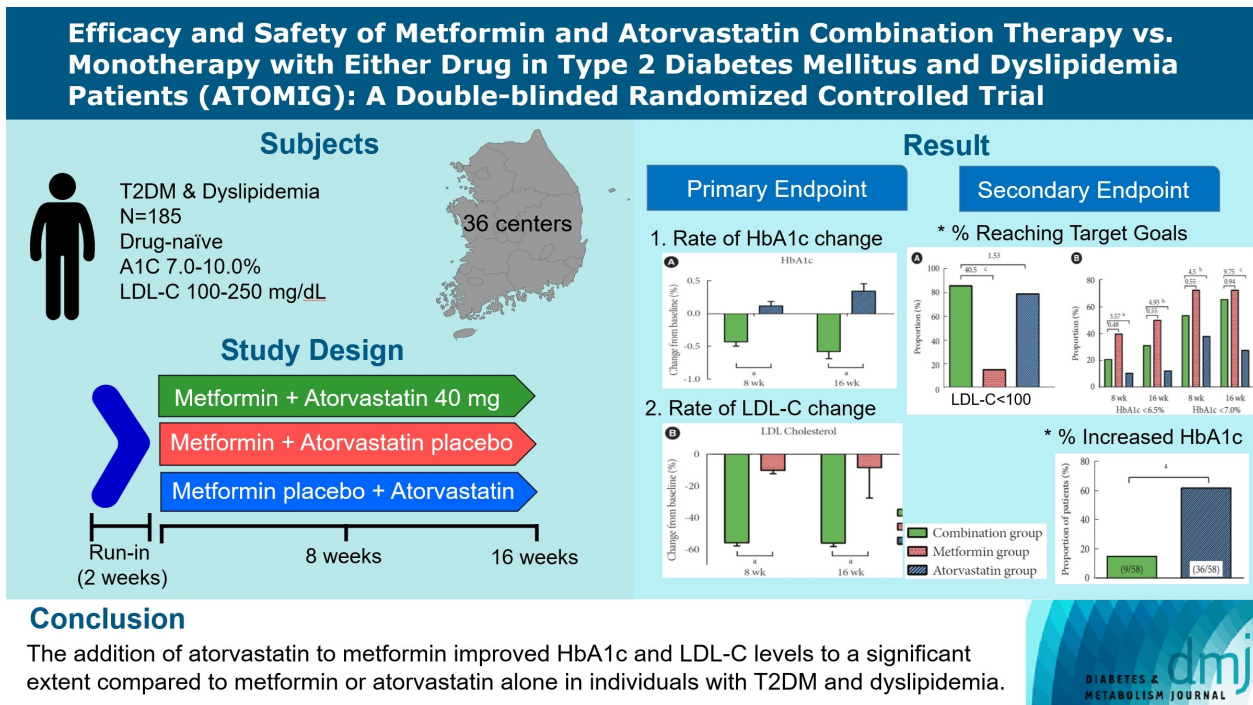


# Efficacy and Safety of Metformin and Atorvastatin Combination Therapy vs. Monotherapy with Either Drug in Type 2 Diabetes Mellitus and Dyslipidemia Patients (ATOMIG): Double-Blinded Randomized Controlled Trial

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Diabetes Metab J Published online May 20, 2024 | <https://doi.org/10.4093/dmj.2023.0077>



## Highlights

- This study evaluated efficacy of metformin and atorvastatin in T2DM and dyslipidemia.
- It was a randomized, double-blind, place-controlled, parallel-group, phase 3 study.
- HbA1c showed significant difference in combination vs. atorvastatin.
- The combination group showed significant LDL-C decrease vs. metformin.
- This study demonstrated metformin mitigates glucose elevation on atorvastatin.

## How to cite this article:

Lee JE, Yu SH, Kim SR, Ahn KJ, Song KH, Lee IK, et al. Efficacy and Safety of Metformin and Atorvastatin Combination Therapy vs. Monotherapy with Either Drug in Type 2 Diabetes Mellitus and Dyslipidemia Patients (ATOMIG): Double-Blinded Randomized Controlled Trial. Diabetes Metab J. Published online May 20, 2024. <https://doi.org/10.4093/dmj.2023.0077>



# Efficacy and Safety of Metformin and Atorvastatin Combination Therapy vs. Monotherapy with Either Drug in Type 2 Diabetes Mellitus and Dyslipidemia Patients (ATOMIC): Double-Blinded Randomized Controlled Trial

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**Background:** It is well known that a large number of patients with diabetes also have dyslipidemia, which significantly increases the risk of cardiovascular disease (CVD). This study aimed to evaluate the efficacy and safety of combination drugs consisting of metformin and atorvastatin, widely used as therapeutic agents for diabetes and dyslipidemia.

**Methods:** This randomized, double-blind, placebo-controlled, parallel-group and phase III multicenter study included adults with glycosylated hemoglobin (HbA1c) levels  $>7.0\%$  and  $<10.0\%$ , low-density lipoprotein cholesterol (LDL-C)  $>100$  and  $<250$  mg/dL. One hundred eighty-five eligible subjects were randomized to the combination group (metformin+atorvastatin), metformin group (metformin+atorvastatin placebo), and atorvastatin group (atorvastatin+metformin placebo). The primary efficacy endpoints were the percent changes in HbA1c and LDL-C levels from baseline at the end of the treatment.

**Results:** After 16 weeks of treatment compared to baseline, HbA1c showed a significant difference of 0.94% compared to the atorvastatin group in the combination group (0.35% vs.  $-0.58\%$ , respectively;  $P<0.0001$ ), whereas the proportion of patients with increased HbA1c was also 62% and 15%, respectively, showing a significant difference ( $P<0.001$ ). The combination group also showed a significant decrease in LDL-C levels compared to the metformin group ( $-55.20\%$  vs.  $-7.69\%$ ,  $P<0.001$ ) without previously unknown adverse drug events.

**Conclusion:** The addition of atorvastatin to metformin improved HbA1c and LDL-C levels to a significant extent compared to metformin or atorvastatin alone in diabetes and dyslipidemia patients. This study also suggested metformin's preventive effect on the glucose-elevating potential of atorvastatin in patients with type 2 diabetes mellitus and dyslipidemia, insufficiently controlled with exercise and diet. Metformin and atorvastatin combination might be an effective treatment in reducing the CVD risk in patients with both diabetes and dyslipidemia because of its lowering effect on LDL-C and glucose.

