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ORIGINAL ARTICLE

Efficacy and safety of dapagliflozin add-on to evogliptin plus metformin therapy in patients with type 2 diabetes: A randomized, double-blind, placebo-controlled study

In-Kyung Jeong MD[1] | Kyung Mook Choi MD[2] | Kyung Ah Han MD[3] | Kyoung-Ah Kim MD[4] | In Joo Kim MD[5] | Seung Jin Han MD[6] | Won Young Lee MD[7] | Soon Jib Yoo MD[8]

[1]Department of Internal Medicine, Kyung Hee University Hospital at Gangdong, Kyung Hee University School of Medicine, Seoul, Korea

[2]Department of Internal Medicine, Korea University Guro Hospital, Seoul, Korea

[3]Department of Internal Medicine, Nowon Eulgi Medical Center, Seoul, Korea

[4]Department of Internal Medicine, Dongguk University Ilsan Hospital, Goyang, Korea

[5]Department of Internal Medicine, Pusan National University Hospital, Busan, Korea

[6]Department of Endocrinology and Metabolism, Ajou University School of Medicine, Suwon, Korea

[7]Department of Internal Medicine, Kangbuk Samsung Hospital, Seoul, Korea

[8]Department of Internal Medicine, Bucheon St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Korea

Correspondence
Soon Jib Yoo, MD, Department of Internal Medicine, Bucheon St. Mary's Hospital, College of Medicine, The Catholic University of Korea, 327 Sosa-ro, Wonmi-gu, Bucheon-si, Gyeonggi-do 14647, Republic of Korea.
Email: sjyoomt@gmail.com

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Abstract

Aim: To evaluate the efficacy and safety of dapagliflozin versus placebo as an add-on in patients with type 2 diabetes who did not achieve adequate glycaemic control with evogliptin and metformin combination.

Patients and Methods: In this multicentre, randomized, double-blind, placebo-controlled Phase 3 trial, patients with glycated haemoglobin (HbA1c) levels ≥7.0% (≥53 mmol/mol) and ≤10.5% (≤91 mmol/mol) who had received stable-dose metformin (≥1000 mg) and evogliptin (5 mg) for at least 8 weeks were randomized to receive dapagliflozin 10 mg or placebo once daily for 24 weeks. Participants continued treatment with metformin and evogliptin. The primary endpoint was change in HbA1c level after 24 weeks of treatment from baseline level.

Results: In total, 198 patients were randomized, and 195 patients were included in the efficacy analyses (dapagliflozin: 96, placebo: 99). At Week 24, dapagliflozin significantly reduced HbA1c levels. The least squares mean difference in HbA1c level change from baseline after 24 weeks of treatment was −0.70% (−7.7 mmol/mol) ($p < 0.0001$). The proportion of participants achieving HbA1c <7.0% (≥53 mmol/mol) was higher in the dapagliflozin group than in the placebo group. Compared to placebo, dapagliflozin significantly reduced fasting plasma glucose, mean daily glucose, 2-h postprandial plasma glucose, fasting insulin, uric acid and gamma-glutamyl transferase levels, homeostatic model assessment for insulin resistance index, body weight, hepatic steatosis index, and albuminuria. Adiponectin level significantly increased from baseline level after 24 weeks of dapagliflozin treatment. Adverse event rates were similar in the two groups.

Conclusion: Dapagliflozin add-on to evogliptin plus metformin improved glycaemic control and was well tolerated by the target patients.

KEYWORDS
body weight, dapagliflozin, drug combination, efficacy, evogliptin, glucose, metformin, safety, type 2 diabetes mellitus

1 | INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a global health issue, with an increasing number of patients.[1,2] The most serious events associated with diabetes are chronic complications such as diabetic retinopathy, nephropathy and neuropathy, as well as cerebrovascular, cardiovascular and peripheral artery diseases.[3] Therefore, the treatment of diabetes requires not only control of hyperglycaemia but also efforts to correct metabolic abnormalities and cardiovascular risk factors, such as dyslipidaemia, hypertension, obesity, non-alcoholic fatty liver disease and hyperuricaemia.

Owing to the progressive nature of T2DM[4] and its multiple pathogenic disturbances,[5] achieving and maintaining glycaemic treatment goals is challenging.[2,6] Therefore, a combination of antidiabetic agents is required to maintain normoglycaemia.[7] According to clinical practice guidelines, active lifestyle improvements and appropriate drug treatments are required from the early stage of diagnosis. It is a general principle of antihyperglycaemic pharmacotherapy for patients with T2DM to perform individualized pharmacotherapy based on evidence for benefits, including a decrease in glucose level, avoidance of hypoglycaemia and weight gain, and reduction of cardiorenal risk using a combination of drugs with different mechanisms of action.[8,9] Among various antidiabetic medications, the combination of dipeptidyl peptidase-4 (DPP-4) inhibitors and sodium-glucose cotransporter-2 (SGLT2) inhibitors is considered one of the best choices in terms of glucose-lowering efficacy, as this carries a low risk of hypoglycaemia and offers additional advantages, such as weight reduction and cardiorenal benefits.[10]

Evogliptin, a DPP-4 inhibitor, enhances glucose-mediated insulin secretion and suppresses glucagon secretion by inhibiting the rapid degradation of glucagon-like peptide-1 (GLP-1).[11] Dapagliflozin, an SGLT2 inhibitor, acts independently of insulin and inhibits renal glucose reabsorption, thus increasing urinary glucose excretion and reducing plasma glucose concentrations.[12] By acting on distinct pathways that are involved in the pathophysiology of T2DM, evogliptin and dapagliflozin exhibit complementary mechanisms of action when added to metformin.[13] Evogliptin and dapagliflozin, when used as monotherapy or as an add-on to metformin therapy in patients with T2DM, improve glycaemic control, and have favourable safety and tolerability profiles.[14,15] Moreover, both agents have a low propensity for hypoglycaemia and are weight neutral (evogliptin)[16] or cause moderate weight reduction of 3.2%–5% (dapagliflozin).[17] Thus, the addition of dapagliflozin to evogliptin and metformin results in a triple combination therapy that includes components with complementary mechanisms of action, a low risk of hypoglycaemia, and the potential for weight reduction in addition to glucose-lowering efficacy.

This Phase 3 study was designed to compare the efficacy and safety of dapagliflozin versus placebo add-on to evogliptin plus metformin therapy in patients with T2DM who did not achieve adequate glycaemic control with evogliptin plus metformin therapy.

