Two-Year Therapeutic Efficacy and Safety of Initial Triple Combination of Metformin, Sitagliptin, and Empagliflozin in Drug-Naïve Type 2 Diabetes Mellitus Patients

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Background: We investigated the long-term efficacy and safety of initial triple therapy using metformin, a dipeptidyl peptidase-4 inhibitor, and a sodium-glucose cotransporter-2 inhibitor, in patients with type 2 diabetes mellitus.

Methods: We enrolled 170 drug-naïve patients with glycosylated hemoglobin (HbA1c) level >7.5% who had started triple therapy (metformin, sitagliptin, and empagliflozin). Glycemic, metabolic, and urinary parameters were measured for 24 months.

Results: After 24 months, HbA1c level decreased significantly from 11.0%±1.8% to 7.0%±1.7%. At 12 and 24 months, the rates of achievement of the glycemic target goal (HbA1c <7.0%) were 72.5% and 61.7%, respectively, and homeostasis model assessment of β-cell function and insulin resistance indices improved. Whole-body fat percentage decreased by 1.08%, and whole-body muscle percentage increased by 0.97% after 24 months. Fatty liver indices and albuminuria improved significantly. The concentration of ketone bodies was elevated at the baseline but decreased after 24 months. There were no serious adverse events, including ketoacidosis.

Conclusion: Initial triple combination therapy with metformin, sitagliptin, and empagliflozin led to achievement of the glycemic target goal, which was maintained for 24 months without severe hypoglycemia but with improved metabolic function and albuminuria. This combination therapy may be a good strategy for drug-naïve patients with type 2 diabetes mellitus.

Keywords: Dipeptidyl-peptidase IV inhibitors; Glycated hemoglobin; Sodium-glucose transporter 2 inhibitors

INTRODUCTION

Landmark clinical trials in the management of type 2 diabetes mellitus (T2DM) have reported that intensive glycemic control reduces the risk of microvascular complications [1,2]. Other studies have reported that intensive glycemic control in the early period of diabetes leads to a significantly lower incidence of macrovascular complications [2,3]. Therefore, achievement of optimal glycemic control is an important aim in the management of T2DM. However, the current data indicate poor attainment of glycemic targets in clinical practice [4]. The traditional sequential treatment paradigm for T2DM, which comprises stepwise addition of antidiabetic agents to initial metformin therapy in response to increased glycosylated hemoglobin (HbA1c) level, is probably the major reason for delays in reaching the glycemic goal and the development of complications [5,6].

More active therapy that uses a combination of antidiabetic agents with complementary mechanisms of action, and that targets multiple physiological defects, is an alternative approach...
to T2DM treatment. The initial dual combination therapy in the early stages of T2DM has been reported to hasten the achievement of glycemic goals, to have a more durable effect, and to preserve β-cell function better than the sequential stepwise approach [7-9]. Compared with metformin monotherapy, initial combination therapy with dipeptidyl peptidase-4 (DPP4) inhibitors and metformin induced greater reductions in HbA1c and fasting glucose levels [10]. Combination therapy using metformin and a DPP4 inhibitor (vildagliptin) has been shown to have long-term benefits in drug-naïve patients with T2DM [11].

Given these findings, international consensus has recognized the need for combination therapy for glucose-lowering in patients with a high HbA1c level [12]. International and Korean clinical guidelines recommend combination therapy when the HbA1c level is >7.5% in the initial assessment [13,14]. However, there are limited data on whether the benefit-risk profile of initial combination therapy is superior to that of the traditional sequential treatment, and for which patients’ initial combination therapy is appropriate.

Few studies have focused on initial triple combination therapy. Abdul-Ghani et al. [15] reported that combination therapy comprising metformin, pioglitazone (a thiazolidinedione), and exenatide in patients with newly diagnosed T2DM was more effective and resulted in fewer hypoglycemic events than sequential add-on therapy comprising metformin, sulfonylurea, and basal insulin. Our group has reported that initial triple combination therapy comprising metformin, sitagliptin, and lobeeglitazone (a thiazolidinedione) resulted in a higher percentage of patients who achieved their target goal over conventional therapy and had fewer adverse events [16]. However, concern has arisen because thiazolidinedione and some DPP4 inhibitors may increase the risk of heart failure [17].

