	158.2±92.2	-18.69 (-37.22 to -0.17)	146.9±75.5	-24.74 (-48.01 to -11.46)*
Add-on	172.4±105.0	143.9±80.5	-29.05 (-58.10 to 0.04)	142.6±68.9	-29.85 (-59.40 to -0.30)*
Switch	179.1±104.2	166.5±98.0	-12.60 (-37.00 to 11.80)	149.5±79.7	-29.67 (-53.51 to -5.83)*
HDL-C (mg/dL)					
Overall	48.7±9.3	50.2±8.7	1.56 (0.26 to 2.87)	51.1±9.5	2.39 (0.70 to 4.07)
Add-on	47.8±7.1	49.5±6.9	1.83 (-0.46 to 4.11)	52.2±11.2	4.39 (0.89 to 7.89)*
Switch	49.2±10.5	50.6±9.7	1.41 (-0.20 to 3.03)	50.4±8.4	1.18 (-0.53 to 2.88)
LDL-C (mg/dL)					
Overall	97.6±17.2	93.5±17.0	-4.04 (-7.22 to -0.86)	89.1±19.9	-7.92 (-12.18 to -3.66)*
Add-on	97.4±18.7	95.4±18.0	-2.25 (-7.93 to -3.43)	88.5±20.4	-8.16 (-15.35 to -0.96)*
Switch	97.7±16.4	92.4±16.5	-5.06 (-8.98 to -1.16)*	89.5±19.8	-7.78 (-13.21 to -2.35)*
SBP (mm Hg)					
Overall	133.7±11.4	124.7±14.5	-8.98 (-12.15 to -5.81)*	124.9±9.1	-8.67 (-10.73 to -6.60)*
Add-on	133.8±12.8	126.4±9.3	-7.40 (-11.71 to -3.09)*	125.2±9.4	-8.33 (-11.63 to -5.02)*
Switch	133.6±10.5	123.7±16.9	-9.91 (-14.33 to -5.49)*	124.7±9.0	-8.87 (-11.57 to -6.16)*
DBP (mm Hg)					
Overall	74.8±9.6	71.9±9.5	-2.95 (-4.54 to -1.36)*	72.2±10.0	-2.52 (-4.42 to -0.62)
Add-on	72.7±10.7	69.1±9.5	-3.83 (-6.42 to -1.23)*	71.4±11.5	-1.27 (-5.26 to 2.73)
Switch	76.0±8.8	73.5±9.1	-2.44 (-4.49 to -0.39)*	72.7±9.0	-3.28 (-5.22 to -1.34)*
Body weight (kg)					
Overall	73.2±9.8	70.5±9.6	-2.67 (-3.08 to -2.26)*	70.2±9.6	-2.98 (-3.44 to -2.52)*
Add-on	72.0±11.3	69.2±11.1	-2.65 (-3.25 to -2.05)*	68.7±10.9	-3.32 (-4.01 to -2.62)*
Switch	74.0±8.8	71.3±8.6	-2.68 (-3.24 to -2.12)*	71.2±8.7	-2.78 (-3.40 to -2.16)*
eGFR (mL/min/1.73 m^2)					
Overall	82.1±15.6	n/a	n/a	80.2±15.3	-2.33 (-3.90 to -0.77)*
Add-on	79.6±16.3	n/a	n/a	77.0±14.5	-3.00 (-5.10 to -0.90)*
Switch	83.6±15.0	n/a	n/a	82.3±15.5	-1.90 (-4.13 to -0.33)
Urine ACR (mg/L)					
Overall	79.3±73.8	n/a	n/a	51.2±62.2	-30.57 (-40.58 to -20.57)*
Add-on	92.0±77.7	n/a	n/a	58.4±70.0	-35.67 (-54.38 to -16.95)*
Switch	71.7±70.8	n/a	n/a	46.6±56.8	-27.37 (-39.02 to -15.72)*
Visceral fat (cm^2)					
Overall	63.8±15.2	n/a	n/a	55.1±14.2	-9.00 (-10.62 to -7.38)*
Add-on	62.6±12.5	n/a	n/a	55.8±11.4	-7.57 (-10.20 to -4.93)*
Switch	64.5±16.7	n/a	n/a	54.7±15.8	-9.84 (-11.93 to -7.76)*
SMI (%)					
Overall	38.14±4.13	n/a	n/a	38.83±4.01	0.70 (0.31 to 1.09)
Add-on	37.55±4.71	n/a	n/a	38.77±4.87	1.23 (0.45 to 2.01)
Switch	38.47±3.77	n/a	n/a	38.87±3.49	0.40 (-0.03 to 0.84)
KITT (%/min)					
Overall	1.6±0.8	n/a	n/a	2.2±0.8	0.62 (0.43 to 0.81)*
Add-on	1.5±0.5	n/a	n/a	2.2±0.9	0.71 (0.37 to 1.06)*
Switch	1.6±0.9	n/a	n/a	2.2±0.8	0.57 (0.34 to 0.80)*

