Received: 25 February 2024 | Revised: 13 May 2024 | Accepted: 23 May 2024

DOI: 10.1111/dom.15705

ORIGINAL ARTICLE

WILEY

Efficacy and tolerability of initial triple combination therapy with metformin, dapagliflozin and saxagliptin compared with stepwise add-on therapy in drug-naïve patients with type 2 diabetes (TRIPLE-AXEL study): A multicentre, randomized, 104-week, open-label, active-controlled trial

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Abstract

Aim: To evaluate the efficacy and tolerability of an initial triple combination therapy (TCT) compared with conventional stepwise add-on therapy (SAT) in patients with newly diagnosed type 2 diabetes (T2D).

Materials and Methods: This multicentre, randomized, 104-week, open-label trial randomized 105 patients with drug-naïve T2D (with HbA1c level ≥ 8.0%, < 11.0%) to the TCT (1000 mg of metformin, 10 mg of dapagliflozin and 5 mg of saxagliptin once daily) or SAT (initiated with metformin, followed by glimepiride and sitagliptin) groups. The primary outcome was the proportion of patients who achieved an HbA1c level of less than 6.5% without hypoglycaemia, weight gain of 5% or higher, or discontinuation of drugs because of adverse events at week 104.

Results: HbA1c reduction from baseline at week 104 was similar between the groups (the least squares mean change was −2.56% in the TCT group vs. −2.75% in the SAT

group). The primary outcome was achieved in 39.0% and 17.1% of the TCT and SAT groups, respectively, with a risk difference of 22.0 (95% confidence interval 3.0, 40.8; $P = .027$). HbA1c level less than 6.5% at week 104 was 46.3% in both the TCT and SAT groups, whereas the incidence of hypoglycaemia, weight gain, or discontinuation of drugs was 16.7% and 62.0% in the TCT and SAT groups, respectively ($P < .001$). TCT was well-tolerated and had fewer adverse events than SAT.

Conclusions: Among newly diagnosed patients with T2D, initial TCT effectively lowered HbA1c levels with higher tolerability and safety than SAT for 104 weeks, suggesting a novel strategy for initial combination therapy in T2D patients.

KEYWORDS

clinical trial, DPP-4 inhibitor, glycaemic control, SGLT2 inhibitor, type 2 diabetes

1 | INTRODUCTION

The findings of the UK Prospective Diabetes Study and its long-term follow-up observations indicated that early and intensive glycaemic control significantly reduces the risk of diabetic complications in patients with type 2 diabetes (T2D).[1,2] Current guidelines for the management of T2D recommend early combination therapy to extend the time to treatment failure and prevent clinical inertia.[3,4] Observational studies have also indicated that early achievement of glycaemic targets is beneficial for delaying the onset of diabetic complications.[5,6] Accordingly, patients who were newly diagnosed with T2D with inadequately controlled hyperglycaemia would be appropriate candidates for early combination therapy.

Multiple strategies for early intensive glycaemic treatment have been suggested in clinical trials, including calorie restriction,[7] intensive insulin therapy,[8,9] and a combination of two or three different classes of antidiabetic agents.[10–12] Most studies have shown the superiority of early intensive treatment over conventional treatment with respect to lowering hyperglycaemia. However, the duration of these studies was generally short; therefore, there is a paucity of data on the benefit of early intensive treatment for durable glycaemic control and the prevention of diabetic complications. Considerations during implementing early combination therapy are the side effects or disadvantages that may occur by intensive glycaemic control.[13] Hypoglycaemia, weight gain, or multiple drug-related adverse events (AEs), which possibly hamper the continuation of combination therapy, should be considered to successfully implement the intensive treatments. Thus, an essential concern remains regarding the classes of antidiabetic drugs that should be combined for early combination therapy.

Dapagliflozin, a sodium-glucose co-transporter-2 (SGLT2) inhibitor, reduces hyperglycaemia via blockade of SGLT2, which increases urinary glucose excretion.[14] Saxagliptin enhances glucose-dependent insulin secretion and reduces glucagon release by inhibiting the enzyme dipeptidyl peptidase-4 (DPP-4), which degrades incretin hormones.[15] Metformin primarily works by reducing glucose production in the liver, as well as improving insulin sensitivity in the peripheral tissues.[16] The combination of those drugs may have multiple benefits, especially in the early stage of diabetes, such as reducing hyperglycaemia and improving diabetes-related metabolic dysfunction through complementary action. It does not increase body weight, and is less probable to induce hypoglycaemia. The proven benefit of dapagliflozin on cardiovascular and renal outcomes can benefit this combination.[17,18]

In this randomized controlled trial, we evaluated the long-term efficacy and tolerability of initial triple combination therapy (TCT), comprising metformin, dapagliflozin and saxagliptin, compared with a control group that received stepwise add-on therapy (SAT), consisting of metformin, then a sulphonylurea, followed by sitagliptin, to achieve HbA1c levels of less than 6.5%.

2 | METHODS

2.1 | Study design and participants

This multicentre, randomized, active-controlled, 104-week, open-label trial was conducted at nine sites (universities and hospitals) in South Korea from April 2018 to August 2022. The trial was conducted in accordance with the Declaration of Helsinki and applicable national regulatory requirements. The study protocol was approved by the institutional review board and independent ethics committees at each site. The overall study design is presented in Figure S1. Details of the study protocol and design have been previously published.[19] This study was registered at ClinicalTrials.gov (registration no. NCT02946632).

Participants aged 18-75 years with drug-naïve, newly diagnosed T2D were eligible for inclusion. Inclusion criteria were inadequately controlled HbA1c levels (≥ 8.0% and < 11.0%), a body mass index of 23 kg/m^2 or higher to less than 40 kg/m^2, and an estimated glomerular filtration of 60 mL/min/1.73m^2 or less. The estimated glomerular filtration rate was determined by the Chronic Kidney Disease-Epidemiology Collaboration creatinine equation. The key exclusion criteria were type 1 diabetes, state of hyperglycaemic crisis corresponding to diabetic ketoacidosis, uncontrolled hyperglycaemia

defined as fasting plasma glucose (FPG) more than 270 mg/dL, atherosclerotic cardiovascular events within 3 months from randomization, pre-existing congestive heart failure meeting the New York Heart Association functional class III or IV, severe hepatic dysfunction, alcohol abuse, pregnancy or breastfeeding, and use of systemic glucocorticoids. A full list of inclusion and exclusion criteria is provided in Table S1. All the participants provided written informed consent.

2.2 | Randomization and masking

Demographic and clinical data were collected, anonymized, uploaded to an interactive web-based system, then reassessed for eligibility. After confirming eligibility, each participant was assigned a randomization number in a strictly sequential manner in accordance with a random assignment table in a 1:1 ratio, generated in advance by a biostatistician. The block randomization method using a block size of 4, stratified by the centre and each subject's initial levels of HbA1c (9.0% vs. ≥ 9.0%), was used to ensure a balanced distribution between the TCT and SAT groups. Randomization was performed using the central randomization website (http://kumc.mebica.net), and the code was generated using the SAS/PLAN procedure.

