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Effects of High-intensity Statin Combined Telmisartan Versus Amlodipine on Glucose Metabolism in Hypertensive Atherosclerotic Cardiovascular Disease Patients With Impaired Fasting Glucose: a Randomized Multi-centre Trial

Chan Joo Lee
Yonsei University College of Medicine
Minji Kim
Yonsei University College of Medicine
Jung-Hoon Sung
CHA University School of Medicine
Tae-Soo Kang
Dankook University College of Medicine
Sungha Park
Yonsei University College of Medicine
Sang-Hak Lee
Yonsei University College of Medicine
Jong-Youn Kim
Yonsei University College of Medicine
Byeong-Keuk Kim (kimbk@yuhs.ac)
Division of Cardiology, Severance Cardiovascular Hospital, Yonsei University College of Medicine, Seoul, Republic of Korea https://orcid.org/0000-0003-2493-066X

Original investigation

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Abstract

Background: Limited data are available regarding the role of angiotensin-II-receptor blockers (ARB) in the prevention of new-onset diabetes mellitus in patients with atherosclerotic cardiovascular disease (ASCVD) and hypertension requiring high-dose statin. This study aimed to compare the effects of telmisartan and amlodipine on glucose metabolism in hypertensive ASCVD patients with impaired fasting glucose (IFG) requiring high-intensity statin.

Methods: A total of 99 patients with hypertensive ASCVD with impaired fasting glucose (100–125 mg/dL or HbA1c 5.7%–6.4%) were randomly assigned to two groups [telmisartan-statin group (n = 48) and amlodipine-statin group (n = 51)] as the add-on therapy to high-dose rosuvastatin therapy (20 mg). The primary endpoint was the value of the homeostatic model assessment for insulin resistance (HOMA-IR) at week 24, and the secondary endpoint was the change in the glucose metabolism indices from baseline to week 24.

Results: The HOMA-IR at week 24 (2.4 [interquartile range, 1.8–3.8] versus 2.6 [1.7–3.7]; P = 0.809) and changes in the HOMA-IR from baseline to week 24 (−7.0 [−29.0 to 21.0] versus −2.3 [−53.3 to 27.3]; P = 0.539) were not significantly different between the telmisartan-statin group and the amlodipine-statin group. However, the fasting glucose level at week 24 was significantly lower in the telmisartan-statin group (107.7 ± 13.4 mg/dL) than in the amlodipine-statin group (113.3 ± 12.4 mg/dL; P = 0.039) and significantly decreased from the baseline in the telmisartan-statin group (−3.2% ± 8.6% versus 3.8% ± 13.2%; P = 0.003). The proportion of patients with IFG (71.1% versus 89.6%; P = 0.047) or hemoglobin A1c level >6.5% (4.2% versus 21.6%; P = 0.023) at week 24 was also significantly lower in the telmisartan-statin group than in the amlodipine-statin group.

Conclusion: Compared to amlodipine, telmisartan did not decrease the HOMA-IR; rather, an improvement in glucose metabolism was noted during the follow-up in hypertensive ASCVD patients with IFG requiring high-dose statin, suggesting the potential role of ARB for reducing risks owing to high-intensity statin.

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https://clinicaltrials.gov/ct2/show/NCT03474562

Introduction

For the primary and secondary prevention of high cardiovascular risk of atherosclerotic cardiovascular disease (ASCVD), strict control of blood cholesterol using statins, is recommended, especially for lowering low-density lipoprotein cholesterol (LDL-C) [1]. Despite several beneficial effects of statin therapy, statin is associated with an increased risk of developing diabetes mellitus (DM) [2]. The meta-analyses of randomized clinical trials showed that statin therapy was associated with an increased risk of new-onset DM [3], and several experimental studies have reported that statins act on beta cells and reduce insulin secretion and inhibit glucose uptake in adipocytes and skeletal muscles, leading to insulin

resistance and DM [4, 5]. Particularly, these phenomena are more pronounced using high-intensity statins than moderate- or low-intensity statins, and statin-induced new-onset DM is more likely to occur in people with a high risk of diabetes [6, 7] Therefore, in patients with insulin resistance such as impaired fasting glucose (IFG) or elevated hemoglobin A1c (HbA1c), the risk of new-onset DM caused by high-intensity statins should be increased [8]. These patients at risk of new-onset DM requiring the management of hypertension and LDL-C could expect a decrease in insulin resistance using appropriate antihypertensive drugs. Among angiotensin II receptor blockers (ARB), telmisartan has been found to reduce insulin resistance by activating peroxisome proliferator-activated receptor gamma (PPARγ) [9]. However, there are insufficient results on the changes in glucose metabolism, including insulin resistance, when high-intensity statins and hypertension drugs are used in combination. Therefore, we aimed to compare the effects of telmisartan and amlodipine on glucose metabolism in hypertensive ASCVD patients with IFG requiring high-intensity rosuvastatin therapy.

