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Efficacy and safety of pioglitazone, empagliflozin and glimepiride as third-line agents in patients with type 2 diabetes inadequately controlled with metformin and DPP-4 inhibitors: A multicentre, phase 4 randomized controlled trial

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Abstract

Aims: To assess the efficacy and safety of three triple-combination therapies in patients with type 2 diabetes (T2D) inadequately controlled on metformin and a dipeptidyl peptidase-4 (DPP-4) inhibitor.

Materials and methods: This multicentre, prospective, randomised, open-label, parallel-group, phase 4 study included patients with T2D inadequately controlled on metformin (≥ 1000 mg) and a DPP-4 inhibitor. Participants were randomised to receive empagliflozin 10 mg/day ($n = 61$), pioglitazone 15 mg/day ($n = 58$) or glimepiride 2 mg/day ($n = 57$). The primary outcome was glycated haemoglobin (HbA1c) level change after 24 weeks of treatment.

Results: The mean age, HbA1c level and diabetes duration of the patients were 58.5 ± 10.0 years, $7.8 \pm 0.7\%$ and 8.1 ± 5.6 years, respectively. HbA1c level decreased after treatment (-0.78 ± 0.09 , empagliflozin; -0.89 ± 0.09 , pioglitazone; and -0.93 ± 0.12 glimepiride). No significant differences were observed in HbA1c reduction among the three triple-combination therapies. The proportions of patients with HbA1c $< 7.0\%$ were similar across the three regimens (65.6%, empagliflozin; 56.9%, pioglitazone; and 63.2%, glimepiride). Significant weight loss was observed in the empagliflozin group (-1.73 ± 3.14 kg), whereas weight gain was observed in the pioglitazone and glimepiride groups (1.11 ± 3.97 kg and 1.11 ± 4.07 kg, respectively). The glimepiride group reported four hypoglycaemic episodes (6.56%), while none were reported in the other groups.

Yun Kyung Cho and Jae-Hyoung Cho contributed equally to this work.

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Conclusions: The addition of empagliflozin, pioglitazone, or glimepiride to metformin and DPP-4 inhibitors significantly improved glycaemic control in patients with T2D. The selection of a third agent should be individualized based on the patient characteristics.

KEYWORDS

antidiabetic drug, glycaemic control, phase IV study, randomised trial, type 2 diabetes

1 | INTRODUCTION

Type 2 diabetes mellitus (T2D) is a multifactorial metabolic disorder characterized by chronic hyperglycaemia due to insulin resistance, impaired insulin secretion, or both. Despite advancements in pharmacologic therapies, maintaining durable glycaemic control remains a major clinical challenge.^{1,2} Poor glycaemic control increases the risk of both microvascular and macrovascular complications, underscoring the need for timely and effective treatment intensification to prevent long-term adverse outcomes.³

While recent guidelines emphasize the use of sodium-glucose cotransporter-2 (SGLT2) inhibitors for their cardiometabolic benefits, combination therapy with metformin and dipeptidyl peptidase-4 (DPP-4) inhibitors remains widely used in routine clinical practice, owing to their established efficacy and low risk of hypoglycaemia.⁴ However, as β -cell function declines over time, many patients require escalation to triple therapy to achieve and sustain glycaemic targets. Selection of a third-line agent must therefore consider not only glucose-lowering potency but also effects on body weight, hypoglycaemia risk, cardiovascular and renal safety, and overall tolerability. Among the available options, SGLT2 inhibitors are associated with favourable metabolic effects, including weight loss and cardiorenal protection⁵; thiazolidinediones (e.g., pioglitazone) offer sustained glycaemic efficacy⁶; and sulfonylureas provide potent glucose-lowering but are limited by weight gain and increased hypoglycaemia risk.¹ Despite the widespread use of these agents, only a few head-to-head comparisons have been conducted to evaluate their relative efficacy and safety when added to metformin and a DPP-4 inhibitor, particularly in Asian populations.

Therefore, we conducted a multicentre, phase 4 randomized controlled trial to compare the efficacy, metabolic effects, hypoglycaemia risk and safety of empagliflozin, pioglitazone and glimepiride as third-line agents in Korean patients with T2D inadequately controlled with metformin and a DPP-4 inhibitor. The findings of this study will inform individualized therapeutic strategies and optimise clinical outcomes in this population.

2 | MATERIALS AND METHODS

2.1 | Study design and participants

This study was a multicentre, prospective, randomized, open-label, parallel-group, phase 4 clinical trial conducted across multiple hospitals in Korea. The study included adult patients aged 18–75 years with T2D inadequately controlled with a combination of metformin (≥ 1000 mg/day) and a DPP-4 inhibitor for at least 3 months prior to randomisation. Inadequate glycaemic control was defined as a glycated haemoglobin (HbA1c) level between 7.0% and 10.0%.

Key exclusion criteria were a history of diabetic ketoacidosis, severe renal impairment (estimated glomerular filtration rate [eGFR] < 45 mL/min/1.73 m²), liver dysfunction (alanine aminotransferase [ALT] or aspartate aminotransferase [AST] > 3 times the upper limit of normal), major cardiovascular disease within the last 6 months, or use of insulin or other glucose-lowering agents beyond metformin and DPP-4 inhibitors within the last 3 months. Pregnant or breastfeeding women were also excluded. Detailed exclusion criteria are described in Figure S1.

A total of 193 patients were screened for eligibility to participate in this study. Following screening, four participants were excluded for various reasons, including not meeting the eligibility criteria. As a result, 189 patients were deemed eligible and were randomized into the study. Out of the 189 eligible participants, 167 (88.4%) completed the study. The reasons for dropout and the relatively low number of participants lost to follow-up underscore the feasibility and tolerance of the treatment regimens used in this trial. The flow of participants through each stage of the trial is illustrated in Figure S1.