**Keywords:** Atorvastatin; Diabetes mellitus; Dyslipidemias; Metformin

## INTRODUCTION

Diabetes is a leading cause of mortality and reduced life expectancy. Additionally, it is also one of the largest global public health concerns, imposing a heavy global burden on public health as well as socio-economic development [1]. To date, the International Diabetes Federation estimated that 463 million adults live with diabetes worldwide in 2019 with a projected 51% increase to 700 million by 2045 [2]. Cardiovascular disease (CVD) is the common cause of morbidity and mortality in patients with diabetes [3] and one of the major contributors to the increase in diabetes-associated cardiovascular (CV) risk is atherogenic dyslipidemia [4,5]. The lipid profile of patients with atherogenic dyslipidemia is characterized by high triglycerides (TGs), low high-density lipoprotein cholesterol, and mildly elevated or normal low-density lipoprotein cholesterol (LDL-C) levels in diabetes. Insulin resistance has been identified as the main factor for the development of atherogenic dyslipidemia. Moreover, several reports have been published on the characteristic changes of atherogenic dyslipidemia even in the pre-diabetic stage [6,7]. Hence, it is very important to manage it from the early stage of diabetes.

Metformin, an antidiabetic drug belonging to the biguanide family, acts to lower fasting blood glucose mainly by reducing the glucose released from the liver. As per the diabetes treat-

ment guidelines published in the world, metformin is recommended as the first-line drug along with lifestyle modification from the initial stage of the diagnosis of diabetes. It has been used to treat diabetes for over 40 years and has been proven to be safe and effective, making it one of the most widely prescribed drugs.

Atorvastatin, a 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) inhibitor, is also one of the most widely used drugs in the world because of its high lipid-lowering efficacy. Especially in Asians, it has the advantage of reaching the target LDL-C even with a relatively low dose [8].

As per the data presented by the Korean Diabetes Association in 2020, about 70% of diabetic patients over 30 years of age have dyslipidemia [9]. Considering their effect on CV risk, it is easy to predict that patients with diabetes will need to take atorvastatin in addition to metformin with high frequency. It is necessary to take drugs for both diseases when blood glucose and lipid levels cannot be controlled with a single drug, the administration of more than two drugs is required. However, taking multiple medications causes inconvenience to the patients. Therefore, it is necessary to develop a combination drug therapy for treating type 2 diabetes mellitus (T2DM) and dyslipidemia, which could improve patient compliance and provide economic benefit to patients by reducing medical costs.

We conducted this phase III clinical trial to evaluate the safety

and efficacy of the combination drug consisting of metformin and atorvastatin. In patients with both diseases, these drugs are widely used as therapeutic agents for T2DM and dyslipidemia, respectively.

## METHODS

### Study design and procedures

This was a multicentric, randomized, double-blinded, placebo-controlled, parallel-group phase III study. It was conducted at 36 centers throughout Korea between August 25, 2015, and February 27, 2017. Patients with T2DM and dyslipidemia, aged 19 to 80 years, were screened at the first visit. Eligible participants were drug-naïve for a specified period (oral hypoglycemic agents for 6 weeks and anti-dyslipidemic agents for 4 weeks [8 weeks for fenofibrates]) and had inadequately controlled T2DM (glycosylated hemoglobin [HbA1c] 7.0% to 10.0%) and dyslipidemia (LDL-C 100 to 250 mg/dL) at screening and baseline visits (Supplementary Table 1).

Participants eligible at the screening visit underwent a 4-week run-in period with a metformin 500 mg extended-release tablet (placebo) once a day. During this period, only those participants with over 70% adherence to medication were enrolled. The final screening test performed at the baseline visit was sent to the central laboratory. Final eligible patients were randomly assigned to one of the following three groups: combination group (metformin+atorvastatin 40 mg), metformin group (metformin+atorvastatin placebo), and atorvastatin group (atorvastatin 40 mg+metformin placebo), then spent 2 weeks for titration of metformin and placebo. During this titration, enrolled participants were instructed to take the investigational drugs (week 1: 2 tablets; week 2: 3 tablets) corresponding to the randomized group once a day with dinner. After the titration period, all participants were directed to take four tablets of the investigational drugs matching each randomized group once a day with dinner for 14 weeks. Participants visited the hospital seven times, including the baseline visit. Additionally, the medical examination and blood sampling were done at each visit as specified in the protocol. This study's protocol is available in Supplementary Fig. 1.

### Study subjects

Of the 318 screened participants, 185 entered the run-in period. They were randomized to the combination, metformin, and atorvastatin groups, including 63, 63, and 59, participants

respectively. All the randomized participants received the investigational drug. Except for 11 participants who violated selection/exclusion criteria and missing results for primary efficacy evaluation, a total of 174 participants, 58 in the combination, metformin, and atorvastatin groups each, were analyzed (Fig. 1).

### Study endpoints

The primary efficacy endpoints were the superiority of the combination group compared to the metformin group for rate of LDL-C change and the atorvastatin group for rate of HbA1c change. The secondary efficacy endpoints included the rate of changes in LDL-C and HbA1c levels of the atorvastatin group and metformin group, respectively, compared to the combination group from baseline to the end of the treatment. The percentage of participants reaching the treatment goal (LDL-C <100 mg/dL, HbA1c <7.0% and 6.5%) after 16 weeks of treatment with the investigational drug were also analyzed. In addition to physical examinations, safety was assessed by monitoring adverse events (AEs), laboratory parameters, electrocardiograms, and vital signs.

### Statistical analyses

The sample size to demonstrate the superiority of the combination group versus the metformin or atorvastatin groups with regards to mean change in HbA1c levels and percent change in LDL-C concentrations was determined using a significance level of 2.5% and a one-sided test. The planned enrolment was of 60 patients per group (total 180), which provided 90% power to detect a mean difference of 0.73% in the HbA1c levels between the combination and atorvastatin groups, assuming common standard deviations (SDs) of 1.1%. This calculation was based on the assumption of a 20% drop-out rate.

Continuous variables were presented as mean  $\pm$  SD if normally distributed, or as median (interquartile range) if not normally distributed. One-way analysis of variance (ANOVA) and paired *t*-tests were used to analyze normally distributed continuous variables. The Kruskal-Wallis test and Wilcoxon signed-rank test were used to analyze non-normally distributed continuous variables. Differences in baseline characteristics between combination groups were analyzed using one-way ANOVA, the Kruskal-Wallis test, Pearson's chi-square test, and Fisher's exact test. Analysis of covariance (ANCOVA) with baseline values as covariates was used to compare changes in variables from baseline to week 24 between treatment groups. Least

square means were calculated using ANCOVA with baseline values as covariates. Safety analyses were performed in the safety set population who received at least one dose of a double-blind study drug and underwent at least one safety assessment after randomization. The chi-square test was used to compare the incidence of AEs among the three groups. Statistical data analyses were performed using SAS version 9.3.1 software (SAS Institute Inc., Cary, NC, USA).

### Ethical approval and consent to participate

All procedures involving human participants performed in this study were as per the ethical standards of the relevant institutional and/or national research committees and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study protocol (ClinicalTrials.gov, NCT02947620) was approved by the independent Institu-

tional Review Boards (IRB No. SMC 2015-04-017-002) of each participating center before patient enrolment. All patients provided written informed consent.