Methods

Study design

This trial, the COMPROMISE (effect of high-dose rosuvastatin combined with telmisartan or amlodipine on glucose metabolism in atherosclerotic cardiovascular disease patients with impaired fasting glucose and hypertension) trial was a 24-week randomized, open-label, parallel, multicenter trial conducted at four sites in South Korea between October 2018 and May 2019. The local ethics review boards of each hospital approved the study protocol. The study was conducted in accordance with the principles of Declaration of Helsinki, and all patients provided written informed consent. After screening, participants were randomly segregated to the combination therapy with telmisartan and high-dose rosuvastatin (telmisartan-statin group) and the combination therapy with amlodipine and high-dose rosuvastatin (amlodipine-statin group) in a 1:1 ratio using pre-coded concealed envelopes generated by permuted-block randomization with a block size of two stratified using the study site.

The study design and flow are presented in Figure 1. All participants were initially treated with telmisartan 40 mg/rosuvastatin 20 mg once daily or amlodipine 5 mg/rosuvastatin 20 mg once daily for the first 12 weeks and were then up-titrated to telmisartan 80 mg/rosuvastatin 20 mg once daily or amlodipine 10 mg/rosuvastatin 20 mg once daily for an additional 12 weeks if the participants did not meet blood pressure (BP) goals (mean sitting systolic BP/ diastolic BP of 140/90 mm Hg).

Study population

Patients aged 19–75 years who met the following conditions were enrolled: 1) patients with clinical ASCVD requiring high-intensity statin therapy (clinical ASCVD included acute coronary syndrome, history of myocardial infarction, stable or unstable angina, history of coronary revascularization, stroke or transient ischemic attack, peripheral arterial disease, or history of peripheral arterial revascularization) [1]; 2) patients who were taking antihypertensive drugs or with a systolic or diastolic BP of >140mmHg or

>90mmHg; and 3) patients who met the criteria for IFG (fasting plasma glucose of 100–125 mg/dL or HbA2c of 5.7%–6.4%) and has not been diagnosed with DM before.

The exclusion criteria were as follows: patients who were treated for secondary or malignant hypertension; uncontrollable DM with HbA1c ≥10%; total cholesterol of ≥300mg/dL; fasting LDL-C of ≤70 mg/dL in statin-naïve patients; fasting triglyceride of ≥500 mg/dL; history of muscular disease or rhabdomyolysis owing to statin use; hypersensitive to statin or ARBs; contraindications stated in the single-pill combination of telmisartan or rosuvastatin (severe renal disease, aspartate aminotransferase or alanine aminotransferase >three-fold upper normal limit or history of active liver disease, creatine phosphokinase >three-fold upper normal limit, or hyperkalemia); those who were participating in clinical trials of other investigational products; those who cannot discontinue all other treatments for hypertension or hyperlipidemia than the investigational products, concomitant medications, and supplements that can affect the therapeutic effects of hypertension and hyperlipidemia; and if the investigator considers participant to be ineligible to participate in the trial.

Efficacy assessments

The primary endpoint was the difference in the homeostatic model assessment for insulin resistance (HOMA-IR) at week 24. HOMA-IR was calculated using the formula: fasting insulin (μU/mL) × fasting glucose (mg/dL)/405. The secondary endpoints were 1) the changes from the baseline to the week 12 or 24 in the following variables: HOMA-IR, homeostasis model assessment of β-cell function (HOMA-B), fasting blood glucose, fasting insulin, HbA1c, lipid profiles (total cholesterol, triglyceride, LDL-cholesterol, and high-density lipoprotein-cholesterol (HDL-C)). HOMA-B was calculated using the formula: [fasting insulin (μU/mL)×360] / [fasting glucose (mg/dL) − 63] and 2) the proportions of participants with fasting plasma glucose of ≥100 mg/dL or HbA1c of ≥6.5% and the new-onset DM at week 24. New-onset DM was defined as the fasting plasma glucose of ≥125 mg/dL or HbA1c of ≥6.5% at week 24. The BP were measured during every visit to the out-patient clinic, and the adverse events and their severity and causal relationship were evaluated during the study period.

Statistical analyses

The sample size was estimated based on the HOMA-IR after treatment, as this was the primary endpoint. It was assumed that the baseline HOMA-IR was 2.6 (standard deviation (SD), 1.5), and it increased by 32% with rosuvastatin 20 mg and decreased by 34% with telmisartan, but increased by 2% with amlodipine according to previous studies [10, 11]. It was assumed that the HOMA-IR decreased to 2.54 and increased to 3.48 after a six-month treatment of telmisartan/rosuvastatin and amlodipine/rosuvastatin, respectively. An estimated sample size of 50 participants per treatment group would be required, considering a dropout rate of 20% and under the statistical conditions as follows: significance level (α), 0.05; power, 0.80 (β = 0.2); and SD (σ), 1.5.