2.2 | Randomization and Interventions

Participants were randomly assigned in a 1:1:1 ratio to receive one of the following three third-line therapies in addition to their ongoing metformin and DPP-4 inhibitor combination regimen: (1) empagliflozin 10 mg/day; (2) pioglitazone 15 mg/day; or (3) glimepiride 2 mg/day. Randomization was performed using a computer-generated random

sequence, stratified by baseline HbA1c level (<8.0% or ≥8.0%) and study site. As this was an open-label study, both participants and investigators were aware of the treatment allocation. All participants were instructed to continue their prescribed doses of metformin and DPP-4 inhibitors throughout the study period.

2.3 | Outcome measures

The primary outcome measure was change in HbA1c levels from baseline to after 24 weeks of treatment. Secondary outcomes included the proportion of patients who achieved an HbA1c level < 7.0%, change in body weight and incidence of adverse events, including hypoglycaemia, urinary tract infection (UTI), oedema and cardiovascular events. Hypoglycaemia was defined as having a plasma glucose level < 70 mg/dL with or without symptoms. All adverse events were monitored and recorded throughout the study period, and their severity was classified according to the Common Terminology Criteria for Adverse Events version 5.0.

2.4 | Sample size calculation

The sample size was calculated based on a non-inferiority design, with empagliflozin as the reference group. To demonstrate that the other two triple-combination therapies (pioglitazone and glimepiride) were non-inferior to empagliflozin in terms of HbA1c level reduction, we set a non-inferiority margin of 0.1%, a one-sided significance level of 0.025 and a power of 90%. Assuming a mean HbA1c level reduction of 0.8% from baseline to 24 weeks post-treatment with a standard deviation of 0.15%, we calculated that 49 patients per group (total of 147 patients) would be required. Accounting for an anticipated dropout rate of approximately 20%, the final sample size was determined to be 62 patients per group, totalling 186 patients. Sample size calculations were performed using PASS software version 12 (NCSS, LLC, Kaysville, UT).

2.5 | Statistical analysis

Efficacy analyses were performed on the intention-to-treat population, defined as all randomized participants who received at least one dose of the study medication and had at least one post-baseline HbA1c measurement. The per-protocol population included participants who completed the study without major protocol violations.

Changes in HbA1c and body weight were analysed using repeated-measures analysis of variance (ANOVA) with treatment group and time as factors. The proportions of patients who achieved an HbA1c level < 7.0% were compared across the treatment groups using the chi-square test. Adverse events were summarised descriptively and compared between treatment groups using Fisher's exact test for categorical variables and ANOVA for continuous variables. A *p*-value < 0.05 was considered statistically significant. All analyses

were performed using SPSS software version 26.0 (IBM Corp, Armonk, NY).

2.6 | Ethical considerations

This study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines and approved by the Institutional Review Boards of all participating centres. Written informed consent was obtained from all participants before enrolment.

3 | RESULTS

3.1 | Participant characteristics

Of 193 patients screened for eligibility, 176 were randomised to three treatment groups: empagliflozin (*n* = 61), pioglitazone (*n* = 58) and glimepiride (*n* = 57). The baseline characteristics of the study participants were well-balanced across the three groups (Table 1). The majority of participants (60.23%) were men, and their mean age, HbA1c level and diabetes duration were 58.45 ± 9.95 years, 7.79 ± 0.68% and 8.10 ± 5.85 years, respectively.

3.2 | Primary outcome: change in HbA1c level

At baseline, HbA1c levels were 7.81 ± 0.63% in the pioglitazone group, 7.79 ± 0.67% in the glimepiride group and 7.77 ± 0.73% in the empagliflozin group (Table 2). At 24 weeks, the mean changes in HbA1c levels were −0.89 ± 0.09%, −0.93 ± 0.12% and −0.78 ± 0.09% for the pioglitazone, glimepiride and empagliflozin groups, respectively (Table 2, Figure 1A). The LSM difference between the pioglitazone and empagliflozin groups at 24 weeks was 0.10% (95% CI: −0.13, 0.32; *p* = 0.3999), and that between the pioglitazone and empagliflozin groups was 0.14% (95% CI: −0.13, 0.42; *p* = 0.2980). The confidence intervals for both comparisons included the predefined non-inferiority margin of 0.1%, indicating that non-inferiority could not be statistically established. However, the Wilcoxon rank sum test results demonstrated that the *p*-values for the comparisons between pioglitazone versus empagliflozin and glimepiride versus empagliflozin both exceeded 0.05, suggesting that the HbA1c reductions observed among the three treatment groups were not statistically different.

At 12 weeks, the mean change in baseline HbA1c level was −0.70 ± 0.08% in the pioglitazone group, −1.02 ± 0.10% in the glimepiride group and −0.72 ± 0.08% in the empagliflozin group (Table 2, Figure 1A). The least squares mean (LSM) difference between the pioglitazone and glimepiride groups was 0.28% (95% confidence interval [CI]: 0.06, 0.50; *p* = 0.0149), indicating a statistically significant greater reduction in HbA1c level in the glimepiride group compared with that in the pioglitazone group. The LSM difference between the

TABLE 1 Baseline characteristics of the study participants across treatment groups.