## RESULTS

### Baseline characteristics

Baseline characteristics of 174 participants used in the analysis of the ATOMIC (Efficacy and Safety of Metformin and Atorvastatin Combination Therapy vs. Monotherapy with Either Drug In Type 2 Diabetes Mellitus and Dyslipidemia Patients [ATOMIC]: Double-Blinded Randomized Controlled Trial) study were shown in Table 1. The mean  $\pm$  SD age was 57.01  $\pm$  10.76 years, mean  $\pm$  SD body mass index and waist circumference were 25.88  $\pm$  3.08 kg/m<sup>2</sup> and 87.62  $\pm$  8.12 cm, respectively. There were no significant differences in variables listed in Table

**Table 1.** Baseline demographics and clinical characteristics

| Variable                 | Combination group (n=58) | Metformin group (n=58) | Atorvastatin group (n=58) | Total (n=174)     |
|--------------------------|--------------------------|------------------------|---------------------------|-------------------|
| Age, yr                  | 56.5 $\pm$ 11.5          | 57.8 $\pm$ 11.1        | 56.8 $\pm$ 9.8            | 57.0 $\pm$ 10.8   |
| Sex, male/female         | 27 (46.6)/31 (53.5)      | 26 (44.8)/32 (55.2)    | 34 (58.6)/24 (41.4)       | 87(50.0)/87(50.0) |
| Body weight, kg          | 67.9 $\pm$ 10.4          | 66.2 $\pm$ 10.7        | 69.7 $\pm$ 12.0           | 67.9 $\pm$ 11.1   |
| Waist circumference, cm  | 88.0 $\pm$ 8.1           | 87.4 $\pm$ 8.3         | 87.5 $\pm$ 8.1            | 87.6 $\pm$ 8.1    |
| BMI, kg/m <sup>2</sup>   | 26.3 $\pm$ 3.2           | 25.6 $\pm$ 3.3         | 25.8 $\pm$ 2.7            | 25.9 $\pm$ 3.1    |
| Duration of diabetes, yr | 4.1 $\pm$ 4.7            | 4.6 $\pm$ 5.3          | 4.9 $\pm$ 5.4             | 4.5 $\pm$ 5.1     |
| HbA1c, %                 | 7.6 $\pm$ 0.8            | 7.3 $\pm$ 0.7          | 7.3 $\pm$ 0.6             | 7.4 $\pm$ 0.7     |
| FPG, mg/dL               | 155.2 $\pm$ 39.0         | 140.1 $\pm$ 29.6       | 141.7 $\pm$ 25.2          | 145.7 $\pm$ 32.3  |
| Insulin, $\mu$ IU/mL     | 13.7 $\pm$ 12.6          | 11.9 $\pm$ 8.4         | 10.6 $\pm$ 3.6            | 12.0 $\pm$ 9.0    |
| HOMA-IR                  | 5.5 $\pm$ 6.1            | 4.3 $\pm$ 4.3          | 3.7 $\pm$ 1.4             | 4.5 $\pm$ 4.4     |
| HOMA- $\beta$            | 58.1 $\pm$ 43.1          | 58.2 $\pm$ 27.7        | 53.2 $\pm$ 24.8           | 56.5 $\pm$ 32.8   |
| SBP, mm Hg               | 128.9 $\pm$ 13.9         | 125.6 $\pm$ 11.9       | 128.2 $\pm$ 13.9          | 127.6 $\pm$ 13.2  |
| DBP, mm Hg               | 80.1 $\pm$ 9.2           | 76.9 $\pm$ 7.6         | 78.4 $\pm$ 9.3            | 78.5 $\pm$ 8.8    |
| Total cholesterol, mg/dL | 207.8 $\pm$ 29.3         | 220.8 $\pm$ 39.9       | 217.2 $\pm$ 33.5          | 215.2 $\pm$ 34.7  |
| HDL-C, mg/dL             | 48.6 $\pm$ 13.5          | 50.5 $\pm$ 12.1        | 52.8 $\pm$ 12.9           | 50.6 $\pm$ 12.9   |
| Triglycerides, mg/dL     | 164.6 $\pm$ 94.6         | 152.9 $\pm$ 55.4       | 164.4 $\pm$ 122.8         | 160.6 $\pm$ 94.6  |
| LDL-C, mg/dL             | 138.8 $\pm$ 25.8         | 152.8 $\pm$ 35.1       | 142.5 $\pm$ 28.0          | 144.7 $\pm$ 30.3  |
| Apolipoprotein A1, mg/dL | 144.9 $\pm$ 26.6         | 149.1 $\pm$ 25.8       | 154.1 $\pm$ 27.1          | 149.4 $\pm$ 26.6  |
| Apolipoprotein B, mg/dL  | 124.4 $\pm$ 22.9         | 131.8 $\pm$ 28.9       | 126.4 $\pm$ 24.2          | 127.5 $\pm$ 25.5  |
| BUN, mg/dL               | 15.2 $\pm$ 3.6           | 15.9 $\pm$ 3.6         | 15.2 $\pm$ 3.4            | 15.4 $\pm$ 3.5    |
| Creatinine, mg/dL        | 0.762 $\pm$ 0.180        | 0.809 $\pm$ 0.168      | 0.821 $\pm$ 0.148         | 0.797 $\pm$ 0.167 |

Values are presented as mean  $\pm$  standard deviation or number (%).

BMI, body mass index; HbA1c, glycosylated hemoglobin; FPG, fasting plasma glucose; HOMA-IR, homeostasis model assessment of insulin resistance; HOMA- $\beta$ , homeostasis model assessment of  $\beta$ -cell function; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; BUN, blood urea nitrogen.

1 among the three groups, except the height which hardly affected the safety or efficacy of this study ( $P=0.0395$ ). Overall, exactly half participants were male patients, and 86 (49.43%) and 27 (15.52%) had a drinking and smoking history, respectively. Additionally, no significant differences were seen between groups. The parameters related to T2DM were similar between groups, the mean  $\pm$  SD HbA1c was  $7.38\% \pm 0.70\%$  and the duration of the disease was  $4.54 \pm 5.13$  years. Regarding dyslipidemia, the mean  $\pm$  SD LDL-C concentration was  $144.71 \pm 30.30$  mg, which corresponded to the high-risk group requiring treatment, if accompanied by diabetes. The mean  $\pm$  SD duration of dyslipidemia was  $3.39 \pm 4.09$  years.