ACR, albumin-to-creatinine ratio; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; KITT, rate constant for plasma glucose disappearance; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; SMI, skeletal muscle mass index; TG, triglyceride; n/a, not applicable.
Values are presented as a mean±standard error.
*p<0.05 compared to baseline in each treatment group; †p<0.05 compared to the add-on treatment group.

reductions in body weight from baseline in both groups, with adjusted mean changes of -3.32 kg in the add-on group and -2.78 kg in the switch group (p<0.05 in both cases) (Table 2, Fig. 4A). A reduction in body weight of >5% at 12 months was achieved by 51.2% in the add-on group and 38.2% in the switch group (Supplementary Fig. 1, only online). Body weight reductions with dapagliflozin were accompanied by significant decreases in VFA (-7.57 cm^2 in the add-on group and -9.84 cm^2 in the switch group, p<0.05 from the baseline); however, no change in SMI (1.23% in the add-on group and 0.40% in the switch group) was observed from baseline (Table 2). Moreover, there was a significant improvement in insulin sensitivity assessed by KITT.

Predictive markers of glycemic response to SGLT2 inhibitors

To identify predictive factors responsible for changes in HbA1c, we performed linear regression analyses. In univariate analysis, higher baseline HbA1c and FPG levels, and lower KITT were associated with better glycemic responses following SGLT2 inhibitor treatment. Even after multivariate analysis, higher baseline HbA1c was significantly associated with better glycemic responses (Supplementary Table 2, only online). In subgroup analysis, higher baseline HbA1c was significantly associated with better responses in both the add-on and switch groups (data not shown).

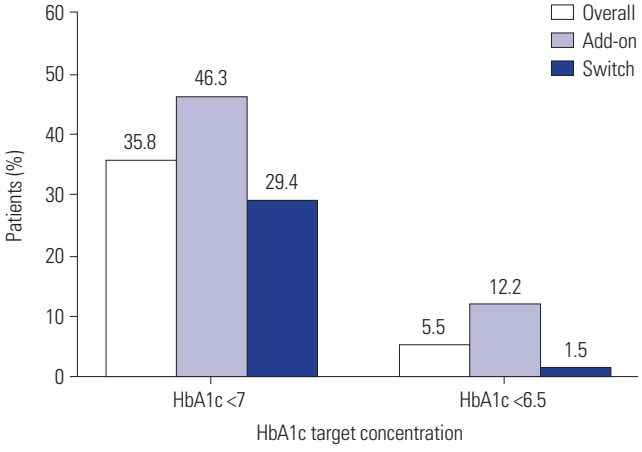

Fig. 3. Percentage of patients who achieved HbA1c <7.0% (left) and <6.5% (right). HbA1c, glycated hemoglobin.

Safety

None of the patients displayed a decrease of >30% in eGFR, and only five patients showed a decrease of >20% in eGFR levels after initiation of dapagliflozin. No patient required renal replacement therapy during the treatment period. Genital tract infections were observed in 2 patients (4.9%) and 4 patients (5.9%) in the add-on group and the switch group, respectively (Table 3). Further, no cases of severe hypoglycemia were observed.