As the trial was open-label with an intensification procedure for antidiabetic drugs in the SAT arm, masking was not maintained.

2.3 | Procedures

In the TCT arm, the participants received Xigduo (10 mg of dapagliflozin and 1000 mg of metformin) and 5 mg of saxagliptin once daily for 104 weeks. Participants were assessed during nine preplanned trial visits (baseline, weeks 4, 12, 24, 40, 56, 72, 88 and 104). At any visit, if the participants could not tolerate or complained of metformin-related gastrointestinal discomfort, a dose reduction to 500 mg of metformin was performed according to the physician's decision. If participants could not tolerate 500 mg of metformin, the drug was discontinued because of AEs related to the drugs.

In the SAT arm, the participants were stratified into two different groups according to HbA1c levels at baseline. When participants' HbA1c levels were 8.0% or higher and less than 9.0%, they received 1000 mg of metformin once daily. At each visit, dose escalation and addition of second or third drugs were performed if FPG levels were 120 mg/dL or higher, or if HbA1c levels were 6.5% or higher, according to the sequential add-on procedure. The target HbA1c of 6.5% was set based on the 2021 Korean Diabetes Association clinical practice guidelines for diabetes.[4] Briefly, the first add-on was the dose escalation of metformin by up to 2000 mg/day, the second add-on was glimepiride by up to 4 mg/day, and the third was sitagliptin by up to 100 mg/day. When participants' HbA1c levels were 9.0% or higher and less than 11.0%, they received 1000 mg of metformin and 2 mg of glimepiride once daily. If the FPG levels were 120 mg/dL or higher, or the HbA1c levels were 6.5% or higher at each visit, the first add-on was the dose escalation of metformin by up to 2000 mg/day and glimepiride by up to 4 mg/day. The second add-on was the daily administration of 100 mg of sitagliptin.

Open-label rescue medications, including insulin but excluding metformin, glucagon-like peptide-1 receptor agonists, other DPP-4 inhibitors, and other SGLT2 inhibitors, were administered to participants with FPG of more than 270 mg/dL (weeks 4 to 12), FPG of more than 240 mg/dL (weeks 13 to 26), or FPG of more than 200 mg/dL (weeks 27 to 104). Participants completed the education programme for lifestyle modification established at each centre at baseline and were required to receive repeated education during the study period. Details of the study procedures are provided in Table S2.

2.4 | Outcome measures

The primary outcome was the proportion of participants who achieved HbA1c levels of less than 6.5% without hypoglycaemia, weight gain, or discontinuation of drugs because of AEs at week 104. Weight gain was defined as at least a 5% increase in body weight from baseline. Any type of hypoglycaemia was recorded at each visit. Hypoglycaemia was defined according to the following criteria suggested by the American Diabetes Association Workgroup on Hypoglycemia: severe hypoglycaemia, documented symptomatic hypoglycaemia, asymptomatic hypoglycaemia, probable symptomatic hypoglycaemia and relative hypoglycaemia (Table S3). Among these, severe hypoglycaemia, documented symptomatic hypoglycaemia and asymptomatic hypoglycaemia were applied as adjudications for the primary outcome. Key secondary outcomes were the proportion of participants who achieved HbA1c levels of less than 7.0% without hypoglycaemia, weight gain, or discontinuation because of AEs at weeks 56 and 104, and the proportion of participants who achieved HbA1c levels of less than 6.5% without hypoglycaemia, weight gain, or discontinuation because of AEs at week 56. Mean changes in HbA1c, FPG, body weight, systolic blood pressure, fat and muscle mass measured using bioimpedance analysis from baseline to week 104 were also assessed. All blood samples were analysed at a central laboratory (GC Biopharma). The median time to attain the target HbA1c level (i.e. < 6.5%) was compared between the treatment arms.

Safety outcomes, including treatment-emergent AEs, serious AEs and discontinuation because of AEs, were collected throughout the trial. Key safety outcomes of interest included genital infection, acute kidney injury and hypoglycaemia. Acute kidney injury was defined as doubling of serum creatinine compared with a recent value, or hospitalization, or initiation of renal replacement therapy for acute kidney injury.

2.5 | Statistical analysis

On the projection of a treatment difference of 30% for the primary outcome between the groups, a sample size of 46 per group would provide a 90% power to show the superiority of the TCT to the SAT

at a two-sided 5% level of significance. Assuming a 10% dropout rate during the study period, a total of 52 subjects per group were to be recruited for this study. The details are provided in the trial design paper.[18]

All statistical analyses were performed in accordance with the study protocols. Continuous variables were summarized as mean and standard deviation or median and interquartile range (IQR; first and third quartiles). Categorical variables are summarized as frequencies and percentages. Baseline characteristics were summarized by treatment group and overall characteristics.

All the participants who received any study drug at least once were included in the safety set. Meanwhile, under an intention-to-treat principle, the full-analysis set (FAS) consisted of all subjects who were randomized to the study treatment, had an HbA1c measurement at baseline, and also had at least one HbA1c measurement afterwards, irrespective of their protocol adherence and continued participation in the study. The per-protocol set (PPS) was for all subjects in the FAS who did not experience any major protocol deviations. The primary population analysed was the FAS, which was supported by the PPS. The primary outcome was analysed using Pearson's chi-square test without imputing missing HbA1c values at 104 weeks. For secondary outcomes, Student's *t*-test was used to compare the difference in values from baseline to weeks 56 and/or 104 between the groups for each of the FAS and PPS. Changes from baseline to weeks 56 and 104 at all visits were also analysed using a mixed model for repeated measures analysis of numeric outcomes or generalized estimating equation analysis of categorical outcomes. For each visit, the least squares means (LSMs) of the continuous outcomes were obtained and compared between the groups. The proportion of patients who achieved HbA1c levels of less than 7.0% without hypoglycaemia, weight gain, or discontinuation because of AEs at 56 and 104 weeks was analysed using the same method as the primary efficacy analysis. The time to reach the target HbA1c level (i.e. < 6.5%) was summarized using Kaplan–Meier survival curves for each group and was compared using the log-rank test. Multivariate analysis using the Cox proportional hazards regression model was also performed.

A 5% significance level was used to test statistical significance, and all statistical analyses were performed using SAS software version 9.4 (SAS Institute, Cary, NC).