2 | METHODS

2.1 | Study participants

Eligible participants were those aged ≥19 years with T2DM treated with the combination of metformin (≥1000 mg/day, any formulation) and evogliptin 5 mg/day for at least 8 weeks. Patients with glycated haemoglobin (HbA1c) levels between 7.0% (53 mmol/mol) and 10.5% (91 mmol/mol) on treatment with metformin and any kind of DPP-4 inhibitor or patients with HbA1c levels between 6.5% (48 mmol/mol) and 9.5% (80 mmol/mol) on treatment with metformin, any kind of DPP-4 inhibitor, and other oral hypoglycaemic agents, fasting plasma glucose (FPG) level less than or equal to 13.88 mmol/L, and body mass index (BMI) between 18.5 and 40 kg/m^2 were recruited for this study. If patients on metformin ≥1000 mg/day, another DPP-4 inhibitor, and/or other oral hypoglycaemic agents met the above criteria at screening, they were randomized after the washout period and single-blind placebo run-in period.

The key exclusion criteria were: type 1 diabetes mellitus; history of metabolic acidosis including lactic acidosis and diabetic ketoacidosis, or diabetic coma and precoma; history of myocardial infarction, unstable angina, coronary artery bypass graft, stroke, or transient ischaemic attack within 3 months of screening or history of New York Heart Association functional Class III–IV heart failure; treatment in the past 8 weeks with insulin of any type or GLP-1 receptor agonists; and estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2.

2.2 | Study design and procedure

This was a multicentre, randomized, double-blind, placebo-controlled, parallel, Phase 3 clinical trial with 24 weeks of treatment (ClinicalTrials.gov, NCT04356742). The trial was conducted at 26 centres in South Korea between 26 May 2020 and 23 February 2022. The study was designed and monitored in accordance with the ethical principles of Good Clinical Practice as defined by the International Conference on Harmonization and the Declaration of Helsinki. The institutional review board or ethics committee at each study site approved the protocol (Kyung Hee University Hospital at Gangdong: 2020-02-032). Participants signed a written informed consent form and agreed to participate in the trial after fully understanding the study.

The eligible patients were treated with the combination therapy of metformin (≥1000 mg/day, any formulation) and evogliptin (5 mg/day) for at least 8 weeks during the washout period and placebo run-in period. After a 2-week single-blind, placebo run-in period, patients with adequate compliance during the run-in period (≥70% based on pill count) were assigned 1:1 to the test or control group via stratified randomization depending on HbA1c level (<8.0% [<64 mmol/mol] /

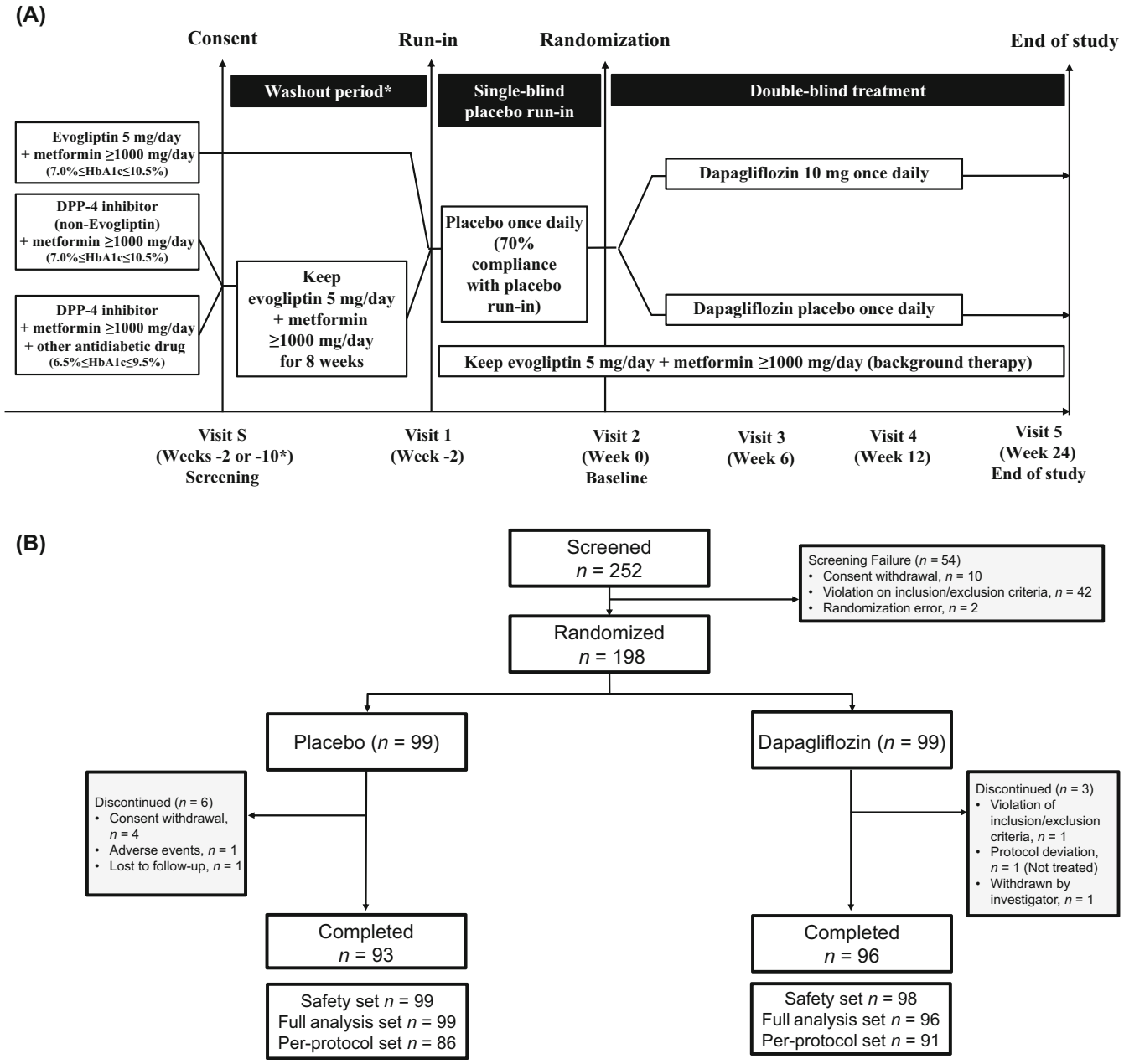

FIGURE 1 Study scheme (A) and patient disposition (B). DPP-4, dipeptidyl peptidase-4; HbA1c, glycated haemoglobin.

≥8.0% [≥64 mmol/mol]) or eGFR (<90 mL/min/1.73 m^2/≥90 mL/min/1.73 m^2) using a computer-generated randomization schedule. eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation. The test group received 10 mg dapagliflozin and the control group received placebo once daily. Dapagliflozin or placebo was added to the evogliptin and metformin therapy (background therapy) for 24 weeks (Figure 1A). During the clinical study, all participants underwent diet and exercise therapy.