The baseline characteristics were compared between the two groups using the χ^2 test for dichotomous variables or the *t* test or Mann–Whitney test for continuous variables. The change in variables during the

study period was investigated using the paired *t*-test or Wilcoxon signed-rank test according to the data distribution. The differences in the change in variables between the two groups were also compared using the *t*-test or Mann-Whitney test. The efficacy endpoints were analyzed using the full analysis set. The multivariate logistic regression models were used for estimating the association between the telmisartan use and new-onset DM. Model 1 included age, sex, BMI, use of beta-blocker, estimated glomerular filtration rate, and fasting plasma glucose as co-variates. Model 2 included HOMA-IR instead of fasting plasma glucose. A P-value of <0.05 was considered statistically significant. All analyses were performed using the software R (version 3.6.0 for Windows; The R Foundation for Statistical Computing, Austria).

Results

Baseline characteristics of participants

A total of 106 patients provided written consent to participate in the study; seven of them were screened out based on the exclusion criteria. Participants were randomly assigned to the telmisartan-statin group (n = 48) and amlodipine-statin group (n = 51). The mean age of participants was 60.1 ± 8.8 years, and 78% were men. The baseline characteristics of the enrolled participants are summarized in Table 1. There were no significant differences between the groups.

Changes in BP and lipid profiles

The changes in BP and lipid profiles at the baseline and week 24 is presented in Table 2. At the baseline, systolic and diastolic BP did not differ between the two groups. At week 12, two participants in the amlodipine group and three in the telmisartan group received an increased dose of the drug because they did not reach the target BP. There was no difference in the systolic and diastolic BP at the end of the study (week 24). The changes in systolic/diastolic BP during the study period within each group did not show statistical significance, and there were no group-differences in the BP change.

For the lipid profile, there were no significant differences in lipid parameters at weeks 0 and 24 between the two groups (Table 2). The Supplementary Table 1 presented the change of lipid profile from the baseline to week 12. In both the groups, the changes in the total cholesterol, triglyceride, and LDL-C did not show statistical significance during the study period, and there was no statistical difference between the groups for each change except for the change in HDL-cholesterol levels in the amlodipine-statin group. The percentage change of HDL-cholesterol level from the baseline to week 24 did not differ between the two groups.

Changes in parameters related to glucose metabolism

The changes in the parameters related to glucose metabolism during the study period is presented in Table 3. The values of parameters at the baseline were similar between the groups. The HOMA-IR at week 24, the primary endpoint of our study, was not significantly different between the telmisartan-statin and

amlodipine-statin groups and the percentage changes in HOMA-IR from weeks 0 and 24 were also not significantly different for both the telmisartan-statin and amlodipine-statin groups (Table 3, Figure 2A). The change in HOMA-B from weeks 0–24 was maintained in the telmisartan-statin group but significantly decreased in the amlodipine-statin group (Table 3).

At week 24, the telmisartan-statin group showed a significantly lower level of fasting blood glucose than the amlodipine-statin group (Table 3, Figure 2B). Fasting blood glucose from the baseline to week 24 significantly decreased in the telmisartan-statin group but not in the amlodipine-statin group (Figure 2B). The percentage changes in fasting glucose from the baseline to week 24 was also significantly different between the two groups. The level of HbA1c and insulin at week 24 were not significantly different between the groups, and the changes in HbA1c and insulin from week 0–24 were also not significantly different in both the groups.

Figure 3 shows the proportion of participants with fasting plasma glucose of ≥100 mg/dL or HbA1c of ≥6.5% at weeks 0 and 24. At week 24, both the proportions of participants with fasting plasma glucose of ≥100 mg/dL (71.1% vs. 89.6%, P = 0.047; Figure 3A) and HbA1c of ≥6.5% (4.2 % vs. 21.6%, P = 0.024; Figure 3B) were significantly lower in the telmisartan-statin group than in the amlodipine-statin group. In addition, the proportion of the new-onset DM at week 24 was significantly lower in the telmisartan-statin group than in the amlodipine-statin group (12.5% vs. 31.4%, P = 0.044; Figure 3C).

In the multivariate logistic analyses (Table 4), the use of telmisartan was an independent protective factor for developing new-onset DM. High baseline fasting plasma glucose was the risk factor for developing new-onset DM, while HOMA-IR was not.

Adverse events during study periods

Of the 99 participants, 16 participants in the telmisartan-statin group and 19 participants in the amlodipine-statin group reported adverse events (Supplementary Table 2). There was no statistical difference between the two groups. None of the adverse events were serious adverse events. There were four cases in which the clinical trial drug was the likely cause of hypotension (one case), headache (one case), edema (one case), and dizziness (one case) in the amlodipine-statin group. There were four cases with facial flushing (one case), hypotension (two cases), and creatine phosphokinase rise (one case) in the telmisartan-statin group.