3 | RESULTS

From 15 January 2018 to 8 August 2019, 138 participants were screened, 105 of whom were randomly assigned to either the TCT (n = 51) or the SAT (n = 54) group. Figure 1 displays the patients disposition in the current study. Four participants (three in the TCT group and one in the SAT group) did not receive treatment, and three in the SAT group did not measure HbA1c after treatment. Consequently, a total of 98 subjects (93.3%) constituted the FAS (48 in the TCT group and 50 in the SAT group). Nineteen major protocol

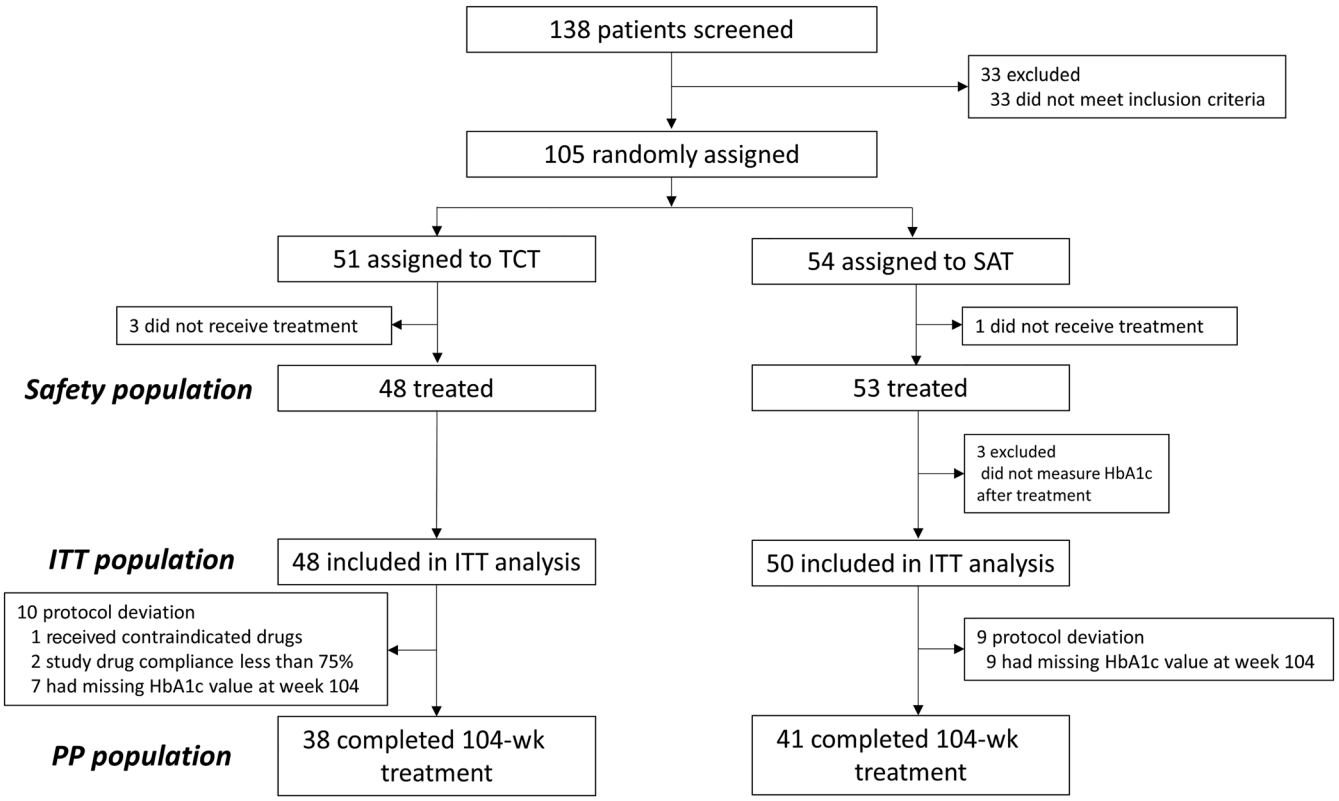

FIGURE 1 Trial profile. ITT, intention-to-treat; PP, per-protocol; SAT, stepwise add-on therapy; TCT, triple combination therapy.

deviations occurred (10 in the TCT group and nine in the SAT group), which resulted in a total of 79 PPS subjects (75.2%). In the TCT group, seven participants did not have their HbA1c measured at week 104, two had study drug compliance of less than 75%, and one used a glucocorticoid as a contraindicated drug. In the SAT group, nine people did not have their HbA1c measured at week 104.

The baseline characteristics were well balanced between the treatment groups (Table 1). The mean age was 49.5 (standard deviation [SD] 11.2) years; 67.6% were men and 32.4% were women. The mean body mass index was 27.5 (SD 4.1) kg/m^2, and the mean HbA1c was 9.3% (SD 0.8). Overall, 37.1% of participants had HbA1c levels of less than 9.0%, while 62.9% had HbA1c levels of 9.0% or higher and less than 11.0%. The most common co-morbidity was dyslipidaemia (47.6%), followed by hypertension (39.0%) and coronary artery disease (5.7%).

From baseline at week 104, similar reductions in HbA1c were observed between the treatment groups; the LSM decrease was −2.56% (standard error [SE] 0.16%) in the TCT group and −2.75%

TABLE 1 Baseline characteristics of study patients.

	Triple combination therapy (n = 51)	Stepwise add-on therapy (n = 54)	Total (n = 105)
Age, y	48.9 (12.9)	50.0 (9.4)	49.5 (11.2)
Sex			
Men	35 (68.6)	36 (66.7)	71 (67.6)
Women	16 (31.4)	18 (33.3)	34 (32.4)
Co-morbidities at screening, n (%)			
Dyslipidaemia	23 (45.1)	27 (50.0)	50 (47.6)
Hypertension	20 (39.2)	21 (38.9)	41 (39.0)
Coronary artery disease	1 (2.0)	5 (9.3)	6 (5.7)
Cerebrovascular disease	1 (2.0)	0	1 (1.0)
Heart failure	0	1 (1.9)	1 (1.0)
Peripheral artery disease	1 (1.9)	0	1 (1.0)
Body weight, kg	77.7 (14.8)	75.6 (14.0)	76.6 (14.4)
BMI, kg/m^2	28.0 (4.2)	27.0 (4.0)	27.5 (4.1)
WC, cm	94.7 (10.2)	93.7 (10.2)	94.2 (10.2)
Fasting serum glucose, mg/dL	196.6 (44.4)	198.5 (43.6)	197.6 (43.7)
HbA1c concentration			
%	9.3 (0.8)	9.3 (0.8)	9.3 (0.8)
< 9.0%	19 (37.3)	20 (37.0)	39 (37.1)
≥ 9.0%, < 11.0%	32 (62.7)	34 (63.0)	66 (62.9)
Systolic blood pressure, mmHg	127.9 (17.3)	128.9 (11.8)	128.4 (14.7)
Diastolic blood pressure, mmHg	79.5 (10.8)	81.4 (9.9)	80.5 (10.3)
Creatinine, mg/dL	0.81 (0.17)	0.79 (0.14)	0.80 (0.16)
eGFR, mL/min/1.73m^2	102.8 (20.4)	100.0 (13.6)	101.4 (17.3)
LDL-C, mg/dL	120.9 (44.1)	128.8 (44.8)	124.9 (44.4)
HDL-C, mg/dL	47.3 (14.7)	47.6 (13.3)	47.4 (14.0)
Triglyceride, mg/dL	168 (121, 225)	141 (100, 205)	149 (110, 220)
Urine albumin-to-creatinine ratio, mg/g	13.8 (8.9, 30.4)	13.9 (6.1, 33.6)	13.8 (7.7, 31.7)
Concomitant drugs, n (%)			
ACE inhibitor or ARB	17 (33.3)	13 (24.1)	30 (28.6)
CCB	11 (21.6)	11 (20.4)	22 (21.0)
Statin	18 (35.3)	25 (46.3)	43 (41.0)
Ezetimibe	4 (7.8)	5 (9.3)	9 (8.6)
Antiplatelet	6 (11.8)	8 (14.8)	14 (13.3)

Note: Data are presented as n (%), mean (SD) or median (IQR).