Patients with an FPG level of >14.99 mmol/L between Weeks 0 and 6, >13.32 mmol/L between Weeks 6 and 12, or >11.10 mmol/L between Weeks 12 and 24 received rescue therapy with glimepiride at the investigator's discretion. In addition to dapagliflozin, evogliptin, metformin, and rescue medications, the use of medication that may influence blood glucose levels was prohibited during the study. The use of weight-reducing medication and continuous systemic administration of corticosteroids or immunosuppressants was also prohibited.

2.3 | Study endpoints

The primary efficacy endpoint was change in HbA1c level at Week 24 from baseline. The secondary efficacy endpoints were HbA1c < 7.0% (<53 mmol/mol) at Week 24, change in FPG level at Week 24 from baseline, mean daily glucose (MDG) level, postprandial glucose (PPG) level at 2 h after breakfast, homeostatic model

assessment of insulin resistance index (HOMA-IR), and quantitative insulin sensitivity check index (QUICKI). HOMA-IR and QUICKI were calculated using the following formulas: HOMA-IR = {fasting insulin (uIU/mL) × fasting glucose (mg/dL)/18}/22.5; QUICKI = 1/{log(fasting insulin (mIU/L)) + log(fasting glucose (mg/dL))}.[18,19] The other secondary endpoints were body weight, blood pressure, liver function, lipid parameters, adiponectin level, uric acid level, and urine albumin-to-creatinine ratio (UACR) at Week 24. The hepatic steatosis index (HSI) was calculated using the following formula: 8 × alanine aminotransferase (ALT) / aspartate aminotransferase (AST) + BMI (+2 if diabetic; +2 if female).[20]

Safety and tolerability were evaluated based on treatment-emergent adverse events (TEAEs), adverse drug reactions (ADRs), hypoglycaemia, vital signs, clinical laboratory parameters, and electrocardiographic findings during the treatment period. Hypoglycaemia episodes were classified as: hypoglycaemia alert value (blood glucose concentration <3.89 mmol/L and ≥3.00 mmol/L; hypoglycaemia to the extent that required immediate intake of carbohydrates or adjustment of drug type and dose); clinically significant hypoglycaemia (blood glucose concentration <3.00 mmol/L; hypoglycaemia to the extent that caused disturbances in the hypoglycaemic defence system); and severe hypoglycaemia (there was no specific glucose threshold level, but a level that required external help to resolve a hypoglycaemic condition).

2.4 | Statistical analysis

Given the primary efficacy endpoint, we assumed a difference of 0.45 between the dapagliflozin and placebo groups. This assumption was based on literature[21] which reported a difference of 0.40. Additionally, the standard deviation of each group was assumed to be 1.0. Assuming randomization at a 1:1 ratio with 80% power and 0.05% level of significance, 78 participants were required for each group. A total of 200 participants, 100 per group, were enrolled, accounting for a 20% dropout rate.

Efficacy analyses were conducted using the full analysis set (FAS), which included all randomized participants who received at least one dose of the study medication and underwent baseline and at least one post-baseline measurement. Among the participants in the FAS, those who completed the study without major protocol deviations were included in the per-protocol (PP) set. However, participants who received rescue therapy during the study were excluded from the PP set. Mixed-effect model for repeated measures (MMRM) analysis was performed to evaluate the superiority of dapagliflozin over placebo in terms of the primary efficacy endpoint (change in HbA1c level [%] after 24 weeks). The MMRM analysis included treatment group, visit, interaction between treatment group and visit, and stratification factors (HbA1c level less than/greater than or equal to 8.0% (64 mmol/mol) and eGFR less than/greater than or equal to 90 mL/min/1.73 m^2) as fixed effects. For the secondary efficacy endpoint analysis, the MMRM and generalized linear mixed models (logistic) were constructed, and analysis of covariance (ANCOVA) was performed. For continuous variables, the analysis model was evaluated using the least squares (LS) mean difference between the groups. The 95% confidence interval (CI) and *p* value corresponding to the LS mean and standard error (SE) of each treatment group, as well as the LS mean difference between the treatment groups are presented. For categorical variables, odds ratio, SE, 95% CI, and *p* value are presented as analysis results.

For subgroup analysis, an interaction analysis was performed between the treatment groups and subgroup factors on the primary efficacy endpoint using ANCOVA. The ANCOVA model included treatment group, subgroup factors, stratification factors, and interactions between the treatment group and subgroup factors.

Safety analyses were conducted using the safety set, which included participants who received the study medication at least once after randomization. Safety analysis for the comparison of incidence rates between the treatment groups was performed using the chi-squared test or Fisher's exact test. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, North Carolina, USA).

3 | RESULTS

3.1 | Participant demographics and baseline clinical characteristics

A total of 252 patients were screened, and 198 were randomized to receive dapagliflozin 10 mg ($n = 99$) or placebo ($n = 99$). After randomization, nine patients discontinued the study, and 189 patients (dapagliflozin, 96; placebo, 93) completed the 24-week treatment. The flow of participants throughout the study and the reasons for discontinuation are summarized in Figure 1B. There were 197 participants (dapagliflozin, 98; placebo, 99) in the safety set, 195 (dapagliflozin, 96; placebo, 99) in the FAS, and 177 (dapagliflozin, 91; placebo, 86) in the PP set. The baseline demographics were similar between the groups (Table 1). The mean age of the participants was 58.66 years; those aged 65 years or older comprised 30.30% of the participants, and 55.56% were male ($n = 110$). The mean BMI was 25.89 kg/m^2, 57.07% of the participants had a BMI of ≥25 kg/m^2. The mean diabetes duration was 11.38 years. The mean HbA1c level was 7.92%, and the mean eGFR was 92.51 mL/min/1.73 m^2.

3.2 | Primary efficacy endpoint

When added to evogliptin and metformin, dapagliflozin significantly decreased the HbA1c level at Week 24 compared to placebo. The LS mean ± SE change in HbA1c level at Week 24 from baseline of the dapagliflozin group (−0.76 ± 0.08%) was superior to that of the placebo group (−0.06 ± 0.08%; Figure 2A). This difference between the two groups was −0.70 ± 0.11% (Figure 2B and Table 2). In the dapagliflozin group, the greatest reduction in HbA1c level was observed at 12 weeks, and the improvement was maintained for 24 weeks.

TABLE 1 Baseline demographics and characteristics (randomized set).

