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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

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ABSTRACT

Introduction Patients with type 2 diabetes are at risk of microvascular and macrovascular complications. Intensive glycaemic control, especially in patients with short duration of diabetes, is the mainstay of management of type 2 diabetes to lower the risk of complications. However, despite the improvement in the understanding of the pathophysiology of type 2 diabetes and development of novel glucose-lowering agents, long-term durable glycaemic control remains a difficult goal to achieve. Several challenging clinical trials proved that an early combination therapy with a variety of glucose-lowering agents had a more favourable effect than conventional stepwise therapy in terms of glycaemic control. We aim to evaluate the efficacy and tolerability of a novel, initial triple combination therapy with metformin, sodium glucose cotransporter 2 inhibitor (dapagliflozin) and dipeptidyl peptidase-4 inhibitor (saxagliptin) compared with conventional stepwise add-on therapy in drug-naïve patients with recent-onset type 2 diabetes.

Methods and analysis This study is a multicentre, prospective, randomised, open-label, parallel group, comparator-controlled trial. A total of 104 eligible participants will be randomised to either the initial combination therapy group or the conventional stepwise add-on therapy group for 104 weeks. The primary endpoint is the proportion of patients who achieved haemoglobin A1c level<6.5% without hypoglycaemia, weight gain or discontinuation due to adverse events at 104 weeks. This trial will determine whether a novel triple combination therapy with metformin, dapagliflozin and saxagliptin has a beneficial effect on durable glycaemic control compared with conventional therapy in drug-naïve patients with type 2 diabetes.

Ethics and dissemination This study protocol was approved by the local institutional review boards and independent ethics committees over the recruitment sites. Results of this study will be disseminated in scientific journals and scientific conferences.

Trial registration number NCT02946632; Pre-results.

Strengths and limitations of this study

► This long-term, multicentre, randomised controlled trial will provide novel concept of early intensive treatment with triple glucose-lowering agents combination in patients with type 2 diabetes.
► Lack of blinding due to open-label concept.
► Long-term treatment period may limit the complete retention of participants.

INTRODUCTION

Type 2 diabetes is a metabolic disorder characterised by hyperglycaemia and increased risk for microvascular and macrovascular complications.[1 2] Landmark clinical trials in the management of type 2 diabetes including the United Kingdom Prospective Diabetes Study (UKPDS), Action to Control Cardiovascular Risk in Diabetes Study, Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation and Veterans Affairs Diabetes Trial have shown that intensive glycaemic control reduced the risk for microvascular complications.[3–6] In addition, intensive glycaemic control in the early period of diabetes progression was associated with a significantly lower incidence of cardiovascular disease and mortality.[7] Based on the data from these trials, many international and local clinical guidelines proposed the glycaemic targets as haemoglobin A1c (HbA1c) level<7.0% in general, and a more stringent target (6.0%–6.5%) in patients whose duration of diabetes was shorter, free from vascular complications or who were young.[8–11]

However, progressive β-cell failure and clinical inertia have limited long-term durable glycaemic control in patients with type 2 diabetes.[12] In the post-hoc analysis in the UKPDS, over 70% of patients who were treated with sulfonylurea or insulin eventually failed to achieve the target HbA1c level

(<7.0%) over 9 years.[13] Treatment with thiazolidinediones or some sodium glucose cotransporter 2 (SGLT-2) inhibitors has shown a more favourable effect on durable glycaemic control than sulfonylurea; however, this also could not achieve long-term sustainable results.[14 15] This evidence consistently suggested the limited ability to sustain favourable glycaemic control with monotherapy, irrespective of the drugs used.

Therefore, some challenging trials focused on the early intensive therapy as an alternative option for managing hyperglycaemia in type 2 diabetes. Intensive insulin therapy targeting near normal range of glycaemia in patients with recent-onset type 2 diabetes had promising results, even long-term resolution of diabetes.[16 17] On the other hand, early combination therapy with two different classes of glucose-lowering agents also had favourable glycaemic control. For example, a dual add-on with SGLT-2 inhibitor plus dipeptidyl peptidase-4 (DPP-4) inhibitor to the patients who failed with metformin monotherapy has shown greater improvement in glycaemic control than single add-on with each drug.[18 19] Recently, a more challenging trial evaluated the initial triple combination therapy in drug-naïve patients with type 2 diabetes.[20] The initial combination with metformin, pioglitazone and exenatide has shown significantly better long-term glycaemic control than stepwise therapy.