### Changes in HbA1c and LDL-C levels after 16 weeks of treatment

HbA1c was decreased by  $0.43\% \pm 0.07\%$  and  $0.58\% \pm 0.11\%$  in the combination group and increased by  $0.12\% \pm 0.07\%$  and  $0.35\% \pm 0.11\%$  in the atorvastatin group compared to baseline

after 8 and 16 weeks of treatment, respectively (Fig. 2A). The difference between these two groups was 0.55% and 0.94% in 8 and 16 weeks, which demonstrated a superior effect on HbA1c reduction in the combination group than in the atorvastatin group ( $P < 0.0001$ ).

Fig. 2B showed that LDL-C was decreased by 55.1% and 55.2% in the combination group and by 10.18% and 7.69% in the metformin group in 8 and 16 weeks of treatment, respectively, which resulted in a significant difference between the two groups, 44.95% and 47.51% ( $P < 0.001$ ).

### Secondary outcome analysis

The ATOMIC study also showed that the difference in LDL-C levels between the combination and atorvastatin groups was 4.73% in 8 weeks and 9.43% in 16 weeks of treatment. In the mid-study period, the difference between the two groups was not significant ( $P=0.086$ ). However, this difference became significant at the end of the study ( $P=0.0011$ ) (Fig. 3A). Addi-

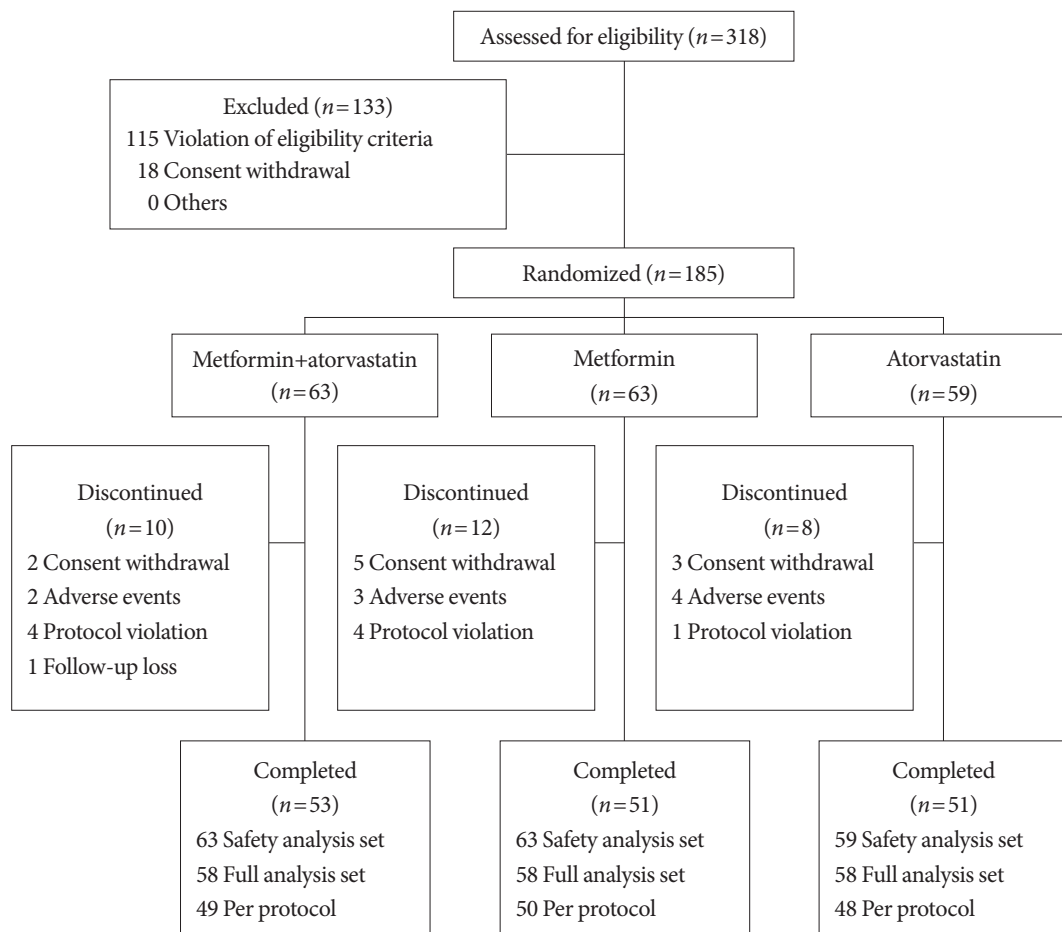
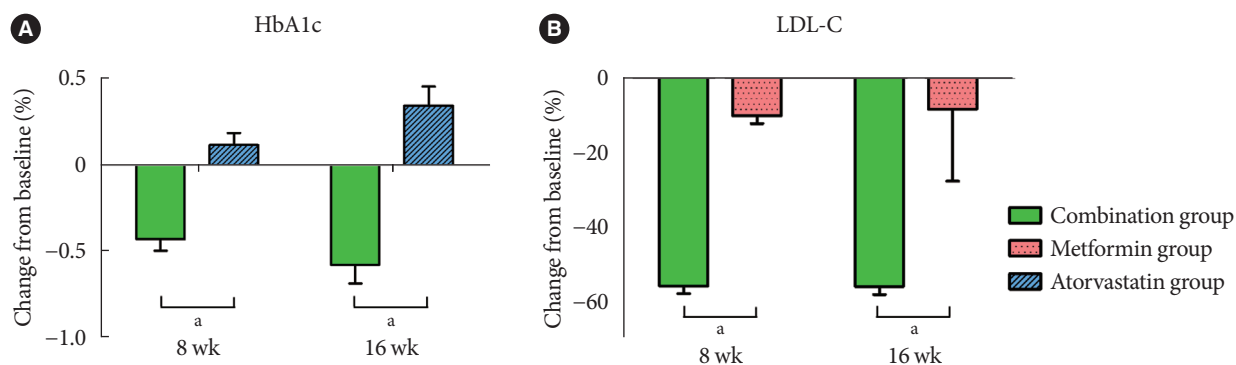


Fig. 1. Flow diagram of the study participants.