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BMI, body mass index; CCB, calcium channel blocker; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol; SD, standard deviation; WC, waist circumference.

(SE 0.16%) in the SAT group, resulting in an estimated treatment difference for the TCT group versus the SAT group of 0.19% ($P = .39$) in the FAS (Figure 2A). The achieved mean HbA1c level was 6.59% (SD 0.98%) and 6.53% (SD 0.71%) in the TCT and SAT groups, respectively ($P = .35$). For the subgroup of HbA1c of 9.0% or higher at baseline, the changes in HbA1c from baseline at week 104 were −2.76% (SE 0.19%) for TCT and −3.17% (SE 0.19%) for SAT; the difference of 0.41% between the groups was not significant ($P = .14$) (Figure 2B). For the subgroup with HbA1c levels of less than 9.0% at baseline, changes in HbA1c from baseline to week 104 were − 2.27% (SE 0.17%) for TCT and −2.03% (SE 0.16%) for SAT, resulting in a between-group difference of −0.24% ($P = .67$) (Figure 2C). In the PPS analysis, the changes in HbA1c from baseline to week 104 were also similar between the groups: −2.76% (SE 0.14%) for TCT and −2.76%

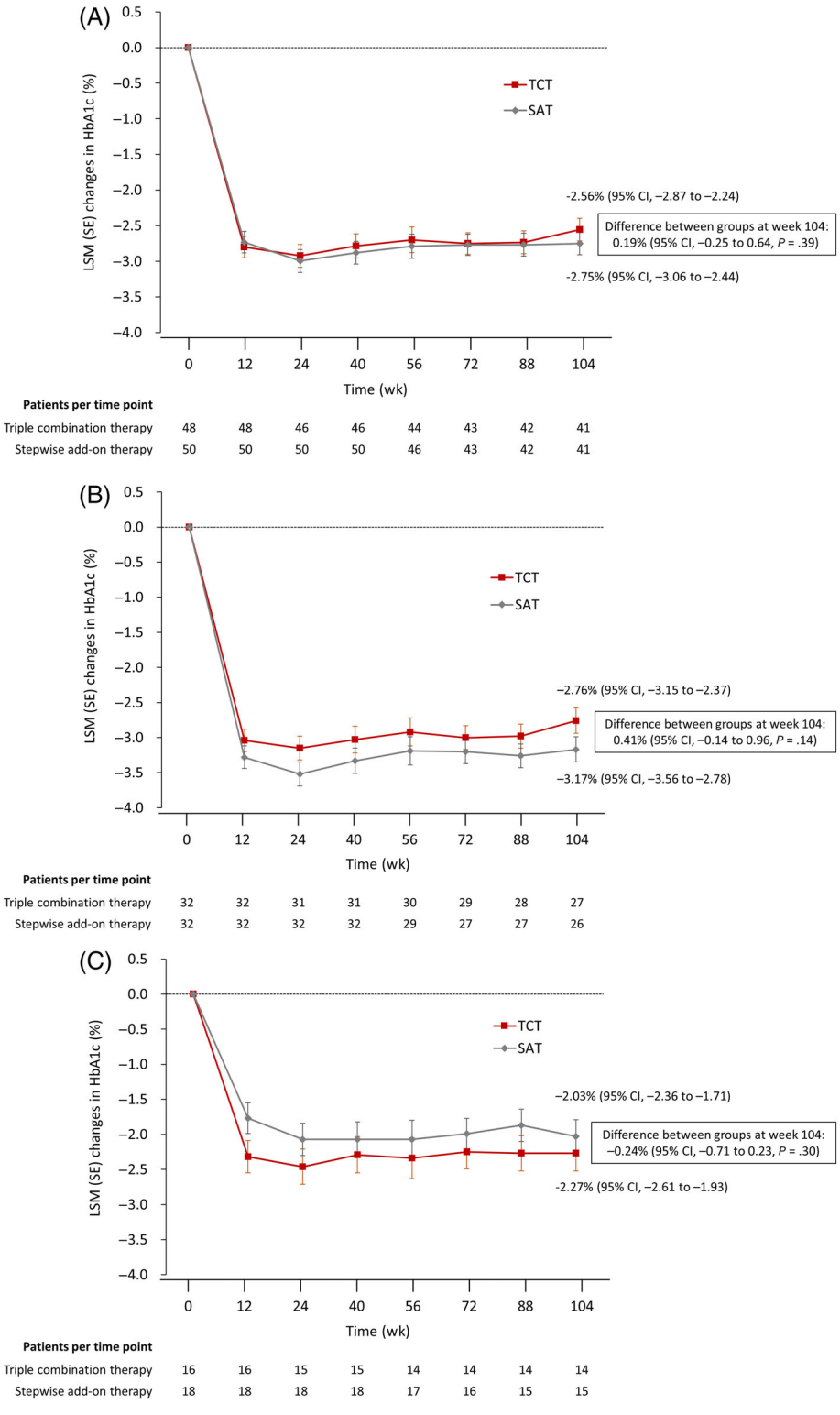

FIGURE 2 Changes in HbA1c levels from treatments in the FAS. Data at each visit and the estimated treatment differences represent LSMs (95% CIs). Changes in HbA1c levels from baseline to week 104 in the TCT and the SAT groups are given in A, For all participants in the ITT set; B, Subgroup of participants whose HbA1c levels at baseline were 9.0% or higher; and C, Subgroup of participants whose HbA1c levels at baseline were less than 9.0%. CI, confidence interval; FAS, full-analysis set; ITT, intention-to-treat; LSM, least squares mean; SAT, stepwise add-on therapy; SE, standard error; TCT, triple combination therapy.

(SE 0.14%) for SAT ($P = .98$). The information on the use of glimepiride and sitagliptin during the trial in the SAT group is displayed in Table S4.