Sodium-glucose cotransporter-2 (SGLT2) inhibitors, a novel class of antidiabetic medication, were introduced in 2010. A randomized controlled trial reported that combination therapy comprising sitagliptin and ertugliflozin (an SGLT2 inhibitor) reduced HbA1c level, body weight, and blood pressure more than the individual agents [18]. In our pilot study, the initial combination of metformin, sitagliptin, and empagliflozin significantly reduced glucose level and did not induce adverse events in drug-naïve Korean patients with T2DM and with an HbA1c level >9% [19]. However, there are limited long-term different using different drug classes in drug-naïve patients [20]. Because of the complementary mechanism of action, investigation of initial triple combination therapy with these new drug classes would be informative. The aim of the present study was to evaluate the efficacy and safety of an initial triple regimen with metformin, sitagliptin, and empagliflozin in patients with T2DM.

**METHODS**

**Study design**

This study was a prospective, observational study and was approved by an independent ethics committee/Institutional Review Board (B-2008/630-104). Written informed consent was acquired from the participants before data collection. Study participants were selected from drug-naïve patients with new-onset T2DM who visited the diabetes clinic at Seoul National University Bundang Hospital from 2017 to 2021 and who met the following criteria: (1) age ≥20 years; (2) HbA1c ≥7.5% at diagnosis; (3) drug-naïve for ≥6 months before enrollment; (4) absence of severe hyperglycemic symptoms; and (5) not pregnant. Patients with severe hyperglycemic symptoms who required insulin therapy were excluded.

Participants started the initial combination therapy of metformin 1,000 mg/day, sitagliptin 100 mg/day, and empagliflozin 10 mg/day at the baseline and were followed for 2 years. Patients were hospitalized for close observation if they consented. The patients visited the clinic at 2, 5, 9, and 12 months in the first year and at 16, 20, and 24 months in the second year. Anthropometric and biochemical variables were measured at every visit.

For patients with an HbA1c level exceeding 8.0% in the initial 6 months, the metformin dosage could be augmented by 25% to 50%, and the empagliflozin dosage could be escalated by 25 mg, subject to the physician’s discretion. The dose of empagliflozin was guided to be maintained at 10 mg throughout the study period, because previous studies reported that no significant difference in the glucose-lowering efficacy of empagliflozin between 10 and 25 mg [21,22]. If the HbA1c level did not achieve the desired glycemic target (<7.0%), the initial triple therapy was sustained. For those patients who met their glycemic goals at the 12-month visit, the medication regimen was either reduced to two agents (reduced group) or remained unchanged (maintained group) based on the physician’s judgment. In instances where patients experienced a temporary rise in glucose levels for any reason during the study, short-term insulin administration was recommended for safety considerations. Upon verification of achieving the glycemic target
at 12 months, either empagliflozin or sitagliptin was discontin-
ued, with the decision based on the patient's body weight and
the physician's assessment.

Anthropometric and biochemical parameters
At every visit, the efficacy indicators (HbA1c, fasting plasma
glucose, postload 2-hour glucose, and fasting insulin levels),
body composition (body weight, muscle mass, and fat mass),
ketone body levels (β-hydroxybutyrate and acetoacetate), pro-
teinuria (urinary protein/creatinine and urinary albumin/cre-
tinine ratios), organ function, and uric acid level were mea-
sured using standard methods.

Height and body weight were measured using standard
methods with the participant in light clothing. Body mass index
(BMI) was calculated by dividing the participant's weight (kg)
by height squared (m²). Waist circumference (WC) was mea-
sured at the umbilical level. Systolic and diastolic blood pressure
were measured with the participant in a seated position using
an electronic blood pressure meter (UA-1020 device, A&D, To-
kyo, Japan). Blood pressure was measured twice, 5 minutes
apart, and the mean value was used in the analysis.

Plasma glucose concentration was measured using the glu-
cose oxidase method (747 Clinical Chemistry Analyzer, Hitac-
hi, Tokyo, Japan). HbA1c level was measured using a Variant
II Turbo HPLC Analyzer (Bio-Rad, Hercules, CA, USA) in a
National Glycohemoglobin Standardization Program level II-
certified laboratory. Fasting plasma C-peptide and insulin levels
were measured by radioimmunoassay (Linco, St. Louis, MO,
USA).