	Pioglitazone 15 mg (N = 58)	Glimepiride 2 mg (N = 57)	Empagliflozin 10 mg (N = 61)	Total (N = 176)
Demographics				
Age (year)	59.09 ± 10.38	57.67 ± 10.72	58.57 ± 8.84	58.45 ± 9.95
Male, sex	34 (58.62)	32 (56.14)	40 (65.57)	106 (60.23)
Hypertension	31 (53.45)	23 (40.35)	27 (44.26)	81 (46.02)
Dyslipidaemia	25 (43.10)	28 (49.12)	25 (40.98)	78 (44.32)
T2D duration (year)	8.55 ± 6.51	7.95 ± 5.73	7.80 ± 5.33	8.10 ± 5.85
BMI (kg/m ²)	25.64 ± 2.94	25.39 ± 3.51	26.06 ± 3.38	25.70 ± 3.28
Systolic BP (mmHg)	128.81 ± 14.59	129.60 ± 16.33	129.58 ± 14.84	129.33 ± 15.18
Diastolic BP (mmHg)	74.50 ± 10.56	74.16 ± 12.71	75.92 ± 12.38	74.87 ± 11.88
Glycaemic variables				
Fasting glucose (mg/dL)	163.60 ± 31.03	158.86 ± 33.74	159.59 ± 33.74	160.68 ± 32.75
HbA1c (%)	7.81 ± 0.63	7.79 ± 0.67	7.77 ± 0.73	7.79 ± 0.68
Biochemistry profile				
AST (IU/L)	27.24 ± 13.11	28.30 ± 12.34	32.39 ± 14.23	29.37 ± 13.39
ALT (IU/L)	27.81 ± 15.28	27.44 ± 13.47	36.05 ± 20.43	30.55 ± 17.13
BUN (mg/dL)	14.38 ± 3.59	14.17 ± 3.99	13.58 ± 3.50	14.04 ± 3.69
Creatinine (mg/dL)	0.80 ± 0.17	0.78 ± 0.19	0.83 ± 0.17	0.80 ± 0.18
eGFR (mL/min/1.73 m ²)	93.13 ± 13.14	94.51 ± 14.46	91.25 ± 11.92	92.92 ± 13.18
Total cholesterol (mg/dL)	146.75 ± 26.24	141.74 ± 35.73	142.80 ± 28.87	143.74 ± 30.41
Triglyceride (mg/dL)	155.46 ± 92.87	138.32 ± 67.36	161.77 ± 86.45	152.07 ± 83.14
HDL-cholesterol (mg/dL)	49.61 ± 13.62	47.75 ± 9.75	46.52 ± 12.82	47.93 ± 12.19
LDL-cholesterol (mg/dL)	71.55 ± 22.15	69.67 ± 30.47	71.69 ± 24.02	70.98 ± 25.66
Homeostasis model assessment				
HOMA-IR	1.34 ± 0.84	1.70 ± 1.27	1.63 ± 1.06	1.56 ± 1.07
HOMA-β (%)	50.06 ± 41.68	46.56 ± 41.23	45.45 ± 28.27	47.25 ± 36.71
Co-morbid medications				
Antihypertensive drugs	25 (43.10)	29 (50.88)	24 (39.34)	78 (44.32)
Lipid-lowering drugs	49 (33.11)	50 (33.78)	49 (33.11)	148 (84.09)
Concurrent antidiabetic medication				
Dose of metformin (mg)	1165.91 ± 474.99	1362.07 ± 614.80	1275.76 ± 473.04	1263.95 ± 521.50

Note: Continuous variables are expressed as mean ± SD, and categorical variables are presented as n (%).

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; BP, blood pressure; BUN, blood urea nitrogen; eGFR: estimated glomerular filtration rate; HbA1c, glycated haemoglobin; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance; HOMA-β, homeostasis model assessment of beta-cell function; LDL-C, low-density lipoprotein cholesterol; SD: standard deviation; T2D, Type 2 diabetes mellitus.

pioglitazone and empagliflozin groups was −0.04% (95% CI: −0.24, 0.16; $p = 0.6961$), which was not statistically significant.

3.3 | Achievement of target HbA1c level

Overall, all three third-line agents demonstrated efficacy in achieving the target HbA1c levels. At 24 weeks, more than half the participants in each treatment group achieved an HbA1c level < 7.0%: 56.9%, 63.16% and 65.57% in the empagliflozin, pioglitazone and glimepiride groups, respectively ($p = 0.6055$) (Figure 1B).

Furthermore, the proportions of patients who achieved an HbA1c level < 6.5% at week 24 were 32.76%, 33.33% and 27.87% for the empagliflozin, pioglitazone and glimepiride groups, respectively ($p = 0.7783$) (Figure 1B). No statistically significant differences were observed among the treatment groups for either level.

3.4 | Fasting glucose changes

All groups showed a significant reduction in fasting glucose levels by week 12. The empagliflozin group had the greatest reduction

TABLE 2 HbA1c changes after 12 and 24 weeks of treatment.

	Pioglitazone 15 mg (N = 58)	Glimepiride 2 mg (N = 57)	Empagliflozin 10 mg (N = 61)
HbA1c (%)			
Baseline, mean $\pm$ SD (%)	7.81 $\pm$ 0.63	7.79 $\pm$ 0.67	7.77 $\pm$ 0.73
Week 12, mean $\pm$ SD	7.11 $\pm$ 0.58	6.77 $\pm$ 0.60	7.04 $\pm$ 0.78
Change, mean $\pm$ SE	−0.70 $\pm$ 0.08	−1.02 $\pm$ 0.10	−0.72 $\pm$ 0.08
LSM difference	−0.04	0.28	
95% CI for LSM difference	−0.24, 0.16	0.06, 0.50	
<i>p</i> value ^a	0.6961	0.0149	
Week 24, mean $\pm$ SD	6.91 $\pm$ 0.60	6.86 $\pm$ 0.82	6.99 $\pm$ 0.84
Change, mean $\pm$ SE	−0.89 $\pm$ 0.09	−0.93 $\pm$ 0.12	−0.78 $\pm$ 0.09
LSM difference	0.10	0.14	
95% CI for LSM difference	−0.13, 0.32	−0.13, 0.42	
<i>p</i> value ^a	0.3999	0.2980	

Abbreviations: CI, confidence interval; HbA1c, glycated haemoglobin; LSM, least squares mean; SD, standard deviation; SE, standard error.