Characteristics	Total ($N = 198$)	Placebo ($N = 99$)	Dapagliflozin ($N = 99$)
Age, years	58.66 ± 9.96	59.14 ± 9.93	58.17 ± 10.01
Age group, *n* (%)			
<65 years	138 (69.70)	71 (71.72)	67 (67.68)
≥65 years	60 (30.30)	28 (28.28)	32 (32.32)
Sex, *n* (%)			
Male	110 (55.56)	53 (53.54)	57 (57.58)
Female	88 (44.44)	46 (46.46)	42 (42.42)
Height, cm	163.36 ± 8.57	162.78 ± 8.21	163.94 ± 8.92
Body weight, kg	69.26 ± 10.89	69.51 ± 10.40	69.02 ± 11.40
BMI, kg/m^2	25.89 ± 3.08	26.18 ± 3.03	25.60 ± 3.13
BMI category, *n* (%)			
<25 kg/m^2	85 (42.93)	38 (38.38)	47 (47.47)
≥25 kg/m^2	113 (57.07)	61 (61.62)	52 (52.53)
SBP, mmHg	128.35 ± 12.44	129.20 ± 11.88	127.49 ± 12.98
DBP, mmHg	77.85 ± 9.54	78.85 ± 9.73	76.85 ± 9.29
Duration of diabetes, years	11.38 ± 6.70	10.92 ± 7.02	11.84 ± 6.37
Metformin dosage, mg/day	1397.60 ± 405.68	1376.52 ± 411.33	1418.69 ± 400.93
HbA1c at screening, %	7.92 ± 0.70	7.89 ± 0.68	7.95 ± 0.73
HbA1c, *n* (%)			
<8.0% (<64 mmol/mol)	123 (62.12)	61 (61.62)	62 (62.63)
≥8.0% (<64 mmol/mol)	75 (37.88)	38 (38.38)	37 (37.37)
AST, IU/L	24.52 ± 10.74	26.47 ± 10.70	22.57 ± 10.47
ALT, IU/L	28.26 ± 16.20	30.90 ± 17.16	25.63 ± 14.80
Gamma-glutamyl transferase, IU/L	36.63 ± 41.82	36.94 ± 33.89	36.31 ± 48.65
Uric acid, mg/dL	4.74 ± 1.21	4.69 ± 1.14	4.80 ± 1.27
eGFR at screening, mL/min/1.73 m^2	92.51 ± 13.70	92.37 ± 13.21	92.66 ± 14.24
eGFR at screening, *n* (%)			
≥90 mL/min/1.73 m^2	120 (60.61)	60 (60.61)	60 (60.61)
60 to <90 mL/min/1.73 m^2	78 (39.39)	39 (39.39)	39 (39.39)
UACR, mg/g creatinine	68.16 ± 298.01	93.87 ± 413.63	42.98 ± 88.90
Concurrent disease, *n* (%)	-	-	-
Hypertension	110 (55.56)	65 (65.66)	45 (45.45)
Dyslipidaemia	186 (93.94)	95 (95.96)	91 (91.92)
Cardiovascular disease	40 (20.20)	20 (20.20)	20 (20.20)

Note: Data are presented as number (%) or mean ± SD.
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HbA1c, glycated haemoglobin; SBP, systolic blood pressure; UACR, urine albumin-to-creatinine ratio.

In participants with higher baseline HbA1c levels (≥8.0% [≥64 mmol/mol]), the difference in the change in HbA1c level between the dapagliflozin and placebo groups was numerically greater (−0.71% [95% CI −1.06 to −0.37]) than that in participants with lower baseline HbA1c levels (<8.0% (<64mmol/mol); −0.64% [95% CI −0.90 to −0.37]) in the dapagliflozin group (Figure 2C).

We analysed the glucose-lowering efficacy of dapagliflozin among various subgroups. The HbA1c-lowering efficacy of dapagliflozin was consistently superior to that of placebo, irrespective of age, BMI, diabetes duration, baseline HbA1c level, eGFR, and albuminuria. In the subgroup analysis, the interaction between the treatment group and subgroup factors was not significant for changes in the HbA1c levels 24 weeks after baseline (Figure S1).

3.3 | Secondary efficacy endpoint

The proportion of participants achieving HbA1c levels <7.0% (<53 mmol/mol) at Week 24 was higher in the dapagliflozin group than in the control group (42.71% vs. 16.16% in placebo; $p = 0.0002$