DISCUSSION

In this real-world study, we demonstrated that dapagliflozin significantly improved glycemic control in Korean patients with T2DM and inadequate glycemic control who were receiving MFM and lobeglitazone with or without a DPP4 inhibitor. The combination treatment with SGLT2 inhibitor also significantly improved FPG, lipid profile, body weight, systolic BP, and insulin sensitivity. Notably, these improvements were sustained during the 12-month treatment period. This finding was consistent with previous studies, which showed that the administration of SGLT2 inhibitors to patients with T2DM and inadequate glycemic control receiving pioglitazone reduces HbA1c, FPG, and body weight. [9,15,16]

Table 3. Recorded Adverse Events

	Total (n=109)	Add-on (n=41)	Switch (n=68)
Severe hypoglycemia	0 (0)	0 (0)	0 (0)
Edema	26 (23.9)	7 (17.1)	19 (27.9)
Dyspnea	0 (0)	0 (0)	0 (0)
Genital infection	6 (5.5)	2 (4.9)	4 (5.9)
General weakness	5 (4.6)	1 (2.4)	4 (5.9)
Increased appetite	10 (9.2)	7 (17.1)	3 (4.4)
Hepatic adverse events	0 (0)	0 (0)	0 (0)
Renal adverse events	0 (0)	0 (0)	0 (0)

Data are presented as a number (%).

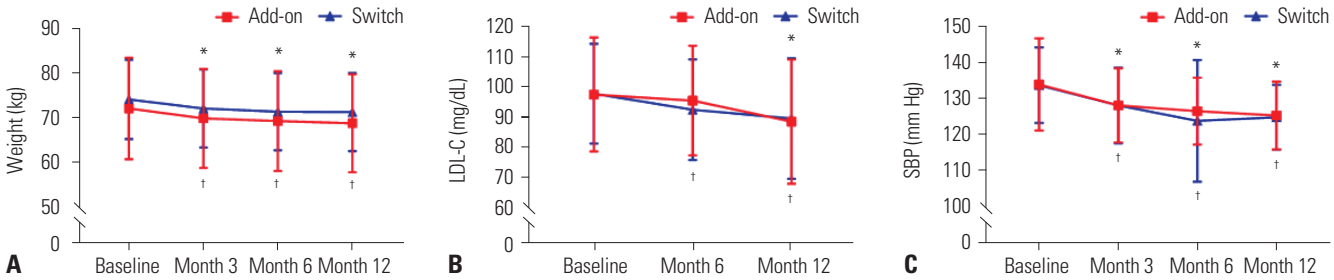

Fig. 4. Mean changes in body weight (A), LDL-C (B), and SBP (C) over time. Data are expressed as the adjusted mean±standard error. LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure. *p<0.05 compared to the baseline in each treatment group; †p<0.05 compared between treatment groups.

https://doi.org/10.3349/ymj.2022.63.9.825

The present study is the first to analyze the efficacy and safety of dapagliflozin as an add-on or switch therapy to lobeglitazone plus MFM in patients with T2DM in a real-world setting. Consistent with previous studies,[9,15-17] our study indicates that the combination of a SGLT2 inhibitor and TZD plus MFM improves glycemic control without increasing the risk of hypoglycemia and with additional benefits of weight loss and improvement in BP, lipid parameters, and insulin sensitivity during a 12-month treatment period. Moreover, this combination was well tolerated, with a similar adverse event profile. Collectively, these results support the administration of SGLT2 inhibitors as an add-on or switch therapy in patients who are receiving a stable dose of TZD but need additional glucose control. This strategy would be a suitable alternative for overweight or obese patients who can continue oral hypoglycemic regimens and who may benefit from weight loss. In this study, dapagliflozin treatment reduced weight by 2.98 kg, and 43.1% of patients achieved >5% weight loss, which, based on body composition analysis, was mainly due to a loss of visceral adipose tissue without affecting muscle mass. Overall, combination therapy with TZD and SGLT2 inhibitor would be very effective in achieving durable glycemic control while minimizing TZD-related side effects, including weight gain.

Moreover, our study demonstrated that switching from DPP4 inhibitors to dapagliflozin in patients with T2DM and inadequate glycemic control on background lobeglitazone and MFM significantly improved glycemic control. Similarly, recent head-to-head studies have suggested that SGLT2 inhibitors may result in a greater glucose-lowering effect than DPP4 inhibitors in people with T2DM and suboptimal control of diabetes at baseline (HbA1c >9%), while a DPP4 inhibitor may achieve a greater glucose-lowering effect in patients with T2DM who have an HbA1c around 7%.[18,19] In our study, all participants in the switch group had inadequate control of diabetes with a mean HbA1c of 8.1%, and approximately 50% of participants had HbA1c ≥8%, which may explain the greater efficacy of SGLT2 inhibitor than DPP4 inhibitor.