Discussion

To the best of our knowledge, our study is the first to demonstrate the usefulness of telmisartan in reducing the risk of statin-induced DM in ASCVD hypertensive patients requiring high-intensity statin. The main findings of this study were 1) for participants with IFG who had hypertension and ASCVD requiring high-intensity statin, both 24-week treatment of amlodipine and telmisartan did not significantly improve HOMA-IR. However, HOMA-B, an indicator of insulin secretion, was maintained in the telmisartan-statin group but significantly reduced in the amlodipine-statin group, suggesting the protective effect of

telmisartan on beta-cell function; 2) fasting glucose tended to increase slightly at week 24 than at the baseline in the amlodipine-statin group, but it decreased significantly during the study period in the telmisartan-statin group, with a significantly lower value at week 24 in the telmisartan-statin group than in the amlodipine-statin group; and 3) the telmisartan-statin group showed a lower proportion of fasting plasma glucose of ≥100 mg/dL or HbA1c of ≥6.5% and a lower rate of new-onset DM at 24 weeks than the amlodipine-statin group. In the multivariate analysis, the use of telmisartan was a significant protective factor for preventing new-onset DM at 24 weeks, demonstrating the beneficial role of telmisartan for ASCVD and IFG patients at-risk of DM and requiring high-intensity statin.

In several studies, statin has been shown to increase the risk of DM through various mechanisms: statin can affect beta-cell function, which is one of the possible mechanism of new-onset DM [12]. In statin-treated beta cells, intracellular Ca^{2+} peaks induced by the uptake of glucose in beta cells are reduced, so a higher concentration of glucose is required for stimulating insulin secretion [13, 14]. In addition, statin treatment affecting pancreatic islet beta cells reduces insulin secretion rate dose-dependently [15]. Another mechanism is that insulin resistance is increased by statins. Statin increases the expression of fatty acid synthesis gene, which leads to a higher amount of fatty acid content in the muscle [16]. The accumulation of fatty acid causes detrimental effect on insulin signaling in muscle cells [17]. Consistent with these results, HOMA-IR, an indicator of insulin resistance, showed a significant dose-dependent increase with rosuvastatin 10, 20, and 40 mg in hyperlipidemia patients with IFG [18]. Thus, the risk of developing DM could be increased by statins, but DM does not develop in all patients receiving statin. Patients with an increased insulin resistance have a higher risk of developing DM with statin medication [3, 6]. It is strongly recommended not to discontinue statins in patients at a high risk of developing ASCVD because the protective effects of statins on cardiovascular disease outweigh the risk of diabetes [1]. However, considering the decrease in quality of life and the increase in medical expenses owing to DM, it is necessary to reduce the development of new-onset DM [19].

In ASCVD patients with hypertension and dyslipidemia, the choice of antihypertensive drugs would be a good way to lower the side effects of statin, especially the risks of new-onset DM. Among antihypertensive drugs, which are classified as first-line, beta-blocker, and thiazide-like diuretics are known to increase insulin resistance [20]. In contrast, renin-angiotensin-aldosterone system (RAAS) blockades, including ARB, can reduce the risk of new-onset DM through an important role in glucose homeostasis; angiotensin II negatively affects glucose uptake by inhibiting Glucose Transporter Type 4 translocation in the muscle and adipocytes, activates the inflammatory cytokine, and promotes the sympathetic nervous system, thereby increasing blood catecholamine levels, resulting in insulin resistance [21, 22]. Whereas calcium channel blockers, one of most common antihypertensive drug, have been reported to be associated with a higher incidence of DM than RAAS blockers in hypertensive patients [23].

Of the many ARBs, telmisartan has been reported to be more effective in lowering the risk of diabetes and differs from other ARBs in that it has a structural similarity to pioglitazone and can activate PPARγ even at low concentrations [9]. A previous study showed that the combination of rosuvastatin with telmisartan decreased HOMA-IR in patients with IFG than irbesartan or olmesartan [10]. Telmisartan may be superior

in preventing cardiovascular disease independently of the BP-lowering effect than amlodipine, a calcium channel blocker. Telmisartan attenuates *MCP-1* gene expression in peripheral blood monocytes and increases *PPAR-r* gene expression than amlodipine and has a positive influence on glycemic control and insulin resistance [24].

Although there was no significant difference in HOMA-IR reduction between the treatments, 24-week telmisartan treatment preserved the level of HOMA-B, significantly reduced the level of fasting plasma glucose and the proportion of participants with fasting plasma glucose of ≥100 mg/dL or HbA1c of ≥6.5%, and increased the change in euglycemic status from IFG, which effectively lowered the incidence of new-onset DM in patients receiving high-intensity statin than the 24-week amlodipine treatment. Prior studies had examined the effects of telmisartan in patients with insulin resistance regardless of the use of statin and evaluated the changes in metabolic parameters using a combination of telmisartan and a moderate dose of rosuvastatin without comparing with amlodipine [10, 25, 26]. Thus, our study was the first to investigate the effects of telmisartan versus amlodipine on glucose homeostasis in hypertensive ASCVD patients with high-dose and high-intensity statin treatment.