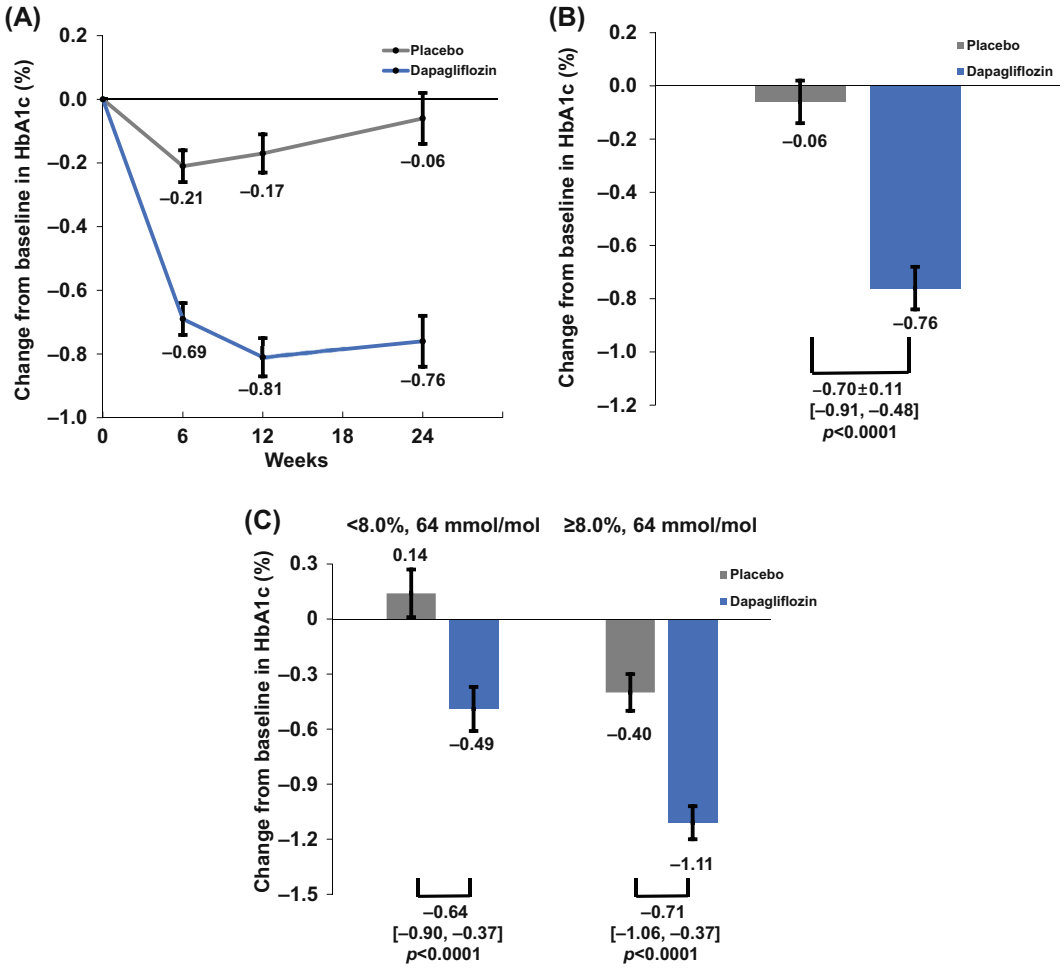

FIGURE 2 Primary efficacy endpoint. (A) Time course of the least squares (LS) mean change in glycated haemoglobin (HbA1c) level from baseline. Testing for difference between the treatment groups (mixed-effect model for repeated measures [MMRM] included treatment group, visit, stratification factor (HbA1c and estimated glomerular filtration rate [eGFR] group), and interaction effect between treatment group and visit as fixed effects). (B) LS mean change in HbA1c level at Week 24. Testing for difference between the treatment groups (MMRM included treatment group, visit, stratification factor (HbA1c and eGFR group), and interaction effect between treatment group and visit as fixed effects). (C) LS mean change in HbA1c level at Week 24 of the higher screening HbA1c value group (≥8.0%, 64 mmol/mol) and lower screening HbA1c value group (<8.0%, 64 mmol/mol). Testing for difference between the treatment groups (analysis of covariance model with treatment group and subgroup as factors, eGFR group as a stratification factor, and treatment group and subgroup as an interaction) in the higher screening HbA1c value groups (≥8%, 64 mmol/mol) and lower screening HbA1c value groups (<8%, 64 mmol/mol).

[Figure 3A]). Dapagliflozin significantly reduced FPG levels at Week 24 compared to the placebo (Figure 3B and Table 2). The LS mean difference in FPG levels between the groups at Week 24 was −1.12 ± 0.20 mmol/L ($p < 0.0001$; Figure 3C and Table 2). Dapagliflozin also significantly decreased levels of MDG and 2-h PPG after breakfast at Week 24 compared to the placebo. The LS mean difference in MDG levels between the groups at Week 24 was −0.95 ± 0.22 mmol/L ($p < 0.0001$; Figure 3D and Table 2), and the difference in 2-h PPG at breakfast was −1.53 ± 0.42 mmol/L ($p = 0.0004$; Figure 3E and Table 2). Among the exploratory variables related to glucose metabolism, dapagliflozin significantly improved HOMA-IR and QUICKI as indices of insulin resistance and sensitivity during the treatment period compared to placebo (Figure 3F,G). Adiponectin levels significantly increased from baseline after 24 weeks of dapagliflozin treatment (Figure 3H and Table 2). Dapagliflozin significantly reduced uric acid levels and body weight compared to placebo at Week 24 (Figure 3I,J and Table 2). Compared to placebo, dapagliflozin significantly reduced ALT levels, gamma-glutamyl transferase levels, and HSI at Week 24 (Table 2). Participants receiving dapagliflozin showed a significant increase in total cholesterol and high-density lipoprotein (HDL) cholesterol levels (Table 2). Serum LDL cholesterol levels increased in the dapagliflozin group, and there was a small reduction in serum triglycerides in dapagliflozin, although neither difference achieved statistical significance.

There was no significant difference in UACR at 24 weeks between the dapagliflozin and placebo groups. However, when subdivided based on the degree of albuminuria, a significant improvement in UACR was observed in the dapagliflozin group compared to the placebo group in participants with UACR of 30–299 mg/g creatinine (Table 2).

TABLE 2 Adjusted mean change from baseline at 24 weeks for primary and secondary efficacy endpoints (full analysis set).

Efficacy Endpoints	Placebo (*N* = 99)	Dapagliflozin (*N* = 96)
HbA_{1c},%		
Baseline, mean ± SD	7.77 ± 0.68	7.87 ± 0.72
Change from baseline, LS mean ± SE	−0.06 ± 0.08	−0.76 ± 0.08
LS mean difference dapagliflozin vs. placebo [95% CI]	−0.70 ± 0.11 [−0.91, −0.48]	
p	<0.0001	
HbA_{1c}, mmol/mol		
Baseline, mean ± SD	61.40 ± 7.42	62.55 ± 7.86
Change from baseline, LS mean ± SE	−0.69 ± 0.86	−8.30 ± 0.86
LS mean difference dapagliflozin vs. placebo [95% CI]	−7.60 ± 1.21 [−9.98, −5.22]	
p	<0.0001	
FPG, mmol/L		
Baseline, mean ± SD	8.31 ± 1.35	8.88 ± 1.61
Change from baseline, LS mean ± SE	−0.22 ± 0.14	−1.33 ± 0.14
LS mean difference dapagliflozin vs. placebo [95% CI]	−1.12 ± 0.20 [−1.51, −0.72]	
p	<0.0001	
MDG, mmol/L		
Baseline, mean ± SD	9.47 ± 1.43	9.87 ± 2.02
Change from baseline	−0.39 ± 0.16	−1.34 ± 0.16
Difference dapagliflozin vs. placebo	−0.95 ± 0.22 [−1.38, −0.51]	
p	<0.0001	
2-h PPG at breakfast, mmol/L		
Baseline, mean ± SD	10.96 ± 2.87	11.23 ± 2.95
Change from baseline	−0.36 ± 0.31	−1.88 ± 0.31
Difference dapagliflozin vs. placebo	−1.53 ± 0.42 [−2.36, −0.69]	
p	0.0004	
Adiponectin, μg/dL		
Baseline, mean ± SD	5.01 ± 1.99	5.31 ± 2.38
Change from baseline, LS mean ± SE	−0.00 ± 0.13	0.41 ± 0.13
LS mean difference dapagliflozin vs. placebo [95% CI]	0.41 ± 0.18 [0.05, 0.78]	
p	0.0256	
Uric acid, mg/dL		
Baseline, mean ± SD	4.69 ± 1.14	4.76 ± 1.24
Change from baseline, LS mean ± SE	0.14 ± 0.08	−0.25 ± 0.08
LS mean difference dapagliflozin vs. placebo [95% CI]	−0.38 ± 0.11 [−0.60, −0.17]	
p	0.0007	
Body weight, kg		
Baseline, mean ± SD	69.51 ± 10.40	69.10 ± 11.46
Change from baseline, LS mean ± SE	−1.03 ± 0.21	−2.82 ± 0.21
LS mean difference dapagliflozin vs. placebo [95% CI]	−1.79 ± 0.29 [−2.36, −1.22]	
p	<0.0001	
SBP, mmHg		
Baseline, mean ± SD	129.20 ± 11.88	127.52 ± 13.13
Change from baseline, LS mean ± SE	−2.83 ± 1.11	−4.85 ± 1.08
LS mean difference dapagliflozin vs. placebo [95% CI]	−2.03 ± 1.52 [−5.03, 0.98]	
p	0.1853	