Serum aspartate aminotransferase (AST), alanine amino-
transferase (ALT), and creatinine levels were measured using
an Architect Ci8200 analyzer (Abbott Laboratories, Abbott
Park, IL, USA). The estimated glomerular filtration rate (eGFR)
was calculated using the creatinine-based Chronic Kidney Dis-
ease Epidemiology Collaboration equation (CKD-EPI). Serum
free fatty acid, total cholesterol, triglyceride, high-density lipo-
protein cholesterol (HDL-C), and low-density lipoprotein
cholesterol (LDL-C) levels were measured using a 747 Clinical
Chemistry Analyzer (Hitachi). Urinary albumin concentration
was measured using turbidimetry (502X, A&T, Tokyo, Japan),
and urinary creatinine was measured using the Jaffe method
(Hitachi 7170, Hitachi). The ratio of urinary protein or albumin
to creatinine concentration (mg/g) was used to identify protein-
uria and albuminuria, respectively. To estimate pancreatic β-cell
function and insulin resistance, the homeostasis model assess-
ment of insulin resistance (HOMA-IR) and β-cell function
(HOMA-β) indices were calculated [23].

The nonalcoholic fatty liver disease (NAFLD) liver fat score
was calculated using the following equation: 1.18×metabolic
syndrome+0.45×diabetes (2, if yes; 0, if no)+0.15×fasting in-
sulin (μIU/L)+0.04×AST (IU/L)−0.94×(AST/ALT)−2.89 [24].
Metabolic syndrome was defined according to National Chole-
sterol Education Program Adult Treatment Panel III guide-
line [25] using ethnic-specific cutoff values for WC [26].

Safety parameters were assessed including the adverse events
gastrointestinal discomfort, urinary tract infection, genital
infection, ketoacidosis, and hypoglycemia. Hypoglycemic
events were recorded based on the patients’ hypoglycemic
symptoms and self-monitored plasma glucose level <70 mg/dL
(3.9 mmol/L).

Statistical analysis
All patients who were enrolled in the analysis completed at
least one follow-up. Patients who were lost to follow-up were
considered as censored data. All available data were included
in the analysis. The summary statistics are shown as mean with
standard deviation. All indicators were compared between the
baseline and after treatment using the paired t-test. Data with
wide variation were analyzed after log transformation and in-
cluded ketone body levels, urinary protein/creatinine ratio,
and urinary albumin/creatinine ratio. Subgroup analysis was
performed in patients grouped according to the change in
drug regimen after 12 months and at the end of the observation
period. The changes in outcomes over time within each
group were analyzed using analysis of variance (ANOVA) and
the post hoc Duncan test. All data analysis was performed us-
ing R software version 4.1.3 (The R Foundation for Statistical
Computing, Vienna, Austria).

RESULTS
Baseline characteristics of study participants
The baseline characteristics of the study participants are shown
in Table 1. The 170 study participants (age 51.0±13.1 years) in-
cluded 67.6% men (n=115, age 49.2±12.7 years) and 32.4%
women (n=55, age 54.6±13.2 years). The baseline HbA1c lev-
els did not differ between men and women (11.0%±1.9% and
11.1%±1.6%, respectively). The baseline total ketone body
levels were elevated across the broad range of 25.0 to 9,150.0
μmol/L. The total ketone body levels were higher in patients

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with baseline HbA1c > 10.0% (n = 78) than in those with baseline HbA1c ≤ 10.0% (n = 34) (757.9 ± 1,510.0 μmol/L vs. 244.7 ± 317.1 μmol/L, P < 0.05). Of the 170 patients in the study, there were 50 (29.4%) patients with hypertension, 48 (28.2%) patients with dyslipidemia, three (1.8%) patients with coronary artery disease, and six (3.5%) patients with stroke. A total of 82 (48.2%) patients hospitalized in the beginning and 112 (65.9%) patients finished the last visit.