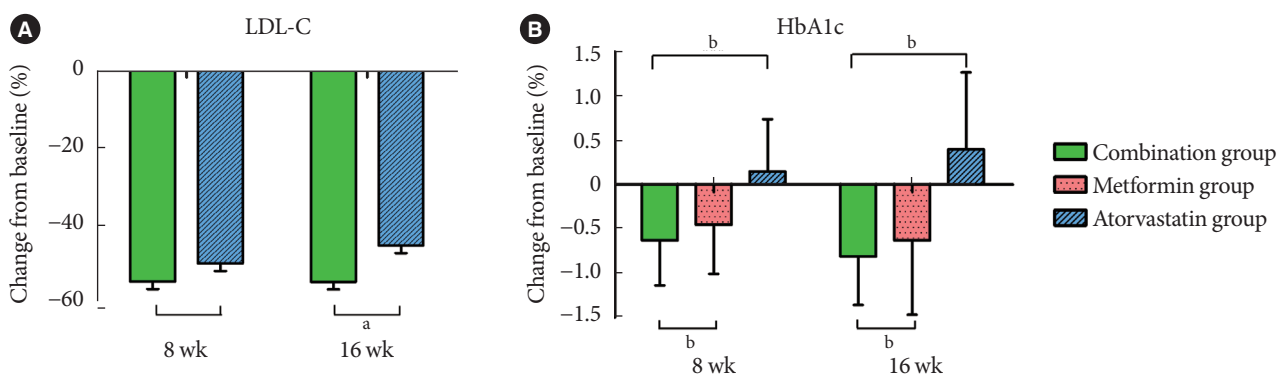
tionally, changes in HbA1c between the combination and metformin group showed a difference of 0.27% and 0.33% in the 8 and 16 weeks of the study, respectively. Furthermore, it was significant throughout the study period (all  $P=0.0035$ ) (Fig. 3B).

Percentages of patients achieving the LDL-C target of <100 mg/dL after 16 weeks of treatment were 86.2%, 15.5%, and 79.3% in the combination, metformin, and atorvastatin groups, respectively (Fig. 4A). There was a significant difference between

the groups administered with atorvastatin (combination and atorvastatin groups) and the group not treated with atorvastatin (metformin group). In cases of increase in HbA1c, the percentages of patients controlled under 6.5% or 7.0% were 31.0%, 50.0%, and 12.1% or 65.5%, 72.4%, and 27.6% in the combination, metformin, and atorvastatin groups, respectively (Fig. 4B). A significant difference was confirmed between groups treated with metformin (combination and metformin groups) and the group not treated with metformin (atorvastatin group).



**Fig. 2.** (A) Least square (LS) mean percent change in glycosylated hemoglobin (HbA1c) level from baseline to weeks 8 and 16 in groups treated with a combination of metformin and atorvastatin (combination group), and atorvastatin alone (atorvastatin group) (LS mean differences:  $-0.55\%$  [95% confidence interval, CI,  $-0.76$  to  $-0.34$ ;  $P<0.001$ ] at 8 weeks;  $-0.94\%$  [95% CI,  $-1.25$  to  $-0.63$ ;  $P<0.001$ ] at 16 weeks). (B) LS mean percent change in low-density lipoprotein cholesterol (LDL-C) levels from baseline to weeks 8 and 16 in groups treated with a combination of metformin and atorvastatin (combination group), and metformin alone (metformin group) (LS mean differences:  $-44.95\%$  [95% CI,  $-50.68$  to  $-39.21$ ;  $P<0.001$ ] at 8 weeks;  $-47.51\%$  [95% CI,  $-53.66$  to  $-41.36$ ;  $P<0.001$ ] at 16 weeks). <sup>a</sup> $P<0.001$ .



**Fig. 3.** (A) Least square (LS) mean percent change in low-density lipoprotein cholesterol (LDL-C) level from baseline to weeks 8 and 16 in groups treated with a combination of metformin and atorvastatin (combination group), and atorvastatin alone (atorvastatin group) (LS mean differences:  $-4.73\%$  [95% confidence interval, CI,  $-10.13$  to  $0.68$ ;  $P=0.0859$ ] at 8 weeks;  $-9.43\%$  [95% CI,  $-15.02$  to  $-3.84$ ;  $P=0.0011$ ] at 16 weeks). (B) Mean percent change in glycosylated hemoglobin (HbA1c) level from baseline to week 8 and 16 in the combination, metformin, and atorvastatin group (combination vs. metformin; differences:  $0.27\%$  [95% CI,  $0.09$  to  $0.44$ ;  $P=0.0035$ ] at 8 weeks and  $0.33\%$  [95% CI,  $0.11$  to  $0.55$ ;  $P=0.0035$ ] at 16 weeks) (combination vs. atorvastatin; difference:  $-0.55\%$  [95% CI,  $-0.76$  to  $-0.34$ ;  $P<0.001$ ] at 8 weeks and  $-0.94$  [95% CI,  $-1.25$  to  $-0.63$ ;  $P<0.001$ ] at 16 weeks). <sup>a</sup> $P<0.05$ , <sup>b</sup> $P<0.001$ .

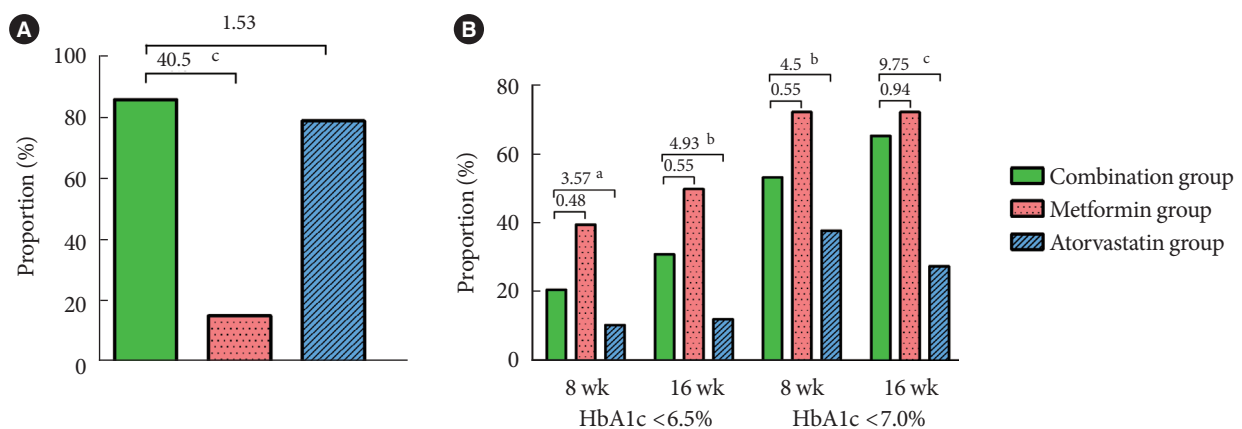
### Clinical factors affecting HbA1c reduction by adding metformin to atorvastatin

There was a significant difference in HbA1c change in the combination and atorvastatin groups (0.94%,  $P < 0.0001$ ) (Fig. 3B), and the proportion of patients with elevated HbA1c compared to baseline were 15.52% and 62.07%, respectively, which showed a significant difference. However, the extent of increase in HbA1c was not significant at 0.45% and 0.9%, respectively (0.44%,  $P = 0.0880$ ) (Fig. 5). When 58 participants taking metformin in addition to atorvastatin (combination group) were divided into a group with a decrease (responder group) and an increase (non-responder group) in HbA1c corresponding to 49 and nine participants, respectively, about 15% of participants of the combination group showed an increase in HbA1c despite taking metformin. As a result of the comparative analy-