(Continues)

TABLE 2 (Continued)

Efficacy Endpoints	Placebo (*N* = 99)	Dapagliflozin (*N* = 96)
DBP, mmHg		
Baseline, mean ± SD	78.85 ± 9.73	76.89 ± 9.25
Change from baseline, LS mean ± SE	−1.54 ± 0.83	−2.23 ± 0.81
LS mean difference dapagliflozin vs. placebo [95% CI]	−0.69 ± 1.14 [−2.95, 1.56]	
p	0.5467	
ALT, U/L		
Baseline, mean ± SD	30.90 ± 17.16	25.60 ± 14.90
Change from baseline, LS mean ± SE	−2.83 ± 1.00	−5.60 ± 0.98
LS mean difference dapagliflozin vs. placebo [95% CI]	−2.77 ± 1.37 [−5.48, −0.07]	
p	0.0444	
r-GT, U/L		
Baseline, mean ± SD	36.94 ± 33.89	36.10 ± 49.15
Change from baseline, LS mean ± SE	0.87 ± 2.57	−8.59 ± 2.54
LS mean difference dapagliflozin vs. placebo [95% CI]	−9.46 ± 3.56 [−16.48, −2.45]	
p	0.0085	
HIS		
Baseline, mean ± SD	38.38 ± 4.82	37.39 ± 4.44
Change from baseline, LS mean ± SE	−0.76 ± 0.24	−1.67 ± 0.24
LS mean difference dapagliflozin vs. placebo [95% CI]	−0.91 ± 0.33 [−1.56, −0.26]	
p	0.0062	
Total cholesterol, mg/dL		
Baseline, mean ± SD	138.69 ± 29.36	136.16 ± 29.39
Change from baseline, LS mean ± SE	2.78 ± 2.05	9.51 ± 2.01
LS mean difference dapagliflozin vs. placebo [95% CI]	6.73 ± 2.82 [1.17, 12.29]	
p	0.0179	
LDL cholesterol, mg/dL		
Baseline, mean ± SD	71.75 ± 25.44	70.08 ± 24.63
Change from baseline, LS mean ± SE	0.72 ± 1.67	4.86 ± 1.63
LS mean difference dapagliflozin vs. placebo [95% CI]	4.11 ± 2.29 [−0.39, 8.62]	
p	0.0734	
HDL cholesterol, mg/dL		
Baseline, mean ± SD	48.95 ± 10.48	49.05 ± 13.02
Change from baseline, LS mean ± SE	0.43 ± 0.63	3.22 ± 0.62
LS mean difference dapagliflozin vs. placebo [95% CI]	2.78 ± 0.87 [1.07, 4.49]	
p	0.0016	
Triglyceride, mg/dL		
Baseline, mean ± SD	132.37 ± 80.35	130.64 ± 67.22
Change from baseline, LS mean ± SE	−8.50 ± 5.77	−2.06 ± 5.67
LS mean difference dapagliflozin vs. placebo [95% CI]	6.44 ± 7.94 [−9.22, 22.10]	
p	0.4185	
UACR, mg/g creatinine		
Baseline, mean ± SD	93.87 ± 413.63	43.76 ± 90.22
Change from baseline, LS mean ± SE	−14.27 ± 5.97	−16.16 ± 5.75

TABLE 2 (Continued)

Efficacy Endpoints	Placebo (*N* = 99)	Dapagliflozin (*N* = 96)
LS mean difference dapagliflozin vs. placebo [95% CI]	−1.89 ± 8.24 [−18.15, 14.37]	
p	0.8188	
	Placebo (*N* = 70)	**Dapagliflozin (*N* = 70)**
UACR, mg/g creatinine [0 ≤ UACR (mg/g creatinine) < 30]		
Baseline, mean ± SD	12.79 ± 6.82	11.96 ± 6.65
Change from baseline, LS mean ± SE	1.59 ± 1.50	3.55 ± 1.46
LS mean difference dapagliflozin vs. placebo [95% CI]	1.96 ± 2.06 [−2.13, 6.04]	
p	0.3449	
	Placebo (*N* = 21)	**Dapagliflozin (*N* = 19)**
UACR, mg/g creatinine [30 ≤ UACR (mg/g creatinine) <300]		
Baseline, mean ± SD	92.67 ± 59.89	83.88 ± 66.60
Change from baseline, LS mean ± SE	0.88 ± 11.40	−40.00 ± 11.36
LS mean difference dapagliflozin vs. placebo [95% CI]	−40.88 ± 14.86 [−71.05, −10.72]	
p	0.0093	
	Placebo (*N* = 8)	**Dapagliflozin (*N* = 7)**
UACR, mg/g creatinine [UACR (mg/g creatinine) ≥ 300]		
Baseline, mean ± SD	1994.23 ± 1507.00	409.78 ± 97.81
Change from baseline, LS mean ± SE	NC	NC

Abbreviations: DBP, diastolic blood pressure; FPG, fasting plasma glucose; HIS, hepatic steatosis index; MDG, mean daily glucose; NC, not calculated (It cannot be estimated by MMRM due to small number of subjects; PPG, postprandial plasma glucose; SBP, systolic blood pressure; UACR, urine albumin-to-creatinine ratio.

Three participants (3.03%) in the placebo group received rescue therapy with glimepiride during the treatment period, but none of the participants in the dapagliflozin group received rescue therapy.

3.4 | Safety outcomes

A summary of the TEAEs is presented in Table S1. Adverse events (AEs) occurred in 27.55% of participants receiving dapagliflozin and 27.27% receiving placebo. Most AEs were mild or moderate in severity. Serious AEs occurred in six out of 197 participants in the safety set, including two participants in the placebo group and four participants in the dapagliflozin group. There was no statistically significant difference in the incidence of serious AEs between the groups. The serious AEs reported were COVID-19 and cerebral infarction in each participant in the placebo group as well as herpes zoster, back pain, rotator cuff syndrome, and acute cholecystitis in each participant in the dapagliflozin group. No serious ADRs were observed, and those that were observed did not lead to discontinuation during the trial (Table S1).

The incidences of TEAEs and ADRs were similar among groups (Table S2). The incidence of genitourinary tract infections in the dapagliflozin group was four cases, while in the placebo group there was one case (Supplementary Table 2). There were no reports of ketoacidosis in either group. Hypoglycaemic episodes were infrequent, and all episodes were hypoglycaemic alerts, which occurred in two participants in the dapagliflozin group (2.04%) and three in the placebo group (3.03%; Table S1).

4 | DISCUSSION

This study demonstrated that the addition of dapagliflozin to evogliptin plus metformin improved glycaemic control without serious AEs in patients with T2DM who were not adequately controlled with the evogliptin plus metformin combination. In addition, dapagliflozin, evogliptin and metformin triple combination therapy significantly reduced body weight, insulin resistance, hyperuricaemia, HSI, and albuminuria compared to evogliptin and metformin therapy.