A higher proportion of participants in the TCT group achieved the primary outcome than those in the SAT group (39.0% vs. 17.1%; $P = .027$) on the FAS (Figure 3A and Table S5). The proportion of participants who achieved HbA1c levels lower than 6.5% at week 104 was similar (46.3%) between the treatment groups (Figure 3B); however, a higher proportion of participants without hypoglycaemia, weight gain, or discontinuation because of AEs was observed: 83.3% in the TCT group and 38.0% in the SAT group ($P < .001$) (Figure 3C), which resulted in a significant difference in the primary outcome between the groups. The target achievement rates of less than 7.0% at week 104 and of less than 6.5% at week 56 were higher in the TCT group than in the SAT group (73.2% vs. 65.9% and 61.4% vs. 50.0%, respectively); however, this did not reach statistical significance (Figure S2).

In the FAS, the achievement of key secondary outcomes included the proportion of participants who achieved HbA1c levels of less than 7.0% without hypoglycaemia, weight gain, or discontinuation because of AEs at week 104 (63.4% vs. 24.4%, $P < .001$) and week 56 (68.2% vs. 26.1%, $P < .001$). The proportion of participants who achieved HbA1c levels of less than 6.5% without hypoglycaemia, weight gain, or discontinuation because of AEs at week 56 (52.3% vs. 19.6%, $P = .001$) was also higher in the TCT group than in the SAT group (Figure 4A).

LSM changes in body weight from baseline at week 104 were −0.56 (SE 0.73) kg in the TCT group and 3.08 (SE 0.72) kg in the SAT group, resulting in a between-group difference of 3.64 kg ($P < .001$) (Figure 4B). Differences in body weight between the groups were observed from week 4 and maintained throughout the study period. The mean waist circumference decreased by 1.57 cm in the TCT group and increased by 1.17 cm in the SAT group, although the difference did not reach statistical significance (Figure S3). Systolic blood pressure also decreased in the TCT group, but increased in the SAT group throughout the trial period (Figure 4C). At week 104, changes in systolic blood pressure were −0.97 (SE 2.32) mmHg in the TCT group and 3.59 (SE 2.28) mmHg in the SAT group ($P = .16$). There was a small decrease in the estimated glomerular filtration rate during the trial in both groups, resulting in −0.24 and −2.65 mL/min/1.73m^2 at week 104, respectively ($P = .84$) (Figure S4). Figure 4D presents a Kaplan–Meier curve for the time to reach HbA1c levels of less than 6.5%, of which the median time was shorter, but not statistically significantly, in the TCT (2.88; IQR 2.76 to 3.45 months) group compared with the SAT (3.19; IQR 2.83 to 8.94 months) group ($P = .091$).

During the 104-week treatment period, AEs occurred in 18 of 48 participants (38%) in the TCT group and 30 of 53 participants (57%) in the SAT group (Table S6). AEs leading to the discontinuation of study drugs were one (2%) in the TCT group and two (4%) in the SAT group. Serious AEs also occurred similarly between the groups: six (12%) in the TCT group and five (10%) in the SAT group. The most common AEs in the TCT group were dizziness (8%) and headache (4%), whereas those in the SAT group were hypoglycaemia (19%), diarrhoea (17%) and headache (4%). Hypoglycaemia was not observed in the TCT group throughout the study period. However, 10 participants (19%) in the SAT group experienced hypoglycaemia. The total number of hypoglycaemic events in the SAT group was 32, including nine events of documented symptomatic hypoglycaemia, five events of asymptomatic hypoglycaemia and 16 events of probable symptomatic hypoglycaemia. Genital tract infections occurred in only one subject in the TCT group. There was no event corresponding to acute kidney injury during the study period.

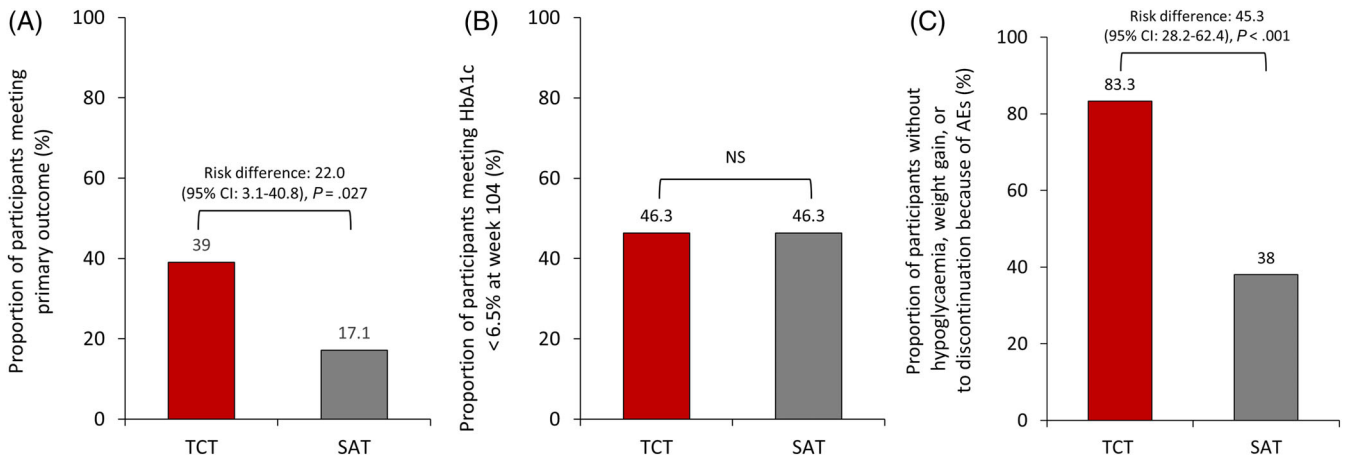

FIGURE 3 Primary outcome. Data represent the proportion of participants in each group or the LSM (SE), unless stated otherwise. A, Proportion of participants meeting the primary outcome (%); B, Proportion of participants achieving HbA1c levels of less than 6.5% at week 104 (%) by treatment groups; and C, Proportion of participants without hypoglycaemia, weight gain, or discontinuation because of AEs (%). AE, adverse event; CI, confidence interval; LSM, least square mean; NS, not significant; SAT, stepwise add-on therapy; SE, standard error; TCT, triple combination therapy.