Telmisartan showed a tendency to improve insulin resistance and beta-cell function in patients with insulin resistance compared to a placebo [25]. In contrast, the numerical improvement in HOMA-IR was not shown in our study. This is probably because the average baseline HOMA-IR was 3.8 in the previous study, but the baseline HOMA-IR was lower in our study. Therefore, the reduction effect by telmisartan might not be well observed. Generally, telmisartan has a favorable effect on glucose metabolism, but there are also reports indicating that telmisartan show a neutral effect on HOMA-IR [27]. One of the novelties of our study was that telmisartan showed no changes in HOMA-B compared to amlodipine. Low HOMA-B is associated with a high risk of diabetes [28], and this is the first human study to confirm that telmisartan can prevent the statin-induced deterioration of beta-cell function.

There are some limitations of this study. First, this study was not double-blinded and not placebo-controlled. Second, because this study targeted patients with clinical ASCVD, most of these patients had hypertension, and the antihypertensive drug previously administered could have affected the metabolic parameters. Hence, a wash-out period should be considered after discontinuation of the antihypertensive drugs. However, the setting of wash-out period was impossible for patients with clinical ASCVD. Third, this study did not target statin-naïve patients. Therefore, it is possible that HOMA-IR was not significantly changed by rosuvastatin at the end of the study compared to the baseline. Finally, the weight changes or lifestyle modification might affect glucose metabolism even with short-term observation, but these were not analyzed.

Conclusion

In summary, the telmisartan-rosuvastatin combination could not significantly improve insulin resistance, but preserved insulin secretion, improved fasting blood glucose, and reduced the risks of new-onset DM than the amlodipine-rosuvastatin combination in hypertensive ASCVD patients with IFG.

List Of Abbreviations

ASCVD, atherosclerotic cardiovascular disease; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; DM, diabetes mellitus; HbA1c, hemoglobin A1c; IFG, impaired fasting glucose; ARB, angiotensin II receptor blockers; PPARγ, peroxisome proliferator-activated receptor gamma; HOMA-IR, homeostatic model assessment for insulin resistance; BP, blood pressure; SD, standard deviation; RAAS, renin-angiotensin-aldosterone system.

Declarations

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Authors' contributions

All authors are involved in the planning and execution of the COMPROMISE trial. CJL analyzed the data and wrote the manuscript. MK assisted in study design. J-HS, T-SK, J-YK and B-KK carried out subject recruitment. J-YK and B-KK are responsible for drafting this article and preparing the figures, tables, and additional files. The other authors critically reviewed the entire article. All authors read and approved the final manuscript.

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Conflict of Interest

None

Ethics approval and consent to participate

The ethics review boards of the Yonsei University College of Medicine (4-2017-1239) and each hospital approved the study protocol. The study was conducted in accordance with the principles of Declaration of Helsinki, and all patients provided written informed consent.

Consent for publication

Not applicable.

Availability of data and materials

Not applicable.

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Tables

Table 1. Baseline characteristics

Variables	Telmisartan-statin	Amlodipine-statin	P-value
	(n=48)	(n=51)	
Age, years	61.0 ± 8.8	59.3 ± 8.8	0.347
Male, n (%)	39 (81.2)	38 (74.5)	0.573
Height, cm	166.8 ± 8.1	166.2 ± 8.4	0.712
Weight, cm	71.7 ± 10.3	72.1 ± 12.1	0.887
Body mass index, kg/m^2	25.7 ± 2.9	26.0 ± 3.1	0.678
Coronary artery diseases, n (%)	48 (100.0)	51 (100.0)	-
Acute coronary syndrome, n (%)	32 (66.7)	41 (80.4)	0.186
Coronary revascularization, n (%)	22 (45.8)	28 (54.9)	0.483
Stroke or transient ischemic attack, n (%)	2 (4.2)	2 (3.9)	0.999
Peripheral arterial disease or history of peripheral arterial revascularization , n (%)	0 (0.0)	2 (3.9)	0.502
Estimated glomerular filtration rate, $mL/min/1.73m^2$	87.8 ± 17.8	85.8 ± 14.7	0.542
AST, IU/L	23.8 ± 8.1	25.5 ± 7.8	0.291
ALT, IU/L	27.7 ± 14.7	30.0 ± 13.8	0.422
Creatine phosphokinase, U/L	117.9 ± 47.6	129.7 ± 69.5	0.325
Combined medication			
Aspirin or clopidogrel	48 (100)	51 (100)	-
Beta-blockade	39 (81.2)	44 (86.3)	0.685
Anti-anginal drugs	24 (50.0)	24 (47.1)	0.927

Data are presented as mean ± standard deviation or number (%).