Owing to progressive pancreatic beta-cell failure and multiple pathogenic mechanisms, combination therapy with antidiabetic agents covering various metabolic disturbances is required to maintain normoglycaemia. Metformin is generally prescribed as the initial step of therapy to improve insulin resistance in patients with T2DM. DPP-4 inhibitors are the second most commonly prescribed antidiabetic agents in South Korea because they reduce HbA1c levels by ∼0.5%–0.6% without AEs, such as hypoglycaemia and weight gain.[2] Therefore, metformin and DPP-4 inhibitors are the most commonly prescribed combination as a dual therapy according to the diabetes factsheet in Korea.[2] Evogliptin increases glucose-dependent insulin secretion and decreases glucagon secretion by inhibiting GLP-1 degradation.[11] When hyperglycaemia is inadequately controlled by metformin and DPP-4 inhibitors, SGLT2 inhibitors are preferred as the next antidiabetic agents. Dapagliflozin has multiple metabolic benefits, including glycaemic control, weight loss, insulin resistance reduction, and hepatic steatosis, hypertension, and hyperuricaemia improvement through glycosuria and natriuresis, by inhibiting SGLT2 expression in

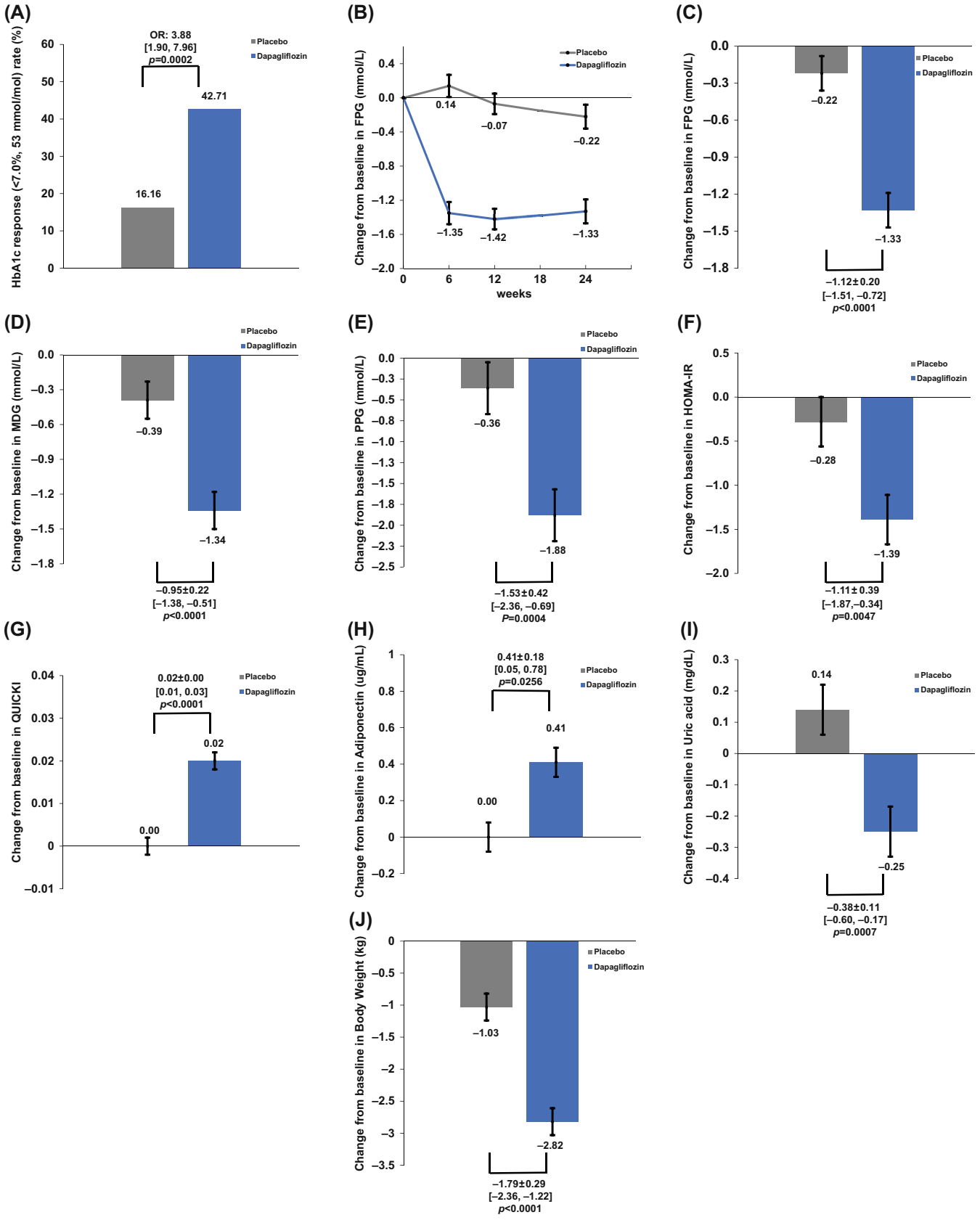

FIGURE 3 Legend on next page.

the proximal tubules.[22] In addition, the cardiorenal benefits of dapagliflozin have been demonstrated in several large randomized clinical trials of cardiovascular outcomes, such as the landmark DECLARE,[23] DAPA-HF[24] and DAPA-CKD trials.[25] Owing to the aforementioned metabolic benefits of dapagliflozin, dapagliflozin add-on to evogliptin plus metformin reduced HbA1c level by 0.7%, mean FPG level by 1.33 mmol/L, and mean MDG level by 0.95 mmol/L at 24 weeks compared to evogliptin plus metformin treatment in this study. This glucose-lowering efficacy was comparable with that reported previously.[26] Triple therapy with dapagliflozin add-on to saxagliptin plus metformin reportedly reduced HbA1c level by 0.74%, mean FPG level by 1.50 mmol/L, and body weight by −2.1 kg at 52 weeks.[26] In addition, it is known that the blood glucose-lowering effect of SGLT2 inhibitors is better when the baseline blood glucose level is higher and renal function is better. Similarly, in our study, the blood glucose level reduction effect was numerically better in patients with baseline HbA1c level of 8% (64 mmol/mol) or higher (−0.71%) than in patients with baseline HbA1c level less than 8% (64 mmol/mol) (−0.64%). In addition, this study showed no significant difference in the glycaemia-lowering effect of dapagliflozin, irrespective of whether the duration of diabetes was more than 10 years or less than 10 years. This finding suggests that SGLT2 inhibitors have insulin-independent mechanisms in reducing blood glucose level; thus, they have a significant glycaemia-lowering effect regardless of the duration of diabetes or insulin secretion ability of the participants.