^a*p* values for the difference between treatment groups with the empagliflozin group as reference were determined using the Wilcoxon rank sum test.

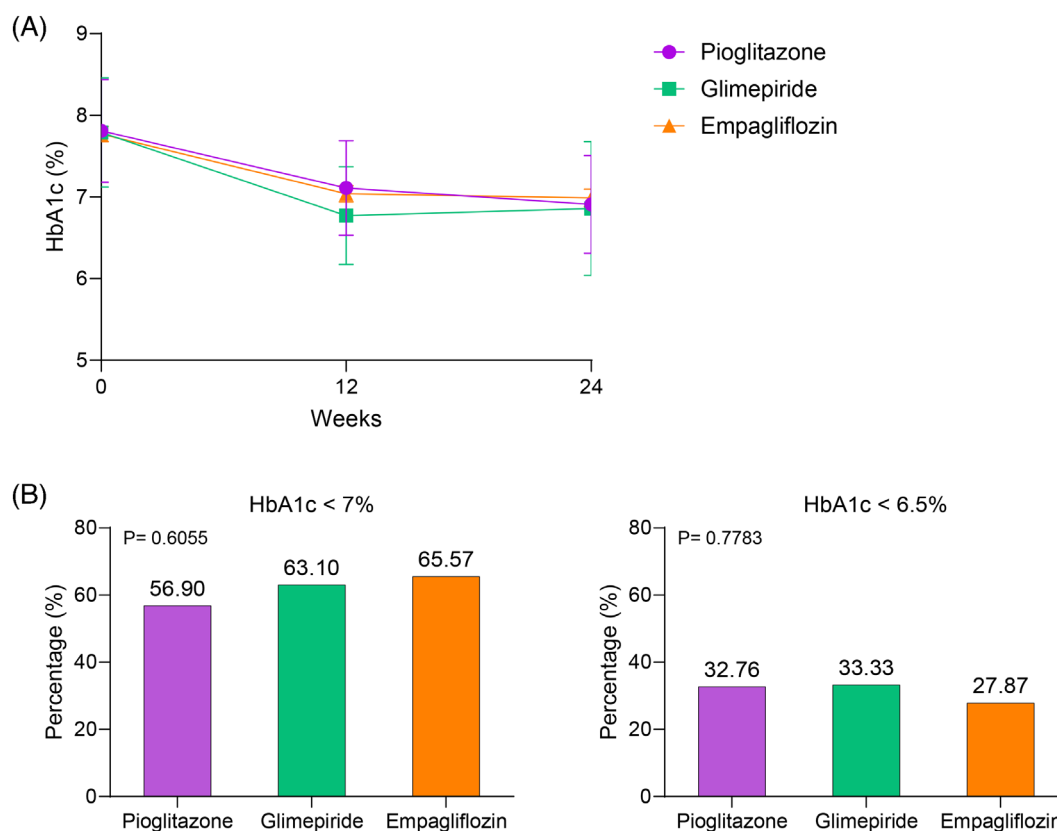


FIGURE 1 Glycaemic outcomes. (A) Changes in glycated haemoglobin (HbA1c) levels from baseline to week 24 across the empagliflozin, pioglitazone and glimepiride groups. Data points represent mean HbA1c values at each time point, and bars indicate the standard error (SE) of the mean. (B) Proportion of patients who achieved HbA1c levels < 7.0% and HbA1c levels < 6.5% after 24 weeks of treatment in the empagliflozin, pioglitazone and glimepiride groups. HbA1c, glycated haemoglobin.

(−31.66 $\pm$ 4.19 mg/dL), followed by the pioglitazone group (−28.29 $\pm$ 4.39 mg/dL) and the glimepiride group (−26.02 $\pm$ 4.67 mg/dL), these differences were not statistically significant (*p* = 0.3382) (Table 3).

3.5 | Body weight changes

Body weight increased significantly in the pioglitazone and glimepiride groups (mean change: 1.11 $\pm$ 0.52 and 1.11 $\pm$ 0.53 kg, respectively),

while it reduced significantly in the empagliflozin group (mean change: -1.73 ± 0.41 kg) (Table 3).

3.6 | Lipid profile, liver function and renal function changes

Lipid profile was assessed as secondary outcomes. Significant improvements in triglyceride and high-density lipoprotein cholesterol (HDL-C) levels were noted in the pioglitazone group. Triglyceride level decreased in all groups, with the largest reduction observed in the pioglitazone group (-37.05 ± 9.13 mg/dL), although the differences did not reach statistical significance ($p = 0.0890$). HDL-C level increased significantly in the pioglitazone (mean change: 6.46 ± 1.29 mg/dL, $p < 0.0001$) and empagliflozin (2.89 ± 0.89 mg/dL, $p < 0.0001$) groups, but decreased in the glimepiride group (-1.74 ± 0.85 mg/dL). Similarly, ALT and gamma-glutamyl transferase levels significantly decreased in the pioglitazone (-7.03 ± 1.46 IU/L and -7.98 ± 2.00 IU/L) and empagliflozin (-8.51 ± 2.33 IU/L and -17.40 ± 5.99 IU/L) groups, but not in the glimepiride group (Table 3). No significant changes in renal function were observed across all three groups.