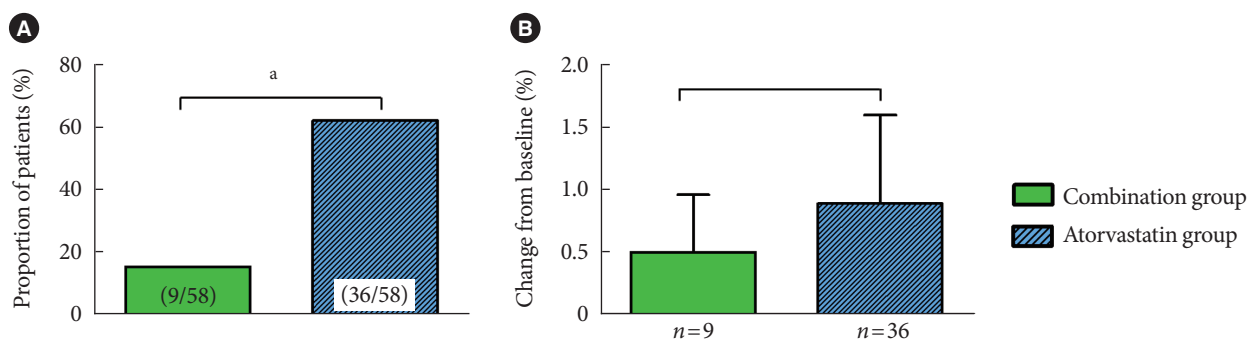
sis of the responder and non-responder groups, there was no clinical factor that showed a significant difference between these two groups (data not shown). Therefore, no potential predictors were identified for patients who would benefit from metformin's addition to offset the atorvastatin's diabetogenic effect.

### Safety analyses

A total of 185 subjects who received study drugs at least once (63 participants in the combination group, 63 participants in the metformin group, and 59 participants in the atorvastatin group) were included in the safety analysis. A total of 126 treatment-emergent adverse events (TEAEs) were reported by 81 participants (43.78%), including 36 (57.14%, 61 cases) in the combination group, 25 (39.68%, 34 cases) in the metformin



**Fig. 4.** (A) Percentages of patients achieving the low-density lipoprotein cholesterol target of < 100 mg/dL after 16 weeks of treatment. (B) Percentages of patients achieving the glycosylated hemoglobin (HbA1c) targets of < 6.5% or  $\leq 7.0\%$  after 16 weeks of treatment. <sup>a</sup> $P < 0.01$ , <sup>b</sup> $P < 0.05$ , <sup>c</sup> $P < 0.001$ .



**Fig. 5.** (A) Percentage of patients with increased glycosylated hemoglobin (HbA1c) in the combination and atorvastatin groups (15.02% vs. 62.07%) (least square [LS] mean differences:  $-46.55$  [95% confidence interval, CI,  $-62.13$  to  $-30.97$ ;  $P < 0.001$ ]). (B) Extent of increased HbA1c in the combination and atorvastatin groups (LS mean differences:  $-0.44\%$  [95% CI,  $-0.96$  to  $0.07$ ;  $P = 0.0880$ ]). <sup>a</sup> $P < 0.001$ .



group, and 20 (33.90%, 31 cases) in the atorvastatin group (Supplementary Table 2). The incidence of TEAEs showed a significant difference between groups. AEs related to study drugs occurred in 52 cases in 39 participants (21.08%) and there was no significant difference between the groups. There were 24 cases in 18 participants (28.57%) in the combination group, 18 cases in 13 participants (20.63%) in the metformin group, and 10 cases in eight participants (13.56%) in the atorvastatin group. According to the severity of AEs, 46 cases were mild, five cases were moderate, and only one case was severe. There were no reports of adverse or serious adverse drug reactions resulting in death. However, nine adverse drug reactions in six subjects (3.24%) resulted in the discontinuation of the study drug. There were three patients (four cases, 4.76%), two patients (four cases, 3.17%), and one patient (one case, 1.69%) in each group, respectively.

## DISCUSSION

This study demonstrated that the difference in the rate of change in LDL-C after 16 weeks of treatment compared to the baseline between the combination and metformin groups was  $-47.51\%$ , which was statistically significant ( $P < 0.0001$ ). Additionally, the difference in the amount of change in HbA1c from the baseline to the end of the study between the combination and atorvastatin groups was  $-0.94\%$ , which was also statistically significant ( $P < 0.0001$ ).

The difference in the mean change of LDL-C during the clinical trial between the combination and atorvastatin groups was  $-9.43\%$  ( $P = 0.0011$ ). As the lipid-lowering effect of metformin has been previously reported, it is thought that the additive effect on the lipid-lowering effect was reflected in the combination group [10]. Despite longstanding widespread use, the molecular mechanism of metformin in lipid metabolism is still controversial. While the metformin-mediated glycemic control is mainly by acting on the liver, high concentrations of metformin have been reported in the intestinal mucosa [11], which is the site of high expression of sterol regulatory element-binding protein-1c (SREBP-1c) mainly involved in de novo lipogenesis. SREBP-1c in the intestine is positively regulated by insulin and negatively by AMP-activated protein kinase (AMPK). Metformin could decrease the concentration of intestine-derived TG-rich protein through AMPK activation, thereby regulating the TG or fatty acid synthesis [12]. Additionally, it also decreased the chylomicron concentration by increasing the glucagon-like

peptide-1 concentration in the intestine [13].

Additionally, the difference in the mean change in HbA1c after 16 weeks of administration compared to the baseline between the combination group and the metformin group was  $0.33\%$  ( $P = 0.0035$ ). The increase in fasting blood glucose and HbA1c in statin-based drugs is also reported in the cautions for use in the U.S. Food and Drug Administration Lipitor monograph. LDL-C is lowered by  $1 \text{ mmol/L}$  ( $38.61 \text{ mg/dL}$ ) and HbA1c is increased by  $0.12\%$  with the administration of statins. Hence, it has been reported that the major factors of CVD are reduced by  $20\%$  [14]. Based on another report, the risk of CVD was reduced in proportion to the amount of LDL-C reduction, with a  $1 \text{ mmol/L}$  decrease in LDL-C reducing the CV risk by  $22\%$ ,  $40\%$  at  $2 \text{ mmol/L}$ , and  $50\%$  at  $3 \text{ mmol/L}$ , respectively [15]. Based on the results of the previous studies, we could suggest that the  $2.05 \text{ mmol/L}$  ( $79.02 \text{ mg/dL}$ ) reduction in LDL-C in the combination group, the result of this trial, might reduce the CV risk by more than  $40\%$ . In this context, the increase in HbA1c might not be clinically meaningful as it outweighs the benefit of significantly reducing the risk of CVD due to statins. Additionally, it is noteworthy that high-dose atorvastatin could increase the HbA1c in 4 months and a metformin combination could significantly prevent the statin-induced aggravation of hyperglycemia in diabetic patients. However, according to this study's results, HbA1c does not decrease in about  $15\%$  of patients despite administering metformin in addition to atorvastatin. We performed additional statistical analyses to find factors that could predict either responders or non-responders to metformin. However, we could not identify any significant predictive factors mainly due to the small number of participants. Hence, further research should be done on a larger number of patients.