IFG, impaired fasting glucose; IGT, impaired glucose tolerance; PAD, peripheral arterial disease; ALT, alanine aminotransferase; AST, aspartate aminotransaminase.

Table 2. Blood pressure and lipid profile changes

group	Telmisartan-statin group	Amlodipine-statin group	P-value
	(n=48)	(n=51)	
Office systolic BP at week 0	130.5 ± 12.1	130.6 ± 15.2	0.990
Office systolic BP at week 24	127.1 ± 11.2	129.4 ± 13.0	0.351
Change from week 0 and 24	-2.9 ± 14.3	-1.7 ± 14.1	0.675
P-value for paired T-test	0.177	0.408	
Office diastolic BP at week 0	80.2 ± 9.2	78.8 ± 9.8	0.473
Office diastolic BP at week 24	80.6 ± 7.5	81.7 ± 8.4	0.497
Change from week 0 and 24	0.6 ± 10.2	2.6 ± 9.1	0.329
P-value for paired T-test	0.593	0.057	
Total cholesterol at week 0, mg/dL	141.7 ± 21.7	142.3 ± 22.6	0.908
Total cholesterol at week 24, mg/dL	141.4 ± 29.8	146.6 ± 32.2	0.425
% change	0.1 ± 21.2	3.7 ± 22.6	0.436
P-value for paired T-test	0.565	0.468	
Triglyceride at week 0, mg/dL	145.0 ± 83.1	139.6 ± 61.9	0.718
Triglyceride at week 24, mg/dL	144.5 ± 68.7	141.8 ± 66.3	0.845
% change	8.0 ± 45.9	6.9 ± 41.9	0.906
P-value for paired T-test	0.673	0.968	
HDL-cholesterol at week 0, mg/dL	48.1 ± 10.1	47.2 ± 10.3	0.671
HDL-cholesterol at week 24, mg/dL	47.9 ± 9.8	50.1 ± 12.0	0.331
% change	0.7 ± 14.3	6.5 ± 15.4	0.061
P-value for paired T-test	0.890	0.008	
LDL-cholesterol at week 0, mg/dL	71.6 ± 21.7	71.9 ± 17.8	0.937
LDL-cholesterol at week 24, mg/dL	70.8 ± 23.8	73.5 ± 30.6	0.635
% change	-0.3 ± 33.6	3.7 ± 38.4	0.596
P-value for paired T-test	0.443	0.764	
Data are presented as mean ± standard deviation.			

BP, blood pressure; HDL, high density lipoprotein; LDL, low density lipoprotein; SBP, systolic blood pressure.

Table 3. The changes of parameters related with glucose metabolism

	Telmisartan-statin group	Amlodipine-statin group	P-value
	(N=48)	(N=51)	
HOMA-IR at week 0	2.8 (1.8 to 4.6)	2.8 (1.7 to 7.2)	0.800
HOMA-IR at week 24	2.4 (1.8 to 3.8)	2.7 (1.7 to 3.7)	0.809
% change	-7.0 (-28.0 to 21.3)	-5.5 (-53.3 to 27.3)	0.539
P-value for Wilcoxon Signed-Rank Test	0.407	0.087	
HOMA-B at week 0	76.4 (46.8 to 122.9)	86.8 (48.7 to 211.3)	0.315
HOMA-B at week 24	74.1 (54.5 to 103.6)	63.6 (45.4 to 102.9)	0.252
% change	-6.0 (-23.3 to 26.9)	-19.8 (-52.7 to 3.3)	0.040
P-value for Wilcoxon Signed-Rank Test	0.467	<0.001	
Fasting glucose at week 0, mg/dL	111.2 ± 10.2	110.0 ± 10.0	0.566
Fasting glucose at week 24, mg/dL	107.7 ± 13.4	113.3 ± 12.4	0.039
% change	-3.2 ± 8.6	3.8 ± 13.2	0.003
P-value for paired T-test	0.016	0.075	
HbA1c at week 0, %	6.0 ± 0.3	6.0 ± 0.6	0.443
HbA1c at week 24, %	6.0 ± 0.3	6.0 ± 0.4	0.498
% change	0.1 ± 3.2	0.5 ± 4.7	0.625
P-value for paired T-test	0.876	0.469	
Insulin at week 0, mIU/L	9.5 (6.4 to 15.9)	10.2 (6.6 to 27.9)	0.361
Insulin at week 24, mIU/L	9.2 (7.2 to 13.8)	9.7 (5.9 to 13.8)	0.750
% change	-3.6 (-31.6 to 19.5)	-6.8 (-52.2 to 21.1)	0.595
P-value for Wilcoxon Signed-Rank Test	0.221	0.082	
Data are presented as mean ± standard deviation or median (interquartile range). HOMA-B, homeostatic model assessment for beta cell function; HOMA-IR, homeostatic model assessment for insulin resistance.			