Unlike other oral hypoglycemic agents that provide no cardiovascular benefits, SGLT2 inhibitors have been shown to reduce cardiovascular disease (CVD) in clinical trials and CVD-REAL studies.[20-23] Based on these observations, the ADA and EASD have recommended that SGLT2 inhibitors and glucagon-like peptide 1 agonists should be considered as a first-line treatment in patients with a history of CVD. Since SGLT2 inhibitors are being frequently used for the treatment of T2DM and early combination therapy is actively recommended, it would be appropriate to find oral hypoglycemic agents that can be used in combination with SGLT2 inhibitors to produce additive or synergistic effects on treatment outcomes. In particular, the combination of SGLT2 inhibitors and TZD is expected to have a strong therapeutic effect as both agents have a unique mechanism of action; TZD improves insulin sensitivity by sensitizing muscle, liver, and adipose tissue to insulin and preserves β-cell function, whereas SGLT2 inhibitors increase urinary excretion of glucose by directly inhibiting SGLT2 in the proximal tubules of the kidneys, independent of insulin action.[3,24] The efficacy and safety of combination treatment with SGLT2 inhibitors and TZD in addition to MFM have already been investigated in several randomized clinical trials (RCTs) with promising results.[9,15-17] Furthermore, the beneficial effects of TZD on atherosclerotic outcomes could additively improve the cardiovascular outcomes of SGLT2 inhibitor administration, and the detrimental effects of TZD on heart failure would be offset by SGLT2 inhibitors.[25] Future prospective cardiovascular outcome trials are warranted to investigate the synergistic effect of combination therapy with SGLT2 inhibitors and TZD plus MFM.

In the current study, the overall incidence of genital tract infections was similar or slightly lower than that reported in previous RCTs. In our study, all reported cases of genital tract infection had mild symptoms. None of the patients included in the present study experienced severe hypoglycemia. No clinically relevant adverse hepatic or renal events were observed during the treatment period. Overall, add-on and switch therapy of dapagliflozin was well tolerated during the 12-month treatment period, with a safety profile consistent with previous reports.

Our study has several limitations. First, due to the retrospective nature of the study, there was no control group, and adverse events were not systematically collected. We reviewed and analyzed self-reported hypoglycemic events or genital tract infections recorded the electronic medical records. Hence, there may be an underestimation of safety data related to the use of a combination of dapagliflozin with lobeglitazone and MFM. Second, only a small number of patients was included in this study from a single medical center; however, we analyzed a broad spectrum of clinical variables, including KITT and body composition, before and after treatment. Third, there may have been changes in other concomitant medications, such as lipid-lowering drugs or antihypertensive drugs, which may influence the metabolic outcome in our study. However, in previous RCTs using combination therapy with SGLT2 inhibitor, TZD, and MFM, improvement in metabolic profiles, including BP and lipid profiles, was comparable to findings in our study. Fourth, there may have been selection bias as we excluded those with poor treatment adherence for primary analysis. Finally, only dapagliflozin was prescribed in this study. Thus, further studies are needed to investigate the long-term effects and tolerability of other SGLT2 inhibitors in combination with lobeglitazone in clinical practice.

Despite these limitations, the present study provides valuable information because we investigated the efficacy and safety profiles of combination treatment with dapagliflozin, lobeglitazone, and MFM in Korean patients with T2DM and inadequate glycemic control in a real-world setting. Very few studies have investigated this particular combination regimen in Ko-

rean patients. Our results were consistent with previous RCTs on SGLT2 inhibitors and pioglitazone, which also demonstrated favorable outcomes, including improved glycemic control and attenuated weight gain.[9,17] Moreover, we incorporated a longer duration of follow-up, with assessment of various clinical parameters before and after treatment. To the best of our knowledge, this is the first study in a Korean population to analyze the efficacy and safety of dapagliflozin as an add-on or a switch therapy in various combinations with background glucose-lowering therapy including lobeglitazone and MFM.