3.7 | Insulin resistance and secretory function

Insulin resistance and pancreatic beta-cell function were evaluated using homeostasis model assessment of insulin resistance (HOMA-IR) and homeostasis model assessment of beta-cell function (HOMA- β), respectively. The pioglitazone and empagliflozin groups showed a reduction in HOMA-IR (-0.36 ± 0.08 and -0.47 ± 0.14 , respectively), while an increase was noted in the glimepiride group (1.95 ± 0.57), with no statistical significance ($p = 0.2401$). Changes in beta-cell function, as assessed by HOMA- β , were similar across the three groups and not statistically significant (Table 3).

3.8 | Safety outcomes

Twenty-three adverse events were reported across all groups: nine (14.75%) in both the pioglitazone and glimepiride groups and five (7.94%) in the empagliflozin group. Hypoglycaemia was observed exclusively in the glimepiride group, with four cases (6.56%), consistent with the established risk profile of sulfonylureas. No instances of hypoglycaemia were reported in the pioglitazone or empagliflozin group. Oedema, predominantly peripheral oedema, was primarily associated with pioglitazone, occurring in four participants (6.56%), while one participant (1.64%) experienced facial oedema. UTI was reported in one participant (1.59%) in the empagliflozin group. Adverse drug reactions (ADRs) were reported in 14 participants: four (6.56%), seven (11.48%) and three (4.76%) in the pioglitazone, glimepiride and empagliflozin groups, respectively. No serious ADRs were reported (Table 4).

4 | DISCUSSION

This multicentre, randomized, open-label phase 4 trial demonstrated that adding empagliflozin, pioglitazone, or glimepiride to dual oral therapy with metformin and a DPP-4 inhibitor significantly improved glycaemic control over 24 weeks in Korean patients with inadequately controlled T2D. While no statistically significant differences in HbA1c reduction were observed among the treatment arms, notable distinctions in metabolic parameters and adverse event profiles underscore the importance of individualized therapeutic strategies.

Mean changes in HbA1c level at week 24 were -0.78% , -0.89% and -0.93% in the empagliflozin, pioglitazone and glimepiride groups, respectively (Table 2). These reductions were both statistically and clinically significant. Over 50% of patients across all groups achieved HbA1c level $< 7.0\%$, with no statistically significant intergroup differences ($p = 0.6055$). These findings align with those of prior studies confirming the efficacy of these agents as add-ons to metformin or third-line therapies,⁷⁻⁹ reinforcing their clinical utility as viable options for intensifying treatment in patients requiring triple therapy.

A key differentiating factor among the three regimens was the effect on body weight. Empagliflozin led to a significant mean weight reduction of -1.73 ± 0.41 kg, while pioglitazone and glimepiride both resulted in weight gain ($+1.11 \pm 0.52$ and $+1.11 \pm 0.53$ kg, respectively; Table 3). The weight-lowering effect of SGLT2 inhibitors has been attributed to glycosuria-induced caloric loss and is consistently reported in both Asian and Western populations.^{10,11} In a prior placebo-controlled trial, empagliflozin 10 mg, placebo added to linagliptin 5 mg and metformin for 24 weeks improved glycaemic control and weight, inducing a 3.1 kg reduction in baseline body weight, mirroring the present findings.¹² This weight reduction is particularly beneficial in obesity or metabolic syndrome cases, where body weight plays a critical role in disease progression and cardiovascular risk.

Regarding lipid metabolism, pioglitazone yielded the most pronounced improvements, significantly increasing HDL-C levels ($+6.46 \pm 1.29$ mg/dL) and reducing triglyceride levels (-37.05 ± 9.13 mg/dL) (Table 3). These effects are consistent with the known mechanism of pioglitazone, which, via activation of peroxisome proliferator-activated receptor gamma (PPAR γ), modulates lipid metabolism and improves both glucose and lipid parameters.^{6,13,14} Empagliflozin also improved lipid profiles, increasing HDL-C levels by $+2.89 \pm 0.89$ mg/dL and decreasing triglycerides by -28.67 ± 12.01 mg/dL. In contrast, glimepiride led to decreased HDL-C levels (-1.74 ± 0.85 mg/dL), with minimal effect on triglycerides. The effects of SGLT2 inhibitors on lipid profiles have been variably reported across the literature. Two major randomized controlled trials showed modest increases in HDL-C levels with both 10 and 25 mg doses of empagliflozin, and no significant changes in triglyceride levels^{12,15}; findings that only partially align with those of our study. However, a more recent meta-analysis using random-effects models revealed that SGLT2 inhibitor treatment resulted in a modest but statistically significant increase in HDL-C levels at approximately 2.3 mg/dL and a reduction in triglycerides at approximately 8.9 mg/dL, lending support to the present findings. Notably, a subgroup analysis within the same meta-analysis

TABLE 3 Changes in secondary outcomes from baseline to week 24 across treatment groups.