Table 4. Independent predictors for developing the new-onset diabetes mellitus

Variables	OR	95% CI	P value
Model 1			
Use of telmisartan (ref=amlodipine)	0.18	0.05-0.61	0.009
Age	0.97	0.90-1.05	0.511
Sex (ref=male)	0.15	0.02-0.86	0.060
BMI at baseline	0.89	0.70-1.12	0.337
Use of beta-blockade (ref=non-user)	2.29	0.49-16.76	0.338
Estimated GFR at baseline	0.99	0.99-1.08	0.112
FPG at baseline	1.12	1.05-1.21	<0.001
Model 2			
Use of telmisartan (ref=amlodipine)	0.27	0.08-0.79	0.022
Age	0.99	0.93-1.07	0.874
Sex (ref=male)	0.24	0.03-1.09	0.097
BMI at baseline	0.92	0.74-1.13	0.420
Use of beta-blockade (ref=non-user)	2.16	0.48-15.58	0.363
Estimated GFR at baseline	1.01	0.97-1.05	0.468
HOMA-IR at baseline	1.02	0.99-1.06	0.153
FPG, fasting plasma glucose; GFR, glomerular filtration rate; HOMA-IR, homeostatic model assessment for insulin resistance.			

Figures

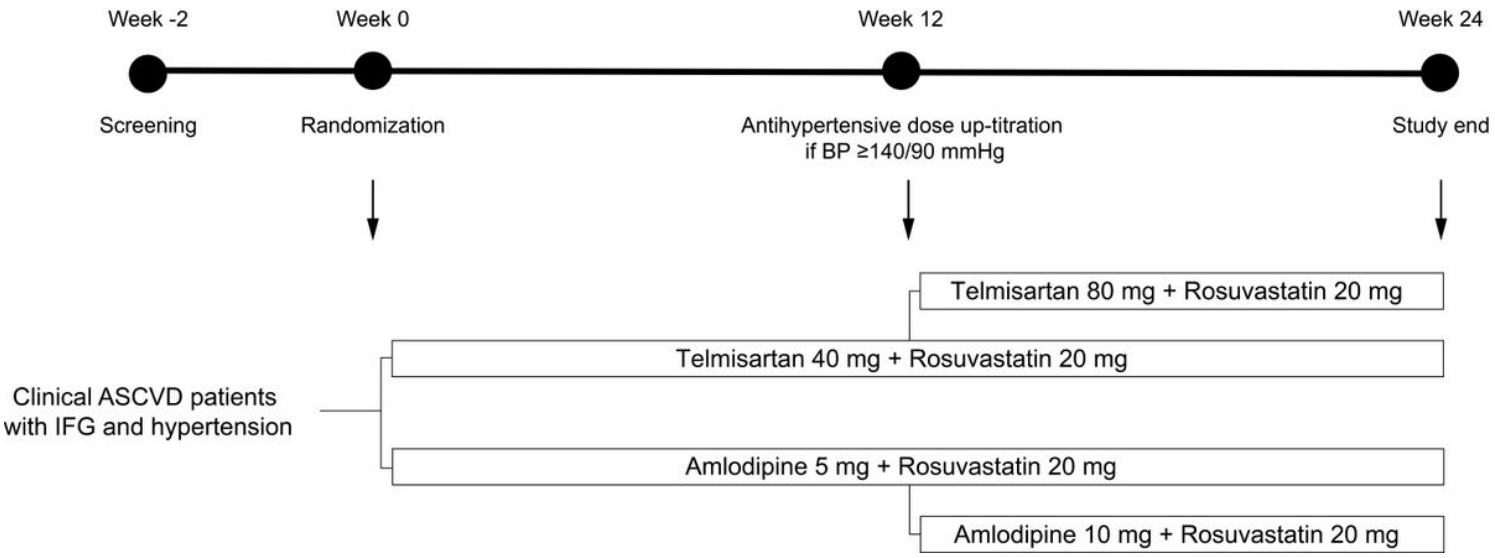

Figure 1

Study design and flow. BP, blood pressure; IFG, impaired fasting glucose.