Similar to this study, the report that compared rosuvastatin and gemigliptin combination with monotherapy was released in 2018 [16]. They used  $20 \text{ mg}$  of rosuvastatin and  $50 \text{ mg}$  of gemigliptin in combination. Additionally, rosuvastatin's dose was gradually increased by  $5 \text{ mg}$  during the 24-week observation period. Based on the results, there was no significant difference in HbA1c between the groups with rosuvastatin alone and with rosuvastatin and gemigliptin until 12 weeks after administration of  $5$  or  $10 \text{ mg}$  of rosuvastatin. On the contrary,  $40 \text{ mg}$  of atorvastatin which was relatively a higher dose was administered in our study; HbA1c showed a significant difference between the groups (combination group vs. atorvastatin group) from 8 weeks (Fig. 3B). It is difficult to make a direct

comparison as the population participating in each study was different. However, HbA1c increased by 0.3% after 24 weeks of taking 20 mg of rosuvastatin and 0.35% after taking 40 mg of atorvastatin for 16 weeks. Additionally, when gemigliptin and metformin were added to rosuvastatin and atorvastatin, respectively, HbA1c decreased by 0.81% and 0.94% compared to the statin-only group. Although medications used in these two studies were different, both metformin and dipeptidyl peptidase-4 inhibitor showed the same results in that they effectively reduced the statin-induced hyperglycemia. Although their lipid-lowering potential could be similar, atorvastatin might be more diabetogenic than rosuvastatin in Asian patients with diabetes. Furthermore, the combination of atorvastatin with metformin could potentially be more beneficial in the case of atorvastatin compared to rosuvastatin to minimize the glucose level elevation during the long-term statin treatment [17].

Combination therapy with metformin and statins demonstrated beneficial effects in patients with diseases other than diabetes mellitus and dyslipidemia. In patients with diabetes and nonalcoholic fatty liver disease (NAFLD), combination therapy was indicated as statin therapy associates negatively with nonalcoholic steatohepatitis and significant fibrosis, whereas a safe use of metformin in diabetic patients and NAFLD was revealed [18]. Combination therapy is also frequently prescribed to women with the polycystic ovarian syndrome (PCOS). Meta-analysis revealed that combined statin-metformin therapy in women with PCOS resulted in improved lipid profile and inflammation markers, but it did not improve insulin sensitivity [19]. Additionally, Chung et al. [20] reported that combination therapy showed a protective effect against the development of diabetic macular edema in diabetic patients with pre-existing diabetic retinopathy. Hence, it could potentially have a beneficial effect in preventing complications in diabetic patients in several ways.

There was no evidence that a significant difference in drug-related AEs was reported in the combination, metformin, and atorvastatin groups. The most frequently reported adverse effects were gastrointestinal symptoms, like nausea, diarrhea, and dyspepsia which are well known side effects of these drugs. In our study, there was no evidence of an increase in drug-related gastrointestinal symptoms in each group. In other clinical studies where metformin and atorvastatin were co-administered, no reports of additional drug-related AEs beyond previously known were reported.

A few limitations observed in this study should be acknowl-

edged. First, this study mostly included middle-aged Asians with moderate to high CVD risk who needed statins. Therefore, it is difficult to extrapolate the current results to the general population. Second, this study only demonstrated the short-term effect of atorvastatin on serum glucose-related parameters, like HbA1c.

In conclusion, this clinical trial indicated the effectiveness of metformin and atorvastatin combination in patients with T2DM and dyslipidemia who were poorly controlled with exercise and diet. No adverse drug reactions other than those previously reported for each drug in the group with metformin and atorvastatin combination therapy were observed. Therefore, metformin and atorvastatin combination therapy could be considered one of the effective treatment methods that could manage serum glucose and lipid levels in patients with T2DM and dyslipidemia.

## SUPPLEMENTARY MATERIALS

Supplementary materials related to this article can be found online at <https://doi.org/10.4093/dmj.2023.0077>.

## CONFLICTS OF INTEREST

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

## AUTHOR CONTRIBUTIONS

Conception or design: M.K.L.

Acquisition, analysis, or interpretation of data: all authors.

Drafting the work or revising: J.E.L., M.K.L.

Final approval of the manuscript: all authors.

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## FUNDING

This study was funded by Daewoong Pharmaceutical and HK inno.N Corp., Republic of Korea.

## ACKNOWLEDGMENTS

The authors acknowledge the efforts of the ATOMIC study group and study participants who devoted their time and energy to this trial.

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**Supplementary Table 1.** Inclusion and exclusion criteria