Therefore, we focused on a different triple combination for safe and efficient glycaemic control: metformin, SGLT-2 inhibitor and DPP-4 inhibitor. An SGLT-2 inhibitor, dapagliflozin, lowers hyperglycaemia via blocking SGLT-2 to increase glucosuria, that is, in an insulin-independent manner.[21 22] A DPP-4 inhibitor, saxagliptin, increases the serum level of Glucagon-like peptide-1 (GLP-1), and potentiates its action of increasing glucose-dependent insulin secretion and lowering glucagon secretion.[23] Therefore, the mechanism of action of these drugs is complementary to that of metformin, and all of these have a low risk of hypoglycaemia and weight gain, suggesting safe and powerful combination regimen.

Based on these backgrounds, we designed a randomised controlled trial to assess the efficacy and tolerability of a novel, initial triple combination therapy with metformin, saxagliptin and dapagliflozin, compared with conventional stepwise add-on therapy with metformin, followed by glimepiride, and sitagliptin in drug-naïve patients with recent-onset type 2 diabetes (the TRIPLE-AXEL study).

METHODS

Study design and overview

The TRIPLE-AXEL study is an investigator-initiated, prospective, randomised, open-label, parallel group, comparator-controlled trial. The eligible patients will be recruited from seven tertiary medical centres in South Korea, according to inclusion and exclusion criteria (box 1). After initial screening, patients will be randomised to the initial triple combination therapy group or the conventional stepwise add-on therapy group and followed

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> **Box 1   Inclusion and exclusion criteria**
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> **Inclusion criteria**
> - ► Drug-naïve patients with type 2 diabetes diagnosed by American Diabetes Association criteria.
> - ► Haemoglobin A1c level ≥8%, <10.5% at screening.
> - ► Age ≥18 years, <65 years.
> - ► Body mass index ≥23 kg/m^2, <35 kg/m^2.
> - ► Estimated glomerular filtration rate ≥60 mL/min/1.73 m^2.
>
> **Exclusion criteria**
> - ► Uncontrolled hyperglycaemia >270 mg/dL after an overnight fast.
> - ► Diabetic ketoacidosis.
> - ► Type 1 diabetes.
> - ► Confirmed cardiovascular disease (acute coronary syndrome, stroke or transient ischaemic attack) within 3 months of screening.
> - ► Congestive heart failure (New York Heart Association functional class III or IV).
> - ► Severe hepatic dysfunction (serum levels of either aspartate aminotransferase, alanine aminotransferase or alkaline phosphatase above three times upper limit of normal.
> - ► Alcohol abuse within 3 months prior to informed consent that would interfere with trial participation or any ongoing condition leading to a decreased compliance to study procedures or study drug intake.
> - ► Pregnant women, women with potential of pregnancy not using adequate contraception method as evaluated by the investigator, lactating women.
> - ► Use of systemic glucocorticoid.

up to the end of the study (104 weeks). The overall scheme of the study is described in figure 1.

At the first visit after randomisation, baseline data including participants' vital signs, anthropometric measures, electrocardiography and laboratory data will be collected according to the protocol. The participants assigned to the initial triple combination therapy group will take two tablets of the study drugs one time a day, and those assigned to the conventional stepwise therapy group will take medications sequentially according to a predetermined order based on their baseline HbA1c levels (details are described in the following section). Participants will undergo a blood test for glycaemic markers at each visit to adjust the medication doses or regimens. At each visit, investigators will check the participants' medical conditions, vital signs and any adverse events (AEs) related to medications including hypoglycaemic events.