In addition to the blood glucose reduction effect, dapagliflozin improves insulin resistance, hyperuricaemia, and hepatosteatosis, and increases adiponectin through weight loss. The BEYOND study showed that dapagliflozin, when added to metformin, significantly reduced body weight (−2.38 kg), body fat mass (−1.49 kg) and abdominal visceral fat area and increased adiponectin levels in Korean patients with T2DM.[27] Here, mean body weight was reduced by 1.79 kg in the dapagliflozin group compared to the placebo group. Although this degree of weight loss appears to be lesser than that reported in other dapagliflozin studies, it was sufficient to improve insulin resistance and HSI. The level of adiponectin, an important insulin-sensitizing adipokine, significantly increased after weight loss and directly correlated with insulin sensitivity. Here, the improvement in insulin sensitivity and increase in adiponectin level with dapagliflozin treatment compared to placebo also contributed to the improvement in hepatosteatosis. Several clinical studies have demonstrated that dapagliflozin improves liver steatosis and attenuates fibrosis.[28]

Dapagliflozin administration usually reduces systolic blood pressure by approximately 3 mmHg.[29] However, in this study, the blood pressure reduction effect of dapagliflozin (−4.85 ± 1.08 mmHg) was not significant compared with that of placebo (−2.83 ± 1.11 mmHg), probably because the proportion of participants with hypertension was 45.45% in the dapagliflozin group, which was significantly lower than the 65.6% in the placebo group. In previous studies of SGLT2 inhibitors, the blood pressure reduction effect of dapagliflozin was more significant in patients with hypertension than in those with normal blood pressure.[29] In addition, as the antihypertensive drug dose was freely adjusted to suit the participant's BP during the study period, changes in the antihypertensive drug doses were reviewed in the two groups: in the placebo group, the antihypertensive drug doses were increased in two participants and decreased in two participants, whereas in the dapagliflozin group, the antihypertensive drug doses were reduced in one participant.

Dapagliflozin administration usually increases low-density lipoprotein (LDL) cholesterol levels and decreases small-dense LDL levels.[30] Here, the increase in LDL cholesterol level in the dapagliflozin group was not significant compared with that in the placebo group, and the HDL cholesterol level in the dapagliflozin group significantly increased compared with that in the placebo group.

In patients with high cardiorenal risk, SGLT2 inhibitors have been shown to improve albuminuria. The DECLARE-TIMI 58 study showed that dapagliflozin has beneficial effects on UACR and renal-specific outcomes across baseline UACR categories, including patients with normal albumin excretion.[31] In the present study, dapagliflozin showed a significant reduction in albuminuria among participants with UACR of 30–299 mg/g creatinine.

Regarding safety outcomes, the incidence of TEAEs and ADRs in the triple combination therapy with dapagliflozin, evogliptin and metformin was similar to that observed with dual combination therapy of evogliptin and metformin. In general, urogenital infection and dehydration are common AEs of SGLT2 inhibitors, and euglycaemic ketoacidosis may occur in rare cases; however, in this study, the frequency

FIGURE 3 Secondary efficacy endpoint. (A) Proportion with glycaemic target achievement (glycated haemoglobin [HbA1c] < 7.0%, 53 mmol/mol) at Week 24, testing for differences between the treatment groups (logistic generalized linear mixed models included treatment groups, visit, stratification factor (HbA1c and estimated glomerular filtration rate [eGFR] group), and the interaction effect between treatment group and visit as fixed effects). (B) Time course of least squares (LS) mean change in fasting plasma glucose (FPG) level from baseline. (C) LS mean change in FPG level at Week 24, testing for differences between the treatment groups (mixed-effect model for repeated measures [MMRM] included treatment group, visit, stratification factor [HbA1c group and eGFR group], and interaction effect between treatment group and visit as fixed effects and baseline value as covariate). (D) LS mean change in mean daily glucose (MDG) level at Week 24. (E) LS mean change in the 2-h postprandial glucose level after breakfast at Week 24, testing for differences between the treatment groups (analysis of covariance model with treatment group as a factor and stratification factor (HbA1c group and eGFR group) and baseline values as covariates). (F) LS mean change in homeostatic model assessment for insulin resistance index (HOMA-IR) at Week 24. (G) LS mean change in quantitative insulin sensitivity check index (QUICKI) at Week 24. (H) LS mean change in adiponectin level at Week 24. (I) LS mean change in uric acid level at Week 24. (J) LS mean change in body weight at Week 24. (F–J) Testing for differences between the treatment groups (MMRM included treatment group, visit, stratification factor [HbA1c group and eGFR group], interaction effect between treatment group and visit as fixed effects, and baseline value as a covariate). OR, odds ratio.

of these ADRs did not increase in the dapagliflozin group. A glucose-lowering effect without hypoglycaemia is particularly important in elderly patients. Here, the triple combination therapy demonstrated superior glucose-lowering efficacy without causing hypoglycaemia in elderly patients.

Despite the clinical relevance of this study, it does have some limitations. First, although it was conducted at multiple centres, it cannot be generalized to different racial groups as it was conducted in a single country. Second, there is a limit to how widely the findings can be applied to a broader range of patients with diabetes, as we excluded patients with diabetes with decreased renal function or concurrent cardiovascular complications. Third, the small sample size of the study may restrict the suitability of subgroup analysis.

In conclusion, dapagliflozin add-on to evogliptin plus metformin improved glycaemic control, significantly reduced body weight, insulin resistance, hyperuricaemia, HSI, and microalbuminuria, and was well tolerated in patients with T2DM not adequately controlled with the evogliptin and metformin combination.

AUTHOR CONTRIBUTIONS

Conception or design: In-Kyung Jeong and Soon Jib Yoo. Acquisition, analysis and interpretation of data: In-Kyung Jeong, Kyung Mook Choi, Kyung Ah Han, Kyoung-Ah Kim, In Joo Kim, Seung Jin Han, Won Young Lee and Soon Jib Yoo. Drafting the work and revising: In-Kyung Jeong and Soon Jib Yoo. Final approval of the manuscript: In-Kyung Jeong, Kyung Mook Choi, Kyung Ah Han, Kyoung-Ah Kim, In Joo Kim, Seung Jin Han, Won Young Lee and Soon Jib Yoo.

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CONFLICT OF INTEREST STATEMENT

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

PEER REVIEW

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DATA AVAILABILITY STATEMENT

The data cannot be shared because the study participants did not agree to share it.

ORCID

In-Kyung Jeong https://orcid.org/0000-0001-7857-546X
Kyung Mook Choi https://orcid.org/0000-0001-6175-0225
In Joo Kim https://orcid.org/0000-0003-1765-0774
Soon Jib Yoo https://orcid.org/0000-0002-9932-4130

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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