	Pioglitazone 15 mg (N = 58)	Glimepiride 2 mg (N = 57)	Empagliflozin 10 mg (N = 61)
Body weight (kg)			
Baseline, mean ± SD	69.36 ± 13.28	69.08 ± 13.16	71.60 ± 13.00
Week 24, mean ± SD	70.47 ± 13.20	70.19 ± 12.68	69.86 ± 13.32
Change, mean ± SE	1.11 ± 0.52 ^a	1.11 ± 0.53 ^a	−1.73 ± 0.41
p-value ^b	<0.0001		
Systolic BP (mmHg)			
Baseline, mean ± SD	128.81 ± 14.59	129.60 ± 16.33	129.58 ± 14.84
Week 24, mean ± SD	128.43 ± 13.56	127.28 ± 15.17	127.48 ± 13.18
Change, mean ± SE	−0.38 ± 1.51	−2.32 ± 1.92	−2.22 ± 1.6
p-value ^b	0.6822		
Diastolic BP (mmHg)			
Baseline, mean ± SD	74.50 ± 10.56	74.16 ± 12.71	75.92 ± 12.38
Week 24, mean ± SD	74.12 ± 11.04	74.47 ± 10.44	75.30 ± 11.14
Change, mean ± SE	−0.38 ± 1.2	0.32 ± 1.25	−0.75 ± 1.49
p-value ^b	0.9443		
Fasting glucose (mg/dL)			
Baseline, mean ± SD	163.60 ± 31.03	158.86 ± 33.74	159.59 ± 33.74
Week 24, mean ± SD	135.31 ± 26.66	132.84 ± 28.02	127.93 ± 24.17
Change, mean ± SE	−28.29 ± 4.39	−26.02 ± 4.67	−31.66 ± 4.19
p-value ^b	0.3382		
Total cholesterol (mg/dL)			
Baseline, mean ± SD	146.75 ± 26.24	141.74 ± 35.73	142.80 ± 28.87
Week 24, mean ± SD	151.79 ± 29.98	132.47 ± 24.89	137.97 ± 25.35
Change, mean ± SE	4.88 ± 2.44	−9.26 ± 3.21 ^a	−4.84 ± 2.67 ^a
p-value ^b	<0.0001		
Triglyceride (mg/dL)			
Baseline, mean ± SD	155.46 ± 92.87	138.32 ± 67.36	161.77 ± 86.45
Week 24, mean ± SD	117.98 ± 65.16	134.37 ± 63.59	133.10 ± 80.11
Change, mean ± SE	−37.05 ± 9.13	−3.95 ± 6.19	−28.67 ± 12.01
p-value ^b	0.0890		
HDL-cholesterol (mg/dL)			
Baseline, mean ± SD	49.61 ± 13.62	47.75 ± 9.75	46.52 ± 12.82
Week 24, mean ± SD	56.09 ± 16.02	46.02 ± 8.66	49.41 ± 12.29
Change, mean ± SE	6.46 ± 1.29 ^a	−1.74 ± 0.85	2.89 ± 0.89 ^a
p-value ^b	<0.0001 ^b		
LDL-cholesterol (mg/dL)			
Baseline, mean ± SD	71.55 ± 22.15	69.67 ± 30.47	71.69 ± 24.02
Week 24, mean ± SD	75.36 ± 24.58	71.42 ± 48.44	68.80 ± 21.82
Change, mean ± SE	3.73 ± 2.2	1.75 ± 5.82	−3.98 ± 2.01
p-value ^b	0.3234		
AST (IU/L)			
Baseline, mean ± SD	27.24 ± 13.11	28.30 ± 12.34	32.39 ± 14.23
Week 24, mean ± SD	25.45 ± 14.93	28.37 ± 13.53	27.56 ± 11.80
Change, mean ± SE	−1.79 ± 1.84	0.07 ± 1.33	−4.84 ± 1.59
p-value ^b	0.2684		

(Continues)

TABLE 3 (Continued)

	Pioglitazone 15 mg (N = 58)	Glimepiride 2 mg (N = 57)	Empagliflozin 10 mg (N = 61)
ALT (IU/L)			
Baseline, mean $\pm$ SD	27.81 $\pm$ 15.28	27.44 $\pm$ 13.47	36.05 $\pm$ 20.43
Week 24, mean $\pm$ SD	20.78 $\pm$ 9.84	28.75 $\pm$ 19.74	27.54 $\pm$ 18.54
Change, mean $\pm$ SE	−7.03 $\pm$ 1.46	1.32 $\pm$ 2.15	−8.51 $\pm$ 2.33
<i>p</i> -value ^b	0.0045		
GGT (IU/L)			
Baseline, mean $\pm$ SD	36.61 $\pm$ 29.65	41.49 $\pm$ 46.76	59.33 $\pm$ 89.65
Week 24, mean $\pm$ SD	25.59 $\pm$ 23.49	39.68 $\pm$ 37.13	44.16 $\pm$ 68.17
Change, mean $\pm$ SE	−7.98 $\pm$ 2.00 ^a	−1.40 $\pm$ 2.71	−17.40 $\pm$ 5.99 ^a
<i>p</i> -value ^b	0.0479		
eGFR (mL/min/1.73 m²)			
Baseline, mean $\pm$ SD	93.13 $\pm$ 13.14	94.51 $\pm$ 14.46	91.25 $\pm$ 11.92
Week 24, mean $\pm$ SD	90.99 $\pm$ 15.68	91.62 $\pm$ 16.21	91.16 $\pm$ 14.00
Change, mean $\pm$ SE	−2.14 $\pm$ 1.08	−2.89 $\pm$ 0.98	−0.09 $\pm$ 1.15
<i>p</i> -value ^b	0.1741		
Urine ACR (mg/g)			
Baseline, mean $\pm$ SD	143.14 $\pm$ 621.75	36.77 $\pm$ 72.19	48.83 $\pm$ 99.09
Week 24, mean $\pm$ SD	163.50 $\pm$ 893.39	32.35 $\pm$ 64.65	34.31 $\pm$ 50.07
Change, mean $\pm$ SE	39.28 $\pm$ 9.9	−0.98 $\pm$ 7.4	−13.46 $\pm$ 9.86
<i>p</i> -value ^b	0.8180		
HOMA-IR			
Baseline, mean $\pm$ SD	1.34 $\pm$ 0.84	1.70 $\pm$ 1.27	1.63 $\pm$ 1.06
Week 24, mean $\pm$ SD	1.02 $\pm$ 0.52	3.01 $\pm$ 12.18	1.20 $\pm$ 0.82
Change, mean $\pm$ SE	−0.36 $\pm$ 0.08	1.95 $\pm$ 0.57	−0.47 $\pm$ 0.14
<i>p</i> -value ^b	0.2401		
HOMA-β			
Baseline, mean $\pm$ SD	50.06 $\pm$ 41.68	46.56 $\pm$ 41.23	45.45 $\pm$ 28.27
Week 24, mean $\pm$ SD	56.46 $\pm$ 42.99	59.13 $\pm$ 36.04	58.39 $\pm$ 34.27
Change, mean $\pm$ SE	9.22 $\pm$ 2.81	8.54 $\pm$ 6.46	11.81 $\pm$ 3.28
<i>p</i> -value ^b	0.9133		