**Changes in parameters related to glycemic regulation**

The HbA1c levels at the baseline and at 2, 5, 9, 12, 16, 20, and 24 months are shown in Fig. 1A. Two patients received insulin
therapy due to an increase in glucose concentrations temporarily. The high baseline HbA1c level decreased significantly from 11.0%±1.8% to 7.9%±1.7% (P<0.05) at 2 months, and to 6.7%±1.5% at 5 months, and it remained lower at 7.0%±1.7% at 24 months (P<0.05). The rates of achievement of the HbA1c target <7.0% were 72.5% at 12 months and 61.7% at 24 months (Supplementary Fig. 1). For the stricter HbA1c target <6.5%, the rates of target goal achievement were 61.8% at 12 months and 51.1% at 24 months.

Similarly, both the fasting plasma and postload 2-hour glucose concentrations decreased significantly (P<0.05). The fasting plasma glucose concentration decreased by 101.4 mg/dL, from 235.7±78.5 mg/dL at the baseline to 133.6±48.1 mg/dL at 24 months (Fig. 1B). The postload 2-hour glucose concentration also decreased by 181.8 mg/dL, from 394.8±114.1 mg/dL at the baseline to 196.9±83.2 mg/dL at 24 months (Fig. 1C).

**Changes in insulin resistance and β-cell function**
The initial triple therapy decreased the fasting insulin level significantly from 9.0±4.6 μIU/mL at the baseline to 8.1±4.5 μIU/mL at 2 months and remained stable thereafter (Fig. 1D). The HOMA-IR indices also decreased from 2 months and were maintained to the end of the study (Fig. 1E). The HOMA-β indices increased sequentially until 5 months and remained stable at the level of 56.6%±42.9% from 9 months (Fig. 1F). These changes indicate improved β-cell function.

Fig. 1. Parameters related to glycemic control over the 24 months. Values are presented as mean±standard deviation. (A) Glycosylated hemoglobin (HbA1c) level. (B) Fasting plasma glucose concentration. (C) Postload 2-hour glucose levels. (D) Fasting insulin levels. (E) Homeostasis model assessment of insulin resistance (HOMA-IR). (F) Homeostasis model assessment of β-cell function (HOMA-β). *P<0.05: paired t-test between the baseline and after treatment.
Changes in body weight, body mass index, and body composition

Body weight and BMI did not change significantly (Fig. 2A and B), but body composition changed significantly after the triple therapy (Fig. 2C and D). Whole-body fat percentage decreased significantly by 1.08% from 30.0±8.1% at the baseline to 27.6±7.6% at 24 months (Fig. 2D). Whole-body muscle percentage showed the opposite trend and increased significantly by 0.97% from 66.1±7.7% at the baseline to 68.3±7.2% at 24 months.

Changes in ketone body and glucagon levels

The initial triple therapy with metformin, sitagliptin, and empagliflozin decreased ketone body levels (Fig. 3A-C). The total ketone body concentration was elevated at the baseline and decreased significantly from 602.1±1,291.4 μmol/L to 174.0±189.4 μmol/L at 24 months (Fig. 3A). Similarly, the levels of β-hydroxybutyrate and acetoacetate also decreased significantly after 24 months (Fig. 3B and C).

We analyzed the data further according to the median ketone body concentration: ≥200 μmol/L and <200 μmol/L (Supplementary Fig. 3). The ketone body concentration in patients with high initial total ketone body level (≥200 μmol/L) decreased substantially by 847 μmol/L, from 1,078±1,683 μmol/L at the baseline to 231±247 μmol/L at 24 months (Supplementary Fig. 3A). However, the ketone body concentration did not change significantly in those with an initial baseline level <200 μmol/L (Supplementary Fig. 3D). Glucagon concentration remained stable except for slight increases at 12 and 16 months (Fig. 3D).

Changes in renal function

The changes in renal function indicators creatinine concentrations, eGFR-CKD-EPI, and urinary protein/creatinine and albumin/creatinine ratios are shown in Fig. 4A-C. The eGFR-CKD-EPI decreased slightly but significantly by 2.3 mL/min/1.73 m² (Fig. 4B). It is noteworthy that both the urinary pro-
tein/creatinine and albumin/creatinine ratios decreased significantly from the baseline to 24 months (Fig. 4C).

**Changes in liver function**

The AST level decreased from 33.4±27.1 IU/L at the baseline to 27.8±12.8 IU/L at 2 months and was maintained for 24 months (Fig. 4D). The ALT level decreased significantly until 16 months; at 24 months, the decrease in ALT level was nearly maintained, but the level did not differ significantly from the baseline value (Fig. 4E). The NAFLD fatty liver score decreased significantly after 24 months from 79.3% at the baseline to 58.1% at 12 months and 66.2% at 24 months (P<0.05 for each comparison) (Fig. 4F).