In conclusion, initiating dapagliflozin as add-on or switch therapy among patients with type 2 diabetes on background lobeglitazone and MFM was associated with better glycemic control, in addition to improvements in metabolic profile and body composition. This combination approach may be a suitable treatment option in clinical settings, particularly in obese patients with inadequately controlled T2DM.

ACKNOWLEDGEMENTS

This study was supported by an Inha University Research Grant and Chong Kun Dang Pharmaceutical Corp., Seoul, Republic of Korea.

The authors thank Dr. Kap Bum Huh for his dedication and contribution to this research.

AUTHOR CONTRIBUTIONS

Conceptualization: Da Hea Seo and So Hun Kim. Data curation: Da Hea Seo and Young Ju Choi. Formal analysis: Da Hea Seo and Young Ju Suh. Funding acquisition: Da Hea Seo. Investigation: Da Hea Seo, Yongin Cho, Seong Hee Ahn, Seongha Seo, and So Hun Kim. Methodology: Da Hea Seo, Yongin Cho, Seong Hee Ahn, Seongha Seo, and So Hun Kim. Project administration: Da Hea Seo, Young Ju Choi, and So Hun Kim. Resources: Da Hea Seo, Young Ju Choi, and So Hun Kim. Software: Da Hea Seo, Young Ju Choi, and So Hun Kim. Supervision: Seongbin Hong, Yong-ho Lee, Young Ju Choi, Eunjig Lee, and So Hun Kim. Validation: Da Hea Seo and So Hun Kim. Visualization: Da Hea Seo and So Hun Kim. Writing—original draft: Da Hea Seo. Writing—review & editing: Da Hea Seo, Yongin Cho, Seong Hee Ahn, Seongha Seo, Seongbin Hong, Yong-ho Lee, Young Ju Choi, Eunjig Lee, and So Hun Kim. Approval of final manuscript: all authors.

ORCID iDs

Da Hea Seo https://orcid.org/0000-0003-2767-0293
Young Ju Suh https://orcid.org/0000-0002-6816-8067
Yongin Cho https://orcid.org/0000-0002-4645-816X
Seong Hee Ahn https://orcid.org/0000-0003-2558-2118
Seongha Seo https://orcid.org/0000-0001-6900-4251
Seongbin Hong https://orcid.org/0000-0002-8189-395X
Yong-ho Lee https://orcid.org/0000-0002-6219-4942
Young Ju Choi https://orcid.org/0000-0003-0868-1472
Eunjig Lee https://orcid.org/0000-0002-9876-8370
So Hun Kim https://orcid.org/0000-0002-2554-3664