Abbreviations: ACR, albumin to creatinine ratio; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BP, blood pressure; eGFR, estimated glomerular filtration rate; GGT, gamma-glutamyl transferase; HbA1c, glycated haemoglobin; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance; HOMA- β , homeostasis model assessment of beta-cell function; LDL-C, low-density lipoprotein cholesterol; SD, standard deviation; SE, standard error.

^aDifference between two groups is not statistically significant.

^b*p*-value for analysis of covariance adjusted for the baseline values.

revealed that these lipid-modifying effects were more pronounced in Asian populations, with a slightly greater increase in HDL-C levels and a more marked decrease in triglyceride levels, compared with those in non-Asian populations.¹⁶ While the mechanisms underlying these ethnic differences remain unclear, these observations suggest that, beyond its established glycaemic benefits, empagliflozin may confer additional advantages in lipid modulation—particularly in Asian patients with T2D, obesity and comorbid dyslipidaemia.

Empagliflozin and pioglitazone both improved insulin resistance, as indicated by changes in HOMA-IR: -0.47 ± 0.14 and -0.36 ± 0.08 , respectively, compared with an increase of $+1.95 \pm 0.57$ in the

glimepiride group ($p = 0.2401$; Table 3). The insulin-sensitising effect of pioglitazone, mediated by PPAR γ activation, is well-documented in the literature.⁶ Emerging data also suggest that SGLT2 inhibitors may improve insulin resistance by reducing glucotoxicity and promoting metabolic flexibility.^{17–20} The reduction in HOMA-IR with empagliflozin in our study supports this growing body of evidence. In contrast, glimepiride was associated with increased HOMA-IR, consistent with its insulin secretagogue action and limited effects on insulin sensitivity. Although changes in HOMA- β were not statistically significant, both empagliflozin and pioglitazone showed trends toward improved β -cell function, with mean increases of $+11.81 \pm 3.28\%$ and $+9.22$

TABLE 4 Adverse events in the empagliflozin, pioglitazone and glimepiride groups.

	Pioglitazone 15 mg (N = 61)	Glimepiride 2 mg (N = 61)	Empagliflozin 10 mg (N = 63)	Total (N = 185)
Adverse events categories				
Adverse event	9 (14.75)	9 (14.75)	5 (7.94)	23 (12.43)
Adverse drug reaction	4 (6.56)	7 (11.48)	3 (4.76)	14 (7.57)
Serious adverse event	2 (3.28)	1 (1.64)	1 (1.59)	4 (2.16)
Serious adverse drug reaction	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Unexpected adverse drug reaction	1 (1.64)	2 (3.28)	2 (3.17)	5 (2.70)
Disease classification ^a				
Cardiac disorders	1 (1.64)	0 (0.0)	0 (0.0)	1 (0.54)
Cardiac arrest	1 (1.64)	0 (0.0)	0 (0.0)	1 (0.54)
Decreased and nonspecific blood pressure disorders and shock	0 (0.0)	0 (0.0)	1 (1.59)	1 (0.54)
Low blood pressure	0 (0.0)	0 (0.0)	1 (1.59)	1 (0.54)
Eye disorders	0 (0.0)	1 (1.64)	0 (0.0)	1 (0.54)
Borderline glaucoma	0 (0.0)	1 (1.64)	0 (0.0)	1 (0.54)
Gastrointestinal disorders	1 (1.64)	0 (0.0)	0 (0.0)	1 (0.54)
Abdominal distension	1 (1.64)	0 (0.0)	0 (0.0)	1 (0.54)
General disorders	4 (6.56)	0 (0.0)	0 (0.0)	4 (2.16)
Face oedema	1 (1.64)	0 (0.0)	0 (0.0)	1 (0.54)
Oedema peripheral	3 (4.92)	0 (0.0)	0 (0.0)	3 (1.62)
Immune system disorders	0 (0.0)	0 (0.0)	1 (1.59)	1 (0.54)
Hypersensitivity	0 (0.0)	0 (0.0)	1 (1.59)	1 (0.54)
Infections and infestations	1 (1.64)	0 (0.0)	1 (1.59)	2 (1.08)
Herpes zoster	1 (1.64)	0 (0.0)	0 (0.0)	1 (0.54)
Urinary tract infection	0 (0.0)	0 (0.0)	1 (1.59)	1 (0.54)
Metabolism and nutrition disorders	0 (0.0)	4 (6.56)	0 (0.0)	4 (2.16)
Hypoglycaemia	0 (0.0)	4 (6.56)	0 (0.0)	4 (2.16)
Neoplasm	1 (1.64)	1 (1.64)	0 (0.0)	2 (1.08)
Basal cell carcinoma	1 (1.64)	0 (0.0)	0 (0.0)	1 (0.54)
Rectal cancer stage 0	0 (0.0)	1 (1.64)	0 (0.0)	1 (0.54)
Nervous system disorders	2 (3.28)	2 (3.28)	2 (3.17)	6 (3.24)
Cerebral infarction	0 (0.0)	0 (0.0)	1 (1.59)	1 (0.54)
Dizziness	1 (1.64)	1 (1.64)	0 (0.0)	2 (1.08)
Headache	0 (0.0)	1 (1.64)	0 (0.0)	1 (0.54)
Hypoesthesia	1 (1.64)	0 (0.0)	0 (0.0)	1 (0.54)
Persistent postural-perceptual dizziness	0 (0.0)	0 (0.0)	1 (1.59)	1 (0.54)
Skin and subcutaneous tissue disorders	1 (1.64)	1 (1.64)	0 (0.0)	2 (1.08)
Erythema multiforme	1 (1.64)	0 (0.0)	0 (0.0)	1 (0.54)
Urticaria	0 (0.0)	1 (1.64)	0 (0.0)	1 (0.54)