| A. Inclusion criteria |   |
|-----------------------|---|
| 1                     | Age 19–80 years   |
| 2                     | Independent individuals   |
| 3                     | Patients with type 2 diabetes mellitus and dyslipidemia at screening and baseline visits  |
| 4                     | Patients with type 2 diabetes mellitus; 6.5% ≤ HbA1c ≤ 10.0% and dyslipidemia; 100 ≤ LDL-C ≤ 250 mg/dL at screening and baseline visits   |
| 5                     | Drug-naïve patients with type 2 diabetes mellitus or patients not taking hypoglycemic agents for the last 6 weeks   |
| 6                     | Drug-naïve patients with dyslipidemia or patients not taking lipid-lowering agents for the last 4 weeks (fenofibrate for 8 weeks)   |
| 7                     | Patients with more than 70% adherence to medication during a 4-week run-in period   |
| B. Exclusion criteria |   |
| 1                     | BMI ≥ 35 or ≤ 18.5 kg/m <sup>2</sup>  |
| 2                     | Patients with type 1 diabetes mellitus with or without a history of acute or chronic metabolic acidosis or ketonemia, including diabetic ketoacidosis   |
| 3                     | Patients with a history of myopathy, rhabdomyolysis, statin/fibric acid-related myopathy, hereditary myopathy, or family history of hereditary myopathy   |
| 4                     | Patients with secondary dyslipidemia related to nephrotic syndrome, hypothyroidism, dysproteinemia, cholestatic liver disease, Cushing's syndrome, etc.   |
| 5                     | Patients with uncontrolled hypertension; systolic blood pressure ≥ 180 mm Hg or diastolic blood pressure ≥ 110 mm Hg  |
| 6                     | Patients with a history of coronary heart disease, like myocardial infarction, unstable angina, coronary artery bypass surgery, or coronary artery angioplasty within 6 months before enrolment                               |
| 7                     | Patients with heart failure with NYHA class III or IV or congestive heart failure   |
| 8                     | Patients with malignancy (except for cases that have been cured or have not recurred within 5 years)  |
| 9                     | Patients with severe infection or severe post-traumatic sequelae  |
| 10                    | Patients with hypopituitarism or adrenal insufficiency  |
| 11                    | Patients with acute and chronic diseases causing tissue hypoxia, including respiratory failure, acute myocardial infarction, shock, etc.  |
| 12                    | Patients with gastrointestinal disorders including diarrhea, vomiting   |
| 13                    | Patients requiring intravenous administration of radioactive contrast media (e.g., intravenous urography, intravenous urography, intravenous cholangiography, intravenous angiography, contrast-enhanced computed tomography) |
| 14                    | Patients with a history of side effects from metformin (biguanides) or atorvastatin   |
| 15                    | Patients with a genetic disease, like galactose intolerance, Lapp lactose deficiency, glucose-galactose malabsorption   |
| 16                    | Patients with active or severe liver disease (AST/ALT ≥ 2.5 times the upper limit of normal)  |
| 17                    | Patients with severe renal disease or renal failure (serum creatinine ≥ 1.5 mg/dL [male patients], 1.4 mg/dL [female patients])   |
| 18                    | CK ≥ 2 times the upper limit of normal  |
| 19                    | Patients with uncontrolled thyroid function (TSH ≥ upper normal limit)  |
| 20                    | Serum triglyceride ≥ 400 mg/dL  |
| 21                    | Concurrent or previous use of GLP-1 agonist or insulin within 6 weeks   |
| 22                    | Patients with a history of treatment for obesity, including medication or bariatric surgery   |
| 23                    | Patients with a history of steroids in the previous 2 weeks   |
| 24                    | Use of prohibited concomitant medications   |
| 25                    | Pregnancy or breast-feeding at screening  |
| 26                    | History of drug or alcohol abuse  |
| 27                    | Inclusion in another clinical trial 3 months before screening   |
| 28                    | Patients determined by the investigator to be unsuitable for clinical trials  |

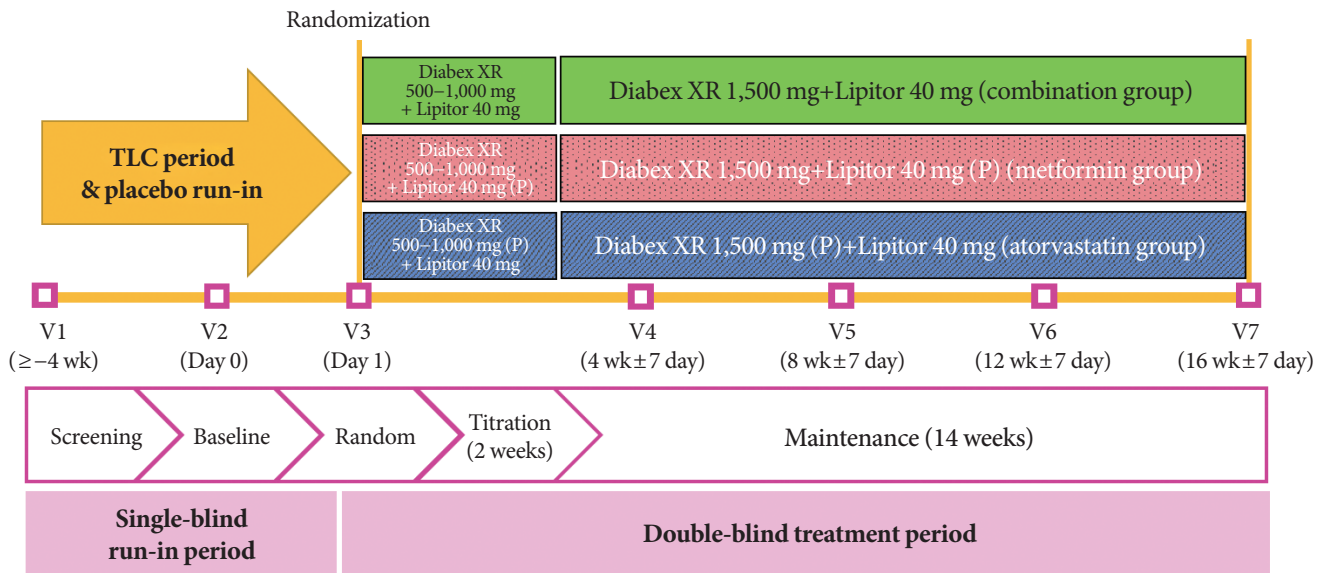
HbA1c, glycosylated hemoglobin; LDL-C, low-density lipoprotein cholesterol; BMI, body mass index; NYHA, New York Heart Association; AST, aspartate aminotransferase; ALT, alanine aminotransferase; CK, creatinine kinase; TSH, thyroid stimulating hormone; GLP-1, glucagon-like peptide-1.

**Supplementary Table 2.** Adverse events

| Variable                                 | Combination group<br>(n=63) | Metformin group<br>(n=63) | Atorvastatin group<br>(n=59) | P value |
|--|-----------------------------|---------------------------|------------------------------|---------|
| Total TEAEs                              | 36 (57.14)                  | 25 (39.68)                | 20 (33.90)                   | 0.0255  |
| Serious AEs                              | 3 (4.76)                    | 1 (1.59)                  | 2 (3.39)                     | 0.6944  |
| AEs reported in $\geq 2.0\%$ of subjects |                             |                           |                              |         |
| Nausea                                   | 6 (9.52)                    | 3 (4.76)                  | 1 (1.69)                     | NA      |
| Diarrhea                                 | 3 (4.76)                    | 4 (6.35)                  | 1 (1.69)                     | NA      |
| Dyspepsia                                | 3 (4.76)                    | 4 (6.35)                  | 1 (1.69)                     | NA      |
| Upper abdominal pain                     | 2 (3.17)                    | 2 (3.17)                  | 0                            | NA      |
| Gastritis                                | 2 (3.17)                    | 2 (3.17)                  | 0                            | NA      |
| Nasopharyngitis                          | 7 (11.11)                   | 0                         | 1 (1.69)                     | NA      |
| Drug withdrawal due to AEs               | 3 (4.76)                    | 2 (3.17)                  | 1 (1.69)                     | 0.8728  |

Values are presented as number (%).

TEAE, treatment-emergent adverse event; AE, adverse event; NA, not applicable.



**Supplementary Fig. 1.** Study design. Diabex XR 500–1,000 mg (P), Diabex XR 500–1,000 mg placebo; Lipitor 40 mg (P), Lipitor 40 mg placebo. TLC, therapeutic lifestyle change.