**Safety**

In this study, 27 adverse events were reported in 170 subjects (16%). The most frequent adverse events were urinary tract genital infection and hepatic enzyme elevation (n=4 each) (Supplementary Table 1). Three patients experienced a hypoglycemic event in this study. No patients experienced severe hypoglycemia or nocturnal hypoglycemia. No other serious adverse events were observed during the study period.

**Subgroup analysis**

A total of 112 patients of the 170 were followed for 24 months; 37 received metformin and empagliflozin, 26 received metformin and sitagliptin, and 49 continued the triple therapy. The baseline characteristics did not differ between these three groups,
except for body weight and BMI, which were significantly lower in the metformin and sitagliptin group than in the other groups (Supplementary Table 2).

Changes in the clinical and biochemical parameters in these three groups are shown in Supplementary Fig. 4. In all groups, the reduced HbA1c levels were maintained for 24 months (Supplementary Fig. 4A). Body weight increased after empagliflozin discontinuation and led to greater changes in body weight in the metformin and sitagliptin group than in the other two groups (Supplementary Fig. 4B). The eGFR-CKD-EPI levels were maintained in the patients who continued empagliflozin administration compared to those with metformin and sitagliptin alone (Supplementary Fig. 4D).

DISCUSSION

In the drug-naïve patients with decompensated T2DM, initial triple therapy using metformin, sitagliptin, and empagliflozin resulted in sustained, rapid, and satisfactory glucose control without severe adverse events. With this initial triple therapy, the HbA1c level decreased from 11.0%±1.8% at the baseline to 7.0%±1.7% at 24 months. Fasting plasma glucose levels also decreased significantly at 2 months. These glycemic benefits were maintained for 24 months and are linked to favorable changes in the surrogate markers for insulin resistance and β-cell function as reported [27].

Over 70% of patients who were treated with sulfonylurea or insulin eventually failed to achieve the target HbA1c level.
Efficacy of triple therapy for type 2 diabetes mellitus

The initial triple therapy appeared to offer the renal protection effects of an SGLT2 inhibitor. For example, the eGFR-CKD-EPI and urinary protein/creatinine and albumin/creatinine ratios remained stable for 24 months. eGFR-CKD-EPI declines at a rate of 1.4 mL/min/1.73 m²/year among people without diabetes, at 1.8 mL/min/1.73 m²/year in those with undiagnosed diabetes, and at 2.5 mL/min/1.73 m²/year in those with diagnosed diabetes [35]. In our study, eGFR-CKD-EPI decreased by 2.32 mL/min/1.73 m² over the 24 months of the initial triple therapy, which is slightly lower than the rate in people without diabetes.

A range of liver diseases often accompany T2DM [36]. Insulin resistance is thought to be a common pathophysiological mechanism of both T2DM and NAFLD [37]. In a previous report [38], initial triple therapy reduced the concentrations of hepatic function markers AST and ALT within the normal range up to 5 months. Improvements in fatty liver markers were reported by a study of an SGLT2 inhibitor [38], a finding that may relate to reductions in both liver and abdominal fat.

The triple therapy showed beneficial effects on liver fat stores [39]. The principle behind the initial triple therapy management of NAFLD involves an indirect effect through improvements in insulin resistance and glycemia, and it may also relate to the treatment of T2DM [40].

The initial triple therapy was well tolerated, and no patient withdrew because of adverse events. The rate of hypoglycemia was lower than in other studies [41]. No serious adverse events, such as hypoglycemia, genitourinary infection, ketoacidosis, or retinopathy progression, were observed during the 24-month study period.

Reducing the number of medications in diabetes management is a major concern from both the remission and drug-related side effects perspectives [42]. It was reported that 12 weeks of treatment with metformin, dapagliflozin, and insulin triple therapy was not long enough to justify stopping the medication because HbA1c level rebounded in >50% of the patients [43]. However, it should be noted that they involved patients who had already been diagnosed with diabetes for an average of 3 years and were mostly taking glucose-lowering medications at the start of the study. In contrast, in our study, the reduced HbA1c level was well maintained after omitting either an SGLT2 inhibitor or a DPP4 inhibitor after good glycemic control for 12 months with initial triple therapy (Supplementary Fig. 4). Further long-term and well-designed studies are needed to support this idea.