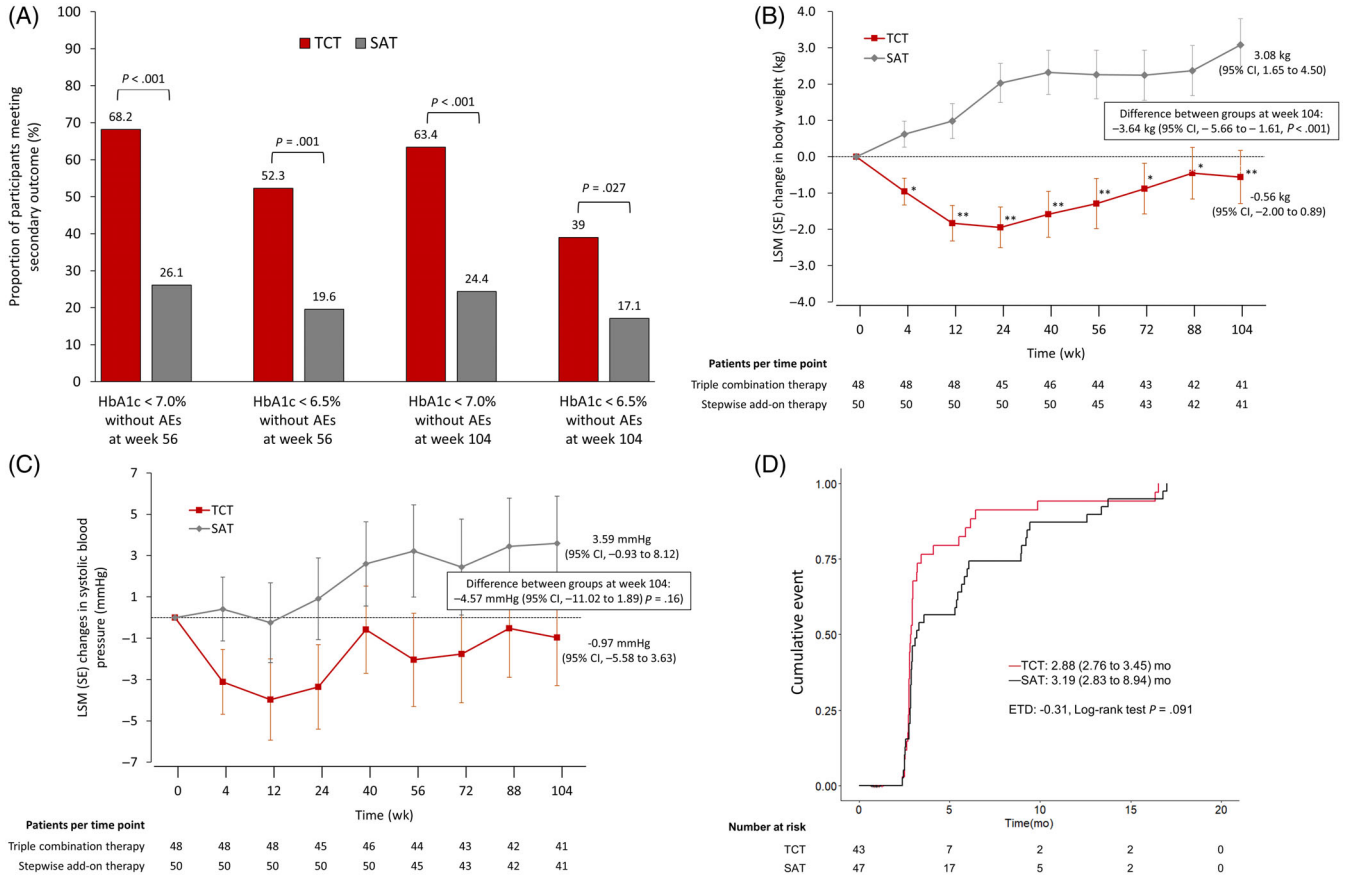

FIGURE 4 Key secondary outcomes. Data represent the proportion of participants in each group or the LSM (SE), unless stated otherwise. A, Proportion of participants meeting key secondary outcomes (%); B, Changes in body weight from baseline to week 104; C, Changes in systolic blood pressure from baseline to week 104; and D, Proportion of participants reaching target Hba1c levels (i.e. ⟨ 6.5%) by treatment groups; **P* < .05, ***P* < .01. AE, adverse event; CI, confidence interval; ETD, estimated treatment difference; LSM, least square mean; SAT, stepwise add-on therapy; SE, standard error; TCT, triple combination therapy.

4 | DISCUSSION

This is the first randomized controlled trial to investigate the long-term efficacy and safety of an initial combination therapy consisting of three different oral antidiabetic drugs, including metformin, SGLT2 inhibitors and DPP-4 inhibitors, compared with the conventional stepwise add-on strategy in newly diagnosed drug-naïve patients with T2D. There were no significant differences in the magnitude and course of HbA1c reduction between the treatment groups. However, the prespecified primary outcome, which includes glycaemic efficacy considering safety and tolerability, was achieved at a higher rate: it more than doubled (39.0% vs. 17.1%) with the initial triple combination strategy compared with the traditional stepwise strategy. The initial combination regimen consisted of three different orally administered antidiabetic drugs that did not result in hypoglycaemia or weight gain, which contributed to positive results in terms of the primary outcome. Although the glycaemic efficacy of each drug in the TCT was modest, the combination of these drugs resulted in a 2-year durable glycaemic efficacy, with greater than a 2.5% reduction in HbA1c levels from baseline. The overall results of this study suggest a novel strategy for initial combination therapy in newly diagnosed T2D patients.

Metformin, a sulphonylurea and a DPP-4 inhibitor were selected in the SAT group because they were the most frequently and sequentially selected drugs for the management of T2D in many countries, including South Korea.[20–22] According to the Korean Diabetes Association Diabetes Fact Sheet 2017,[22] the most frequently prescribed antidiabetic drugs were metformin (86.8%), followed by DPP-4 inhibitors (61.8%), sulphonylureas (45.5%), thiazolidinediones (11.2%) and SGLT2 inhibitors (7.0%). Therefore, the most prevalent regimen as TCT comprised metformin, a DPP-4 inhibitor and a sulphonylurea. In addition, considering the stronger glycaemic efficacy of sulphonylureas compared with DPP-4 inhibitors, especially during the early stages of treatment[23]—which would be beneficial for alleviating glucotoxicity in the early stages of diabetes— in the SAT group, the treatment sequence was metformin followed by glimepiride, then saxagliptin. It has been proven again that metformin and sulphonylureas have rapid and strong hypoglycaemic effects when used in the early stages of T2D, but the risk of hypoglycaemia and weight gain must be taken.[24,25] Specifically, early engagement of a sulphonylurea in the

SAT group seemed to contribute similar glycaemic efficacy as TCT. As described earlier, a rapid correction in blood glucose in the early stage of diabetes has several long-term benefits. This study showed which method of stabilizing hyperglycaemia is safe and effective. However, there remain questions regarding whether the early TCT proposed in this study is cost-effective. This needs to be verified by further research.