^aCoding dictionary: MedDRA Ver 26.1.

± 2.81%, respectively (Table 3), supporting their potential for disease-modifying effects with longer duration of use.

Safety outcomes in this trial revealed class-specific adverse event profiles. Hypoglycaemia occurred exclusively in the glimepiride group, reaffirming the increased risk associated with sulfonylureas.¹ Pioglitazone was associated with peripheral and facial

oedema, likely due to fluid retention—a well-characterised adverse effect of thiazolidinediones.⁶ Empagliflozin showed a favourable safety profile, with low incidence of adverse events and a single case of UTI. Notably, no serious ADRs were reported in any treatment arm, underscoring the general tolerability of all regimens in the studied population.

This study has several limitations that merit consideration. First, the open-label design may have introduced reporting or detection bias, particularly for subjective endpoints, such as adverse events. However, the primary outcome, HbA1c, was an objective laboratory-based measure, and adverse events were monitored using standardized forms across all study sites to mitigate potential bias. Second, the 24-week duration may be insufficient to assess the long-term durability of glycaemic control or to capture delayed adverse events, including cardiovascular outcomes or skeletal complications, potentially associated with agents such as pioglitazone. However, long-term studies are required to extrapolate these findings. Third, the study population was limited to Korean patients, which may affect the generalisability of the results to other ethnic groups. Nevertheless, this represents a strength from another perspective, as the study contributes valuable data specific to East Asian populations, which often exhibit lower BMI, higher visceral adiposity and distinct insulin resistance phenotypes compared to Western populations. Population-specific evidence is essential to guide tailored therapeutic strategies. Our findings help bridge this gap by validating known pharmacological profiles in a well-characterized Korean cohort. Future studies with extended follow-up periods and more diverse cohorts are required to validate and extend these observations.

Despite the aforementioned limitations, this study has notable strengths and important clinical implications. Specifically, the differential effects observed in secondary outcomes such as body weight, lipid profiles and insulin sensitivity highlight the distinct metabolic profiles of the three agents. For instance, empagliflozin is associated with weight reduction and modest improvements in HDL-C levels, suggesting its benefits for patients with obesity or metabolic syndromes. Pioglitazone led to the most favourable changes in triglyceride and HDL-C levels, reinforcing its role in patients with pronounced insulin resistance or atherogenic dyslipidaemia, despite its known effect on weight gain. In contrast, glimepiride showed robust glycaemic efficacy but was accompanied by weight gain, a reduction in HDL-C and a higher incidence of hypoglycaemia, which may limit its use in certain patient groups. Although modest in absolute terms, these differences were clinically meaningful. They underscore the importance of moving beyond a one-size-fits-all approach and instead adopting a patient-centred treatment strategy that considers individual metabolic profiles, comorbidities and treatment goals. This nuanced understanding can help guide personalised and effective decision-making when selecting third-line agents for routine clinical practice.

In conclusion, this study showed that adding empagliflozin, pioglitazone, or glimepiride to a combination of metformin and a DPP-4 inhibitor significantly improves glycaemic control in Korean patients with T2D inadequately managed with dual oral therapy. All three agents significantly reduced HbA1c levels when added as a third oral glucose-lowering drug, while exhibiting distinct profiles with respect to body weight, lipid parameters, insulin sensitivity and adverse events. These findings underscore the need for a patient-centred approach when selecting a third-line therapy, considering individual metabolic characteristics, comorbidities and treatment priorities.

Long-term studies are required to further assess the durability of glycaemic control and the broader cardiometabolic outcomes associated with these combination regimens in diverse populations.

AUTHOR CONTRIBUTIONS

LWJ designed the research. LWJ, CJH, HS, PJH, LB-W, YJH, KJH, CSW, HY-C and SK-H conducted the study and collected the data. CYK and CJH performed the analysis and wrote the original draft manuscript in consultation with LWJ. LWJ, CJH, HS, PJH, LB-W, YJH, KJH, CSW, HY-C and SK-H revised the manuscript, provided an intellectual contribution to the interpretation of results, and read and approved the final manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interests.

PEER REVIEW

The peer review history for this article is available at <https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/dom.70030>.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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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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