This study has limitations. First, this was a single-arm study...
that did not allow comparison with different regimens. Second, the power of the subgroup analyses may have been limited because the study was not designed primarily to investigate differences according to the changes in regimens.

In conclusion, the initial combination therapy of metformin, sitagliptin, and empagliflozin for drug-naïve patients with T2DM with a high HbA1c level decreased glucose level rapidly and markedly without inducing clinically significant adverse events. It is noteworthy that the improved glycemic regulation lasted up to 24 months without any rebound in HbA1c level. Further benefits such as improved insulin sensitivity, β-cell function, body composition, and metabolic profile including blood lipid levels, liver enzymes, and renal protection were also identified. These findings suggest that initial triple combination therapy targeting different pathophysiological abnormalities in T2DM is a viable option for inducing normoglycemia rapidly and safely in patients with T2DM and high HbA1c level.

SUPPLEMENTARY MATERIALS

Supplementary materials related to this article can be found online at https://doi.org/10.4093/dmj.2023.0128.

CONFLICTS OF INTEREST

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

AUTHOR CONTRIBUTIONS

Conception or design: S.L.
Acquisition, analysis, or interpretation of data: Y.H.P., M.S., S.Y.L., S.L.
Drafting the work or revising: Y.H.P., M.S., S.Y.L.
Final approval of the manuscript: Y.H.P., M.S., S.Y.L., S.L.

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None

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11. Matthews DR, Paldanius PM, Proot P, Chiang Y, Stumvoll M,
### Supplementary Table 1. Adverse events

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Patients (n=170)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urogenital tract infection</td>
<td>4 (2.4)</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>3 (1.8)</td>
</tr>
<tr>
<td>Liver enzyme elevation</td>
<td>4 (2.4)</td>
</tr>
<tr>
<td>Gastrointestinal discomfort</td>
<td>3 (1.8)</td>
</tr>
<tr>
<td>Skin disease</td>
<td>2 (1.2)</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>2 (1.2)</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>2 (1.2)</td>
</tr>
<tr>
<td>Sleep disorder</td>
<td>2 (1.2)</td>
</tr>
<tr>
<td>Headache</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>Others</td>
<td>3 (1.8)</td>
</tr>
</tbody>
</table>

Values are presented as number (%). Patients may be counted more than one.
**Supplementary Table 2.** Baseline characteristics of patients according to the regimen changed at 12 months

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Metformin+Empagliflozin ((n=37))</th>
<th>Metformin+Sitagliptin ((n=26))</th>
<th>Triple maintained ((n=49)^a)</th>
<th>(P) value(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight, kg</td>
<td>80.0±13.1</td>
<td>65.6±14.6</td>
<td>74.1±17.2</td>
<td>0.002</td>
</tr>
<tr>
<td>Body mass index, kg/m(^2)</td>
<td>27.4±3.7</td>
<td>23.3±4.2</td>
<td>26.3±4.5</td>
<td>0.001</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>131.2±10.9</td>
<td>128.1±15.0</td>
<td>133.5±16.6</td>
<td>0.358</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>80.2±8.5</td>
<td>77.3±12.3</td>
<td>80.9±11.4</td>
<td>0.427</td>
</tr>
<tr>
<td>HbA1c, %</td>
<td>10.6±1.4</td>
<td>11.4±1.9</td>
<td>11.0±1.8</td>
<td>0.161</td>
</tr>
<tr>
<td>Fasting glucose, mg/dL</td>
<td>221.4±82.5</td>
<td>232.3±70.4</td>
<td>240.7±82.6</td>
<td>0.543</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>190.4±48.8</td>
<td>190.2±43.9</td>
<td>202.9±66.9</td>
<td>0.512</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>151.5±69.9</td>
<td>149.2±108.5</td>
<td>203.0±221.0</td>
<td>0.240</td>
</tr>
<tr>
<td>HDL-C, mg/dL</td>
<td>44.4±8.3</td>
<td>51.8±15.3</td>
<td>50.3±12.6</td>
<td>0.033</td>
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<tr>
<td>LDL-C, mg/dL</td>
<td>116.0±36.1</td>
<td>115.5±33.9</td>
<td>123.3±46.7</td>
<td>0.636</td>
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<tr>
<td>Total ketone, μmol/L</td>
<td>623.1±1,251.8</td>
<td>458.7±663.9</td>
<td>662.9±1,657.0</td>
<td>0.836</td>
</tr>
<tr>
<td>Serum creatinine, mg/dL</td>
<td>0.82±0.17</td>
<td>0.76±0.21</td>
<td>0.78±0.20</td>
<td>0.448</td>
</tr>
<tr>
<td>eGFR-CKD-EPI, mL/min/1.73 m(^2)</td>
<td>100.0±16.7</td>
<td>99.5±13.9</td>
<td>100.2±18.5</td>
<td>0.985</td>
</tr>
<tr>
<td>Urinary protein/Cr ratio, mg/g</td>
<td>140.1±188.6</td>
<td>167.9±128.4</td>
<td>393.5±1,552.6</td>
<td>0.482</td>
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<tr>
<td>Uric acid, mg/dL</td>
<td>5.2±1.5</td>
<td>4.4±1.3</td>
<td>4.5±1.6</td>
<td>0.060</td>
</tr>
<tr>
<td>AST, IU/L</td>
<td>34.4±15.8</td>
<td>29.2±13.7</td>
<td>34.7±34.5</td>
<td>0.644</td>
</tr>
<tr>
<td>ALT, IU/L</td>
<td>46.8±27.6</td>
<td>31.8±24.2</td>
<td>41.7±46.3</td>
<td>0.276</td>
</tr>
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</table>