Enrolment and randomisation

Eligible participants at screening who meet the inclusion criteria will be randomly assigned to either the triple combination therapy group or the conventional stepwise therapy group. Randomisation codes will be generated in blocks to ensure approximate balance (1:1) between the two treatment arms using a stratified block randomisation. Eligible subjects will be randomised within 2 weeks after the screening visit. The randomisation code will be sequentially generated within each centre as well as based on subject's initial level of HbA1c (<9% versus ≥9%). Once a block of randomisation codes is exhausted, the next
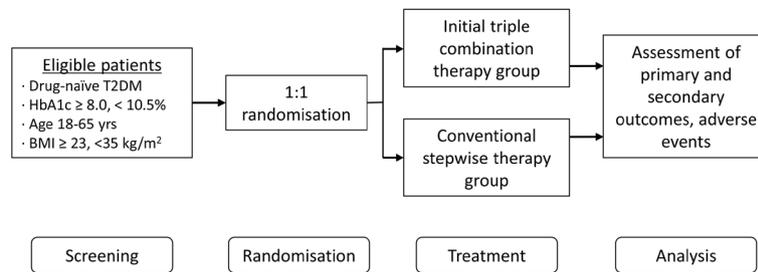
Figure 1 Overall study design. BMI, body mass index; HbA1c, haemoglobin A1c; T2DM, type 2 diabetes mellitus.

available block will be used within each stratum. For each randomised subject, the envelope will provide the investigator with a unique randomisation number matching the treatment arm assigned to the subject. Following randomisation, the assigned therapy will be applied to the subject as soon as possible.

Study procedures
Initial triple combination group
Participants in the initial combination therapy group will be started on Xigduo (metformin 1000 mg plus dapagliflozin 10 mg combination), saxagliptin 5 mg one time a day before breakfast, maintained for 104 weeks. At any visits, if participants have gastrointestinal discomfort probably due to metformin, dose reduction (metformin in Xigduo to 500 mg) is possible based on physicians' decision. If patients are still intolerable to the lower dose of metformin, it should be discontinued and recorded as an AE.

Conventional stepwise therapy group
Participants in the conventional stepwise therapy group will be further stratified to two different procedure regimens according to the baseline level of HbA1c. First, if participants' baseline HbA1c level≥8.0%, and<9.0%, they will be started on metformin 1000 mg one time a day before breakfast. At each visit, fasting plasma

glucose (FPG) and HbA1c levels will be measured, and the sequential add-on therapy will be held according to the regimen described in table 1. Second, if participants' baseline HbA1c level≥9.0%, and <10.5%, they will be started on metformin 1000 mg one time a day plus glimepiride 2 mg one time a day before breakfast. The subsequent add-on regimen is described in table 2. At any visit, if severe or recurrent hypoglycaemia is observed, step down is possible based on physicians' decision. Similar to the initial triple combination groups, if patients have gastrointestinal discomfort probably due to metformin, dose reduction (to 500 mg metformin) is possible based on physicians' decision.

Rescue therapy
Open-label rescue medications including insulin except metformin, GLP-1 receptor agonist, other DPP-4 inhibitors and other SGLT-2 inhibitors can be given to participants with FPG>270 mg/dL (week 4–12), or FPG>240 mg/dL (week 12–26), or FPG>200 mg/dL (week 26–104).

Endpoints
Primary endpoint
The primary objective of this study is to determine the efficacy and tolerability of the initial triple combination therapy with metformin, dapagliflozin and saxagliptin compared with conventional stepwise add-on therapy

Table 1 Sequential add-on therapy regimen in the conventional treatment group (baseline haemoglobin A1c (HbA1c) level≥8.0%, <9.0%)

Order	Regimen
The first add-on	if FPG level≥120 mg/dL, metformin is increased to 2000 mg (1000 mg two times a day
The second add-on	if FPG level≥120 mg/dL, or HbA1c level≥6.5%, glimepiride 1 mg or 2 mg/day is started before breakfast
The third add-on	if FPG level≥120 mg/dL, or HbA1c level≥6.5%, glimepiride is increased to 4 mg/day maximally (based on physician' s decision)
The fourth add-on	if FPG level≥120 mg/dL, or HbA1c level≥6.5%, sitagliptin 100 mg/day is added
	*if FPG level<120 mg/dL, or HbA1c level<6.5% at each visit, the previous regimen is maintained. At any visit, if severe or recurrent hypoglycaemia, step down is possible based on physician's decision. At any visit, if patients have gastrointestinal discomfort probably due to metformin, dose reduction (to 500 mg as metformin) is possible based on physician's decision. If patients still intolerable to lower dose of metformin, it should be discontinued and recorded as adverse events.

FPG, fasting plasma glucose.