The efficacy of initial or early combination therapy in patients with T2D has been investigated in numerous clinical trials. Most combination regimens consisted of two different classes of oral antidiabetic drugs, one of which was mostly metformin.[10,26–28] In these clinical trials, initial dual combinations showed greater glycaemic efficacy than individual monotherapies; however, most were generally short-term trials, which did not guarantee the long-term efficacy and safety of initial combination therapy. The Vildagliptin Efficacy in combination with metfoRmIn For earlY treatment of T2D (VERIFY) trial proved the long-term glycaemic durability of the initial dual combination therapy of metformin and vildagliptin.[29] However, the trial only enrolled patients whose HbA1c levels mildly increased by 6.5% to 7.0%, which limits the application of the results to patients with higher HbA1c levels. To the best of our knowledge, the only randomized controlled trial of initial TCT was the Efficacy and Durability of Initial Combination Therapy for Type 2 Diabetes (EDICT) study with metformin, pioglitazone and exenatide.[12] The study showed the long-term glycaemic durability of the triple regimen for more than 3 years.[30] However, those regimens included an injectable drug, which may contribute to a higher rate of AEs and dropout in the triple combination arm. Therefore, when planning initial combination therapy, it is essential to determine which drugs should be included in the combination regimen. We combined metformin, dapagliflozin and saxagliptin, and administered metformin and dapagliflozin as fixed-dose combination tablets. Accordingly, participants in the TCT group took two tablets for a study period of 104 weeks without any change or escalation of drugs, which could be an easily accessible treatment regimen for both patients and physicians.

Changes in HbA1c levels during the trial period, including the first 12 weeks, did not differ between the groups. The time to reach HbA1c levels of less than 6.5% also did not differ. A higher proportion of participants (62.3%) in the SAT group had HbA1c levels of 9.0% or higher, in which case dual combination therapy with metformin and glimepiride was initiated, resulting in a rapid reduction of HbA1c. In addition, the procedure of the SAT was set to the 'treat-to-target' strategy targeting HbA1c levels of 6.5%, while that of the TCT was the 'shoot and forget' strategy. In the subgroup analysis based on baseline HbA1c levels, the changes in HbA1c levels between the groups were somewhat different. The SAT group showed better glycaemic efficacy in the case of HbA1c levels at baseline of 9.0% or higher, while the TCT group was better in the subgroup of HbA1c at baseline less than 9.0%, although it did not reach statistical significance. These results suggest that the long-term glycaemic efficacy of TCT is dependent on initial HbA1c levels. Therefore, patients with moderately increased HbA1c levels may be the optimal target population for TCT.

Compared with SAT, TCT provided greater reductions in body weight (−3.64 kg), waist circumference (−2.74 cm) and systolic blood pressure (−3.62 mmHg). The observed reduction in the metabolic variables was similar to that observed after dapagliflozin monotherapy in previous clinical trials. The addition of metformin and saxagliptin did not affect the overall metabolic effects of dapagliflozin for 2 years. The reduction in body weight, waist circumference and blood pressure in the TCT group may contribute to cardiovascular risk reduction compared with the SAT group. As the participants of the trial were newly diagnosed T2D patients with a mean age of 49.7 years, mostly without pre-existing cardiovascular diseases, few cardiovascular events occurred during the trial of 104 weeks. A post-trial observational study is being planned to observe the cardiovascular effects of the initial TCT.

TCT was tolerable, with fewer AEs compared with SAT (38.0% vs. 56.6%) for 104 weeks. The most common AE of TCT was dizziness, which occurred in four of the 48 participants. Genital tract infections, an AE of interest in the TCT group, occurred in a small number of participants (one of 48). Urinary tract infection, ketoacidosis, hypotension and hypoglycaemia were not documented during TCT. In the SAT group, 19% (10 of 53) of participants experienced 32 events of any type of hypoglycaemia, although there were no severe hypoglycaemic events in the SAT group. More gastrointestinal disorders occurred in the SAT group, probably because of a higher dose of metformin than in the TCT group; the mean dose of metformin was 1593.8 mg in the SAT group and 863.4 mg in the TCT group during the study period.

This study has several limitations. The number of participants was set to secure statistical power between the treatment groups; however, it was small compared with previous clinical trials. There were some discrepancies in the proportion of participants according to baseline HbA1c levels (≥ 9.0% and < 9.0%) in the SAT and TCT groups. Specifically, a larger number of subjects had HbA1c levels of 9.0% or higher in the SAT group, which resulted in more than double the number of participants receiving initial dual combination therapy over monotherapy in the SAT group. The trial duration of 2 years was not sufficient to assess microvascular or cardiovascular outcomes, considering that the participants were not old or at a high risk of vascular complications.

In conclusion, for 104 weeks, initial TCT with 1 g of metformin, dapagliflozin and saxagliptin effectively lowered HbA1c levels, with higher tolerability and safety than conventional SAT involving metformin, glimepiride and sitagliptin in drug-naïve patients with T2D. In addition, the initial TCT was associated with an improvement in multiple cardiovascular risk factors compared with SAT.

AUTHOR CONTRIBUTIONS

SGK conceptualized this study. NHK, JSM, YL, HCC, SHK, SL and MKM revised the study design. EK and JL contributed to the statistical analysis. All the authors interpreted the data and were involved in the trial. NHK drafted the manuscript. All the authors contributed to the revision, editing and approval of the manuscript. All authors had full access to all data in the study and had the final responsibility for the decision to submit the manuscript for publication.

ACKNOWLEDGEMENTS

We thank all participants and study personnel. Project management support was provided by Yang Hui Park and You-Seon Nam from AstraZeneca, South Korea. This study was funded by AstraZeneca.

CONFLICT OF INTEREST STATEMENT

SGK has received consulting fees and honoraria from AstraZeneca, Boehringer Ingelheim, Celltrion and Handok; and grants for medical research from AstraZeneca, Boehringer Ingelheim and Celltrion. NHK has received lecture fees from AstraZeneca, Eli Lilly, Novo Nordisk, Sanofi, Takeda, Boehringer Ingelheim, Celltrion, Handok and Abbott; and a grant from CKD Pharmaceutical. JSM has been a member of advisory boards or consulted with Novartis; has received grant support from Handok; and has also served on the speakers' bureau of AstraZeneca, Boehringer Ingelheim, CKD Pharmaceutical, Dong-A ST, Eli Lilly & Co., Handok, HK InnoN, Novo Nordisk, Sanofi, Takeda and Yuhan. SL has been a member of advisory boards, or has consulted, for Merck, Sharp & Dohme and Novo Nordisk; and has received grant support from AstraZeneca, Merck, Sharp & Dohme and Astellas. YHL, THK, HCC, SHK, DLK, MKM, EK and JL declare no competing 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.15705.

DATA AVAILABILITY STATEMENT

Data are available upon request, six months after primary publication acceptance. Access will be provided after the proposal has been approved by the review committee of the TRIPLE-AXEL study.