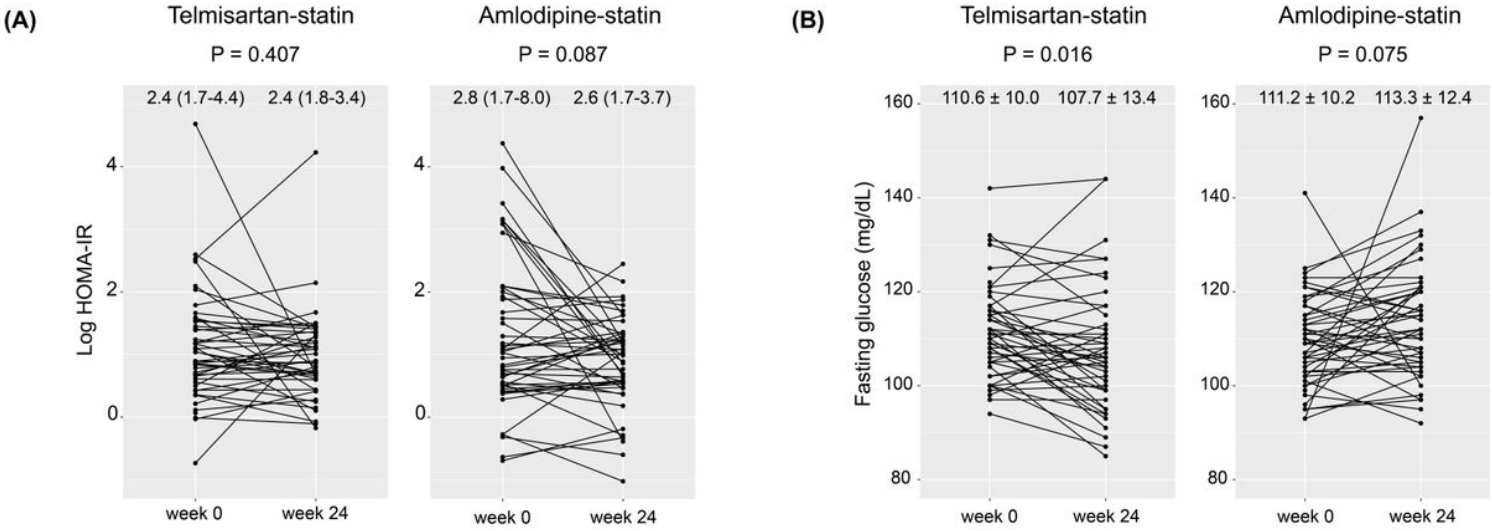

Figure 2

The change of HOMA-IR (A) and fasting glucose level (B) from week 0 to week 24 in each group. Values on the figure were median (interquartile range) or mean ± standard deviation. P values for Wilcoxon Signed Rank test (A) and paired T-test (B).

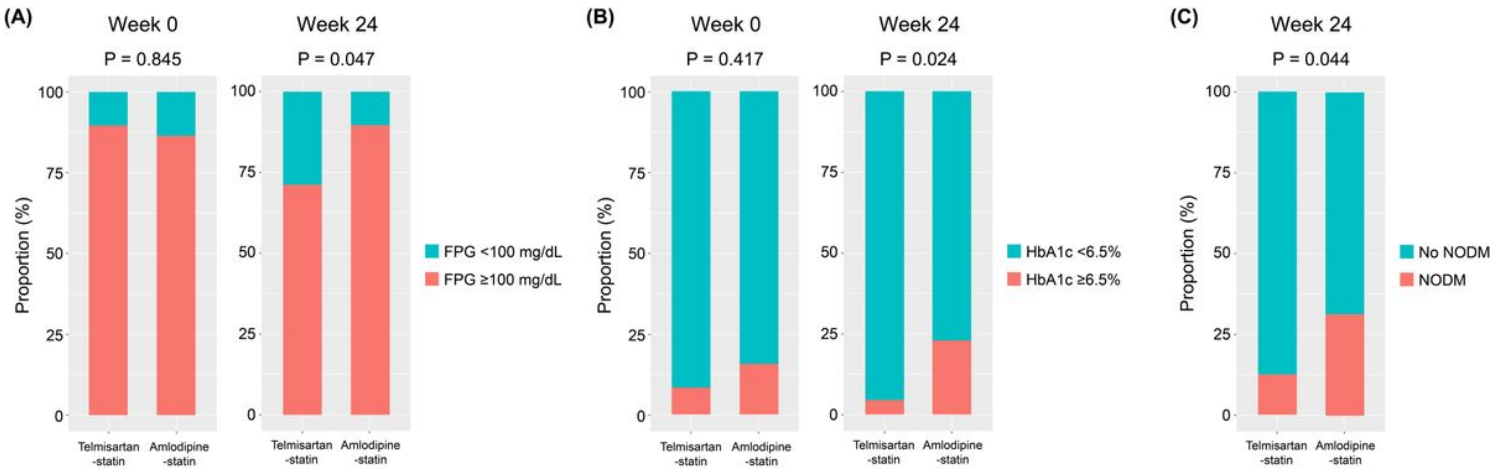

Figure 3

The proportion of participants with fasting plasma glucose ≥100 mg/dL (A) and HbA1c ≥6.5% (B) at week 0 and week 24 and new-onset DM (C) at week 24. FPG, fasting plasma glucose; NODM, new-onset DM.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplCOMPROMISEver6.0.docx
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