Table 2 Sequential add-on therapy regimen in the conventional treatment group (baseline haemoglobin A1c (HbA1c) level≥9.0%, <10.5%)

Order	Regimen
The first add-on	if FPG level≥120 mg/dL, metformin is increased to 2000 mg (1000 mg two times a day) and glimepiride is increased to 4 mg (2 mg two times a day)
The second add-on	if FPG level≥120 mg/dL, or HbA1c level≥6.5%, sitagliptin 100 mg/day is added
	*if FPG level<120 mg/dL, or HbA1c level<6.5% at each visit, the previous regimen is maintained. At any visit, if severe or recurrent hypoglycaemia, step down is possible based on physician's decision. At any visit, if patients have gastrointestinal discomfort probably due to metformin, dose reduction (to 500 mg as metformin) is possible based on physician's decision. If patients still intolerable to lower dose of metformin, it should be discontinued and recorded as adverse events.

FPG, fasting plasma glucose.

with metformin and/or sulfonylurea and/or sitagliptin in drug-naïve patients with type 2 diabetes. Therefore, we set the primary endpoint as the proportion of patients who achieved HbA1c level<6.5% without hypoglycaemia, weight gain or discontinuation due to AEs at 104 weeks. Weight gain is defined as gaining body weight≥5% of initial body weight.

Secondary endpoints

► Proportion of patients who achieved HbA1c level<6.5% without hypoglycaemia, weight gain or discontinuation due to AEs at 56 weeks.
► Time to reach target HbA1c level (<6.5%).
► Change in HbA1c level from baseline to week 56 and 104.
► Change in FPG from baseline to week 56 and 104.
► Proportion of patients who achieve HbA1c level<7.0% without hypoglycaemia, weight gain or discontinuation due to AEs at 56 and 104 weeks.
► Change in body weight from baseline to week 56 and 104.
► Change in systolic blood pressure from baseline to week 56 and 104.
► Changes in fat and lean mass at 56 and 104 weeks.

Safety

An AE is defined as any untoward medical occurrence (any unfavourable and unintended sign, symptom or disease) in a study participant. AEs of special interests are hypoglycaemia, gastrointestinal trouble, urinary tract infection, genital tract infection, volume depletion, pancreatitis, severe cutaneous events and hypersensitivity reactions. Any type of hypoglycaemia will be recorded at each visit. Each hypoglycaemic event will be defined based on the five criteria suggested by the American Diabetes Association (ADA) Workgroup on Hypoglycaemia: severe hypoglycaemia, documented symptomatic hypoglycaemia, asymptomatic hypoglycaemia, probable symptomatic hypoglycaemia and relative hypoglycaemia.[24] Among these, severe or confirmed hypoglycaemia will be applied to the adjudication of the primary outcome.

At each visit during the whole study period, any AEs will be recorded by investigators. The intensity of AEs will be judged as mild, moderate or severe according to the

frequency, duration and tolerability of the signs or symptoms. The medical judgement also will be used to determine the relationship considering all relevant factors.

STATISTICAL ANALYSES
Sample size calculation

The tolerability will be measured using a composite endpoint with no hypoglycaemia, no weight gain or discontinuation due to a safety concern. It is assumed that the initial triple combination therapy will show a total of at most 10% intolerability (5% for hypoglycaemia, 0% for weight gaining or 5% for discontinuation due to AEs), while the stepwise add-on therapy will show a total of at most 70% intolerability (20% for hypoglycaemia, 30% for weight gaining or 20% for discontinuation due to AEs). A total of 10 subjects per group provided 90% power to detect a difference of 60% tolerability decrease (90% vs 30%) for the initial triple combination therapy compared with the stepwise add-on therapy with a two-sided 5% level of significance.

To compare the efficacy of therapies, we assume that half of the subjects who are tolerable to the therapies will reach the target HbA1c level. A total of 46 subjects per group, then, are needed to provide 90% power in order to detect a 30% (45% vs 15%) increase in HbA1c target goal achievement rate of the initial triple combination therapy compared with the stepwise add-on therapy with a two-sided 5% level of significance based on normal approximation with unpooled variance.

Assuming that about 10% of subjects would be lost to follow-up during study periods, we aim to recruit 52 subjects per group (104 subjects in total) for this study.

Statistical methods and analysis

Statistical analyses will be performed in accordance with the study protocol. For data summaries, continuous variables will be summarised using the mean, SD, median, IQR (the first and third quartiles) and range (the minimum and maximum values). Categorical variables will be summarised using frequency counts and percentages. Data will be summarised by treatment group and overall.