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REFERENCES

1. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet*. 1998;352(9131):837-853.
2. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-year follow-up of intensive glucose control in type 2 diabetes. *N Engl J Med*. 2008;359(15):1577-1589.
3. ElSayed NA, Aleppo G, Aroda VR, et al. Pharmacologic approaches to glycemic treatment: standards of Care in Diabetes-2023. *Diabetes Care*. 2023;46(Suppl 1):S140-S157.
4. Hur KY, Moon MK, Park JS, et al. 2021 clinical practice guidelines for diabetes mellitus of the Korean Diabetes Association. *Diabetes Metab J*. 2021;45(4):461-481.
5. Kim KJ, Choi J, Bae JH, et al. Time to reach target glycosylated hemoglobin is associated with long-term durable glycemic control and risk of diabetic complications in patients with newly diagnosed type 2 diabetes mellitus: a 6-year observational study. *Diabetes Metab J*. 2021;45(3):368-378.
6. Laiteerapong N, Ham SA, Gao Y, et al. The legacy effect in type 2 diabetes: impact of early glycemic control on future complications (the Diabetes & Aging Study). *Diabetes Care*. 2019;42(3):416-426.
7. Lean ME, Leslie WS, Barnes AC, et al. Primary care-led weight management for remission of type 2 diabetes (DiRECT): an open-label, cluster-randomised trial. *Lancet*. 2018;391(10120):541-551.
8. Ryan EA, Imes S, Wallace C. Short-term intensive insulin therapy in newly diagnosed type 2 diabetes. *Diabetes Care*. 2004;27(5):1028-1032.
9. Weng J, Li Y, Xu W, et al. Effect of intensive insulin therapy on beta-cell function and glycaemic control in patients with newly diagnosed type 2 diabetes: a multicentre randomised parallel-group trial. *Lancet*. 2008;371(9626):1753-1760.
10. Hadjadj S, Rosenstock J, Meinicke T, Woerle HJ, Broedl UC. Initial combination of empagliflozin and metformin in patients with type 2 diabetes. *Diabetes Care*. 2016;39(10):1718-1728.
11. Rosenstock J, Kim SW, Baron MA, et al. Efficacy and tolerability of initial combination therapy with vildagliptin and pioglitazone compared with component monotherapy in patients with type 2 diabetes. *Diabetes Obes Metab*. 2007;9(2):175-185.
12. Abdul-Ghani MA, Puckett C, Triplitt C, et al. Initial combination therapy with metformin, pioglitazone and exenatide is more effective than sequential add-on therapy in subjects with new-onset diabetes. Results from the efficacy and durability of initial combination therapy for type 2 diabetes (EDICT): a randomized trial. *Diabetes Obes Metab*. 2015;17(3):268-275.
13. Cersosimo E, Johnson EL, Chovanes C, Skolnik N. Initiating therapy in patients newly diagnosed with type 2 diabetes: combination therapy vs a stepwise approach. *Diabetes Obes Metab*. 2018;20(3):497-507.
14. List JF, Woo V, Morales E, Tang W, Fiedorek FT. Sodium-glucose cotransport inhibition with dapagliflozin in type 2 diabetes. *Diabetes Care*. 2009;32(4):650-657.
15. Shubrook J, Colucci R, Guo A, Schwartz F. Saxagliptin: a selective DPP-4 inhibitor for the treatment of type 2 diabetes mellitus. *Clin Med Insights Endocrinol Diabetes*. 2011;4:1-12.
16. Rena G, Hardie DG, Pearson ER. The mechanisms of action of metformin. *Diabetologia*. 2017;60(9):1577-1585.
17. Wiviott SD, Raz I, Bonaca MP, et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. *N Engl J Med*. 2019;380(4):347-357.
18. Heerspink HJL, Stefánsson BV, Correa-Rotter R, et al. Dapagliflozin in patients with chronic kidney disease. *N Engl J Med*. 2020;383(15):1436-1446.
19. Kim NH, Lim S, Kwak SH, et al. Efficacy and tolerability of novel triple combination therapy in drug-naïve patients with type 2 diabetes from the TRIPLE-AXEL trial: protocol for an open-label randomised controlled trial. *BMJ Open*. 2018;8(9):e022448.
20. Dennis JM, Henley WE, McGovern AP, et al. Time trends in prescribing of type 2 diabetes drugs, glycaemic response and risk factors: a retrospective analysis of primary care data, 2010-2017. *Diabetes Obes Metab*. 2019;21(7):1576-1584.
21. Abrahami D, D'Andrea E, Yin H, et al. Contemporary trends in the utilization of second-line pharmacological therapies for type 2 diabetes in the United States and the United Kingdom. *Diabetes Obes Metab*. 2023;25:2980-2988.
22. Bae JH, Han KD, Ko SH, et al. Diabetes fact sheet in Korea 2021. *Diabetes Metab J*. 2022;46(3):417-426.
23. GRADE Study Research Group, Nathan DM, Lachin JM, Balasubramanyam A, et al. Glycemia reduction in type 2 diabetes - glycemic outcomes. *N Engl J Med*. 2022;387(12):1063-1074.

24. Cai X, Gao X, Yang W, Han X, Ji L. Efficacy and safety of initial combination therapy in treatment-Naïve type 2 diabetes patients: a systematic review and meta-analysis. *Diabetes Ther*. 2018;9(5):1995-2014.
25. Yu O, Azoulay L, Yin H, Filion KB, Suissa S. Sulfonylureas as initial treatment for type 2 diabetes and the risk of severe hypoglycemia. *Am J Med*. 2018;131(3):317 e311-317 e322.
26. Haak T, Meinicke T, Jones R, Weber S, von Eynatten M, Woerle HJ. Initial combination of linagliptin and metformin improves glycaemic control in. *Diabetes Obes Metab*. 2012;14(6):565-574.
27. Rosenstock J, Chuck L, González-Ortiz M, et al. Initial combination therapy with canagliflozin plus metformin versus each. *Diabetes Care*. 2016;39(3):353-362.
28. Rosenstock J, Rood J, Cobitz A, Biswas N, Chou H, Garber A. Initial treatment with rosiglitazone/metformin fixed-dose combination therapy. *Diabetes Obes Metab*. 2006;8(6):650-660.
29. Matthews DR, Paldánius PM, Proot P, Chiang Y, Stumvoll M, Del Prato S. Glycaemic durability of an early combination therapy with vildagliptin and metformin versus sequential metformin monotherapy in newly diagnosed type 2 diabetes (VERIFY): a 5-year, multicentre, randomised, double-blind trial. *Lancet*. 2019;394(10208):1519-1529.
30. Abdul-Ghani M, Puckett C, Adams J, et al. Durability of triple combination therapy versus stepwise addition therapy in patients with new-onset T2DM: 3-year follow-up of EDICT. *Diabetes Care*. 2021;44(2):433-439.

SUPPORTING INFORMATION

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

How to cite this article: Kim NH, Moon JS, Lee Y, et al. Efficacy and tolerability of initial triple combination therapy with metformin, dapagliflozin and saxagliptin compared with stepwise add-on therapy in drug-naïve patients with type 2 diabetes (TRIPLE-AXEL study): A multicentre, randomized, 104-week, open-label, active-controlled trial. *Diabetes Obes Metab*. 2024;26(9):3642-3652. doi:10.1111/dom.15705