REFERENCES

1. Buse JB, Wexler DJ, Tsapas A, Rossing P, Mingrone G, Mathieu C, et al. 2019 update to: 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). Diabetes Care 2020;43:487-93.
2. Lebovitz HE. Thiazolidinediones: the forgotten diabetes medications. Curr Diab Rep 2019;19:151.
3. van Baar MJB, van Ruiten CC, Muskiet MHA, van Bloemendaal L, IJzerman RG, van Raalte DH. SGLT2 inhibitors in combination therapy: from mechanisms to clinical considerations in type 2 diabetes management. Diabetes Care 2018;41:1543-56.
4. Kim SG, Kim DM, Woo JT, Jang HC, Chung CH, Ko KS, et al. Efficacy and safety of lobeglitazone monotherapy in patients with type 2 diabetes mellitus over 24-weeks: a multicenter, randomized, double-blind, parallel-group, placebo controlled trial. PLoS One 2014;9:e92843.
5. Jin SM, Park CY, Cho YM, Ku BJ, Ahn CW, Cha BS, et al. Lobeglitazone and pioglitazone as add-ons to metformin for patients with type 2 diabetes: a 24-week, multicentre, randomized, double-blind, parallel-group, active-controlled, phase III clinical trial with a 28-week extension. Diabetes Obes Metab 2015;17:599-602.
6. American Diabetes Association. 9. Pharmacologic approaches to glycemic treatment: standards of medical care in diabetes—2021. Diabetes Care 2021;44(Suppl 1):S111-24.
7. Nelinson DS, Sosa JM, Chilton RJ. SGLT2 inhibitors: a narrative review of efficacy and safety. J Osteopath Med 2021;121:229-39.
8. Blevins T. Combination therapy for patients with uncontrolled type 2 diabetes mellitus: adding empagliflozin to pioglitazone or pioglitazone plus metformin. Expert Opin Drug Saf 2015;14:789-93.
9. Kovacs CS, Seshiah V, Swallow R, Jones R, Rattunde H, Woerle HJ, et al. Empagliflozin improves glycaemic and weight control as add-on therapy to pioglitazone or pioglitazone plus metformin in patients with type 2 diabetes: a 24-week, randomized, placebo-controlled trial. Diabetes Obes Metab 2014;16:147-58.
10. Hong AR, Koo BK, Kim SW, Yi KH, Moon MK. Efficacy and safety of sodium-glucose cotransporter-2 inhibitors in Korean patients with type 2 diabetes mellitus in real-world clinical practice. Diabetes Metab J 2019;43:590-606.
11. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, Feldman HI, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med 2009;150:604-12.
12. Cruz-Jentoft AJ, Baeyens JP, Bauer JM, Boirie Y, Cederholm T, Landi F, et al. Sarcopenia: European consensus on definition and diagnosis: report of the European Working Group on sarcopenia in older people. Age Ageing 2010;39:412-23.
13. Akinmokun A, Selby PL, Ramaiya K, Alberti KG. The short insulin tolerance test for determination of insulin sensitivity: a comparison with the euglycaemic clamp. Diabet Med 1992;9:432-7.
14. Kim SK, Choi YJ, Huh BW, Kim CS, Park SW, Lee EJ, et al. Ratio of waist-to-calf circumference and carotid atherosclerosis in Korean patients with type 2 diabetes. Diabetes Care 2011;34:2067-71.
15. Kovacs CS, Seshiah V, Merker L, Christiansen AV, Roux F, Salsali A, et al. Empagliflozin as add-on therapy to pioglitazone with or without metformin in patients with type 2 diabetes mellitus. Clin Ther 2015;37:1773-88.e1.
16. Forst T, Guthrie R, Goldenberg R, Yee J, Vijapurkar U, Meininger G, et al. Efficacy and safety of canagliflozin over 52 weeks in patients with type 2 diabetes on background metformin and pioglitazone. Diabetes Obes Metab 2014;16:467-77.
17. Rosenstock J, Vico M, Wei L, Salsali A, List JF. Effects of dapagliflozin, an SGLT2 inhibitor, on HbA(1c), body weight, and hypo-

glycemia risk in patients with type 2 diabetes inadequately controlled on pioglitazone monotherapy. Diabetes Care 2012;35:1473-8.
18. Rosenstock J, Hansen L, Zee P, Li Y, Cook W, Hirshberg B, et al. Dual add-on therapy in type 2 diabetes poorly controlled with metformin monotherapy: a randomized double-blind trial of saxagliptin plus dapagliflozin addition versus single addition of saxagliptin or dapagliflozin to metformin. Diabetes Care 2015;38:376-83.
19. DeFronzo RA, Lewin A, Patel S, Liu D, Kaste R, Woerle HJ, et al. Combination of empagliflozin and linagliptin as second-line therapy in subjects with type 2 diabetes inadequately controlled on metformin. Diabetes Care 2015;38:384-93.
20. Kosiborod M, Lam CSP, Kohsaka S, Kim DJ, Karasik A, Shaw J, et al. Cardiovascular events associated with SGLT-2 inhibitors versus other glucose-lowering drugs: the CVD-REAL 2 study. J Am Coll Cardiol 2018;71:2628-39.
21. Neal B, Perkovic V, Mahaffey KW, de Zeeuw D, Fulcher G, Erondu N, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. N Engl J Med 2017;377:644-57.
22. 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;373:2117-28.
23. Mahaffey KW, Neal B, Perkovic V, de Zeeuw D, Fulcher G, Erondu N, et al. Canagliflozin for primary and secondary prevention of cardiovascular events: results from the CANVAS program (Canagliflozin Cardiovascular Assessment Study). Circulation 2018;137:323-34.
24. Yki-Järvinen H. Thiazolidinediones. N Engl J Med 2004;351:1106-18.
25. Dormandy JA, Charbonnel B, Eckland DJ, Erdmann E, Massi-Benedetti M, Moules IK, et al. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomised controlled trial. Lancet 2005;366:1279-89.