The primary analysis population will be the full analysis set (FAS) and supportive analyses using the per-protocol

set (PPS) will also be performed. The primary efficacy endpoint, the proportion of subjects who achieve HbA1c level<6.5% without hypoglycaemia, weight gain or discontinuation due to AEs at 104 weeks, between the initial triple combination therapy and the conventional stepwise add-on therapy will be analysed using Pearson's X^2 test without imputing any missing values of HbA1c at 104 weeks. If any variable of the baseline characteristics differs between groups, a generalised estimating equation (GEE) analysis will be performed to adjust its difference.

For secondary variables, changes from the baseline will be compared between groups by Student's t-test using the difference of the values from baseline to week 56 and 104 for the FAS and PPS. Changes from baseline to week 56 and 104 through all visits will be analysed using GEE analysis for both FAS and PPS. The outcome variable will be the change from baseline. The proportion of patients who achieve HbA1c level<7.0% without hypoglycaemia, weight gain or discontinuation due to AEs at 56 and 104 weeks will be analysed using the same method as the primary efficacy analysis. Time to reach target HbA1c level (<6.5%) will be summarised using Kaplan-Meier survival curves for each group, and will be compared using log-rank test between groups. A multivariable analysis with Cox's proportional hazard regression model will also be performed, if necessary. Specifically, baseline covariates showing significant difference with $p<0.05$ as well as those discreetly chosen by clinical judgement will be adjusted as potential confounders in the multivariable model.

Statistical significance will be assessed based on two-sided 5% level of significance, and all statistical analyses will be performed using Statistical Analysis System (SAS) software, V.9.3 (SAS Institute).

Patient and public involvement

Patients and public were not actively involved in the research question and protocol development including outcome measures. The participants will be provided information of the final study results by the clinical research information service.

DISCUSSION

The study is designed to compare the effects of two different medication regimens on long-term glycaemic control in type 2 diabetes: metformin plus dapagliflozin plus saxagliptin versus metformin, followed by glimepiride, and sitagliptin. In addition, it also compares the efficacy of an early intensive therapy versus a conventional stepwise therapy.

Many clinical guidelines for the management of type 2 diabetes, including ADA/European Association for the Study of Diabetes guideline, and Korean Diabetes Association guideline recommend stepwise add-on therapy from a single agent (usually metformin) to a combination of second and third glucose-lowering agents.[10 11] It is based on large amount of evidence including numerous randomised controlled trials, and economic rationality.

However, for a long-term treatment period, most patients with type 2 diabetes have failed to sustain favourable glycaemic control with monotherapy, and even dual or triple combination therapy, eventually requiring insulin therapy. Remarkable advances in the understanding of the pathophysiology of type 2 diabetes and development of novel glucose-lowering agents have made it possible to apply a variety of therapeutic options to patients with type 2 diabetes. However, we still do not have any perfect strategy for the management of hyperglycaemia. It is regarded as mainly due to the progressive β-cell failure in the natural course of type 2 diabetes, and the absence of clear therapeutics preserving β-cell secretory function.[25–27] As mentioned above, the early intensive insulin therapy showed a potential to preserve β-cell function in a specific clinical setting. In drug-naïve patients with type 2 diabetes, early short-term intensive insulin therapy with continuous insulin infusion in a hospitalised setting induced long-term favourable glycaemic control, and this was associated with improvement of first-phase insulin secretion.[17] Similar results were reproduced in a large-scale randomised trial comparing the effects of transient intensive insulin therapy versus oral hypoglycaemic agents on long-term glycaemic control.[16] In that study, Homeostatic model assessment (HOMA)-β and acute insulin response also improved significantly after intensive insulin therapy, implying that intensive interventions that reduce glucotoxicity would be an effective strategy for long-term sustainable glycaemic control especially in an early phase of type 2 diabetes.

However, it is difficult to apply the same insulin regimen to all drug-naïve patients in a routine clinical setting although it ensures promising results. Insulin therapy, with multiple daily injections or continuous insulin infusion, has psychological and practical barriers to both patients and clinicians. In addition, hypoglycaemia or weight gain is inevitable with those regimens. Therefore, we need more practical and safe options for early intensive therapies, and this study will demonstrate the potential benefit of an early triple combination therapy in patients with type 2 diabetes. From the results of oral glucose tolerance test before and after the trial, we will be able to identify changes in the insulin secretory functions and insulin resistance after each treatment.

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