Values are presented as mean±standard deviation.
HbA1c, glycosylated hemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; eGFR-CKD-EPI, estimated glomerular filtration rate by Chronic Kidney Disease Epidemiology Collaboration equation; Cr, creatinine; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

\(^a\)Triple: continuing metformin, sitagliptin, and Empagliflozin, \(^b\)\(P\) values assessed by analysis of variance (ANOVA).
Supplementary Fig. 1. Glycemic target goal achievement and glycosylated hemoglobin (HbA1c) distribution at 0, 12, and 24 months. (A) Glycemic target goal achievement rates at 0, 2, 5, 12, and 24 months. (B) HbA1c distribution at 0 month. (C) HbA1c distribution at 12 months. (D) HbA1c distribution at 24 months.
Supplementary Fig. 2. Trends in the concentrations of ketone bodies according to the baseline glycosylated hemoglobin (HbA1c) of >10.0% (A) total ketone, (B) β-hydroxybutyrate, (C) acetoacetate; and of ≤10.0%, (D) total ketone, (E) β-hydroxybutyrate, (F) acetoacetate. Values are presented as mean±standard deviation. Logarithmically transformed values were used for comparisons of concentrations of fasting glucagon, total ketone bodies, β-hydroxybutyrate, and acetoacetate. *P<0.05: paired t-test between the baseline and after treatment.
Supplementary Fig. 3. Trends in the levels of ketone bodies with baseline total ketone levels set at ≥200 μmol/L (A) total ketone, (B) β-hydroxybutyrate, (C) acetoacetate; and at <200 μmol/L, (D) total ketone, (E) β-hydroxybutyrate, (F) acetoacetate. Values are presented as mean ± standard deviation. Logarithmically transformed values were used for comparisons of fasting glucagon, total ketone, β-hydroxybutyrate, and acetoacetate. *P < 0.05: paired t-test between the baseline and after treatment.
Supplementary Fig. 4. Changes from 12-month values in key clinical parameters for the different regimens during the 24 months of the study. Values are presented as mean±standard error. Regimens used after 12 months: (A) glycosylated hemoglobin (HbA1c), (B) body weight, (C) body mass index (BMI), (D) estimated glomerular filtration rate by Chronic Kidney Disease Epidemiology Collaboration equation (eGFR-CKD-EPI), (E) alanine transaminase (ALT), and (F) total cholesterol. MTF+EMPA, metformin with empagliflozin; MTF+SITA, metformin with sitagliptin; Triple, continuing metformin, sitagliptin, and empagliflozin. *P<0.05 vs. the extent of changes between the groups (analysis of variance [ANOVA] and post hoc Duncan test).