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Achievement of combined goals of low-density lipoprotein cholesterol and non-high-density lipoprotein cholesterol with three different statins: Results from VOYAGER☆,☆☆

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ABSTRACT

Background: Guidelines suggest that the combination of low-density lipoprotein cholesterol (LDL-C) and non-high-density lipoprotein cholesterol (non-HDL-C) is the most clinically relevant goal for lipid-lowering treatments.
Methods: Data from VOYAGER, an individual patient data meta-analysis including 32,258 patients from 37 clinical trials, was used to determine the percentage of patients reaching combined goals of LDL-C and non-HDL-C following treatment with simvastatin, atorvastatin, or rosuvastatin. Paired comparisons were made between each dose of rosuvastatin and the same or higher doses of simvastatin and atorvastatin.
Results: Each dose of rosuvastatin brought significantly more patients to the combined goal of LDL-C <100 mg/dL and non-HDL-C <130 mg/dL than the same or double dose of atorvastatin; atorvastatin 80 mg was significantly superior to rosuvastatin 10 mg (all $p < 0.001$). Each dose of rosuvastatin helped significantly more patients reach the combined goal than any dose of simvastatin (all $p < 0.001$), except for rosuvastatin 10 mg versus simvastatin 80 mg (non-significant). Also, each dose of rosuvastatin helped significantly more patients to reach the combined goal of LDL-C <70 mg/dL and non-HDL-C <100 mg/dL than the same or double dose of atorvastatin (all $p < 0.001$). Every dose of rosuvastatin was significantly superior to all doses of simvastatin (all $p \leq 0.020$), except for rosuvastatin 10 mg versus simvastatin 40 mg and 80 mg (non-significant).
Conclusions: Physicians' choice of statin and dose is important in helping patients achieve the combined LDL-C and non-HDL-C goals recommended in established guidelines.

1. Introduction

Low-density-lipoprotein cholesterol (LDL-C) has long been the primary target of cholesterol-lowering therapy and is recommended in most national and international guidelines [1–3]. However, there is also evidence that non-high-density lipoprotein cholesterol (non-HDL-C) may be an even better predictor of cardiovascular events [4–8]. Therefore, this measure also has a place in most guidelines [1–3] and was recently emphasized as a target in the 2013 position paper by the International Atherosclerosis Society [8]. In particular, non-HDL-C is claimed to provide a better risk estimation in certain patient groups, for example, those with hypertriglyceridemia combined with diabetes, the metabolic syndrome, or chronic kidney disease [2].

Several US guidelines and the European Society of Cardiology (ESC)/European Atherosclerosis Society (EAS) guidelines suggest a combined target of LDL-C <100 mg/dL and a non-HDL-C goal 30 mg higher (<130 mg/dL), especially in patients with elevated triglycerides [1,2,8,9]. In addition, for very high-risk patients, optional targets of LDL-C <70 mg/dL and non-HDL-C <100 mg/dL are included [1,2]. According to these recommendations, very high-risk patients include those with multiple major risk factors (especially diabetes), severe and poorly controlled risk factors (especially continued cigarette smoking), multiple risk factors for metabolic syndrome (especially

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Table 1
Baseline characteristics and lipid parameters of patients in the VOYAGER database.

Characteristics	n = 32,258
Age (years), mean (SD)	60.0 (11.1)
18–64, %	63.6
65–69, %	15.2
≥70, %	21.2
Men, %	56.7
Race, %	
White	79.9
Black	5.1
Hispanic	4.1
Asian	8.3
Other	2.6
Body mass index (kg/m^2), mean (SD)	28.8 (5.5)
Diabetes, %	27.5
Atherosclerotic disease, %	48.0
Baseline lipid levels (mg/dL), mean (SD)	
LDL-C	170.9 (38.7)
HDL-C	48.7 (12.7)
Non-HDL-C	205.2 (41.8)
TG, median (interquartile range)	162.2 (120.4, 215.0)
ApoB	159.3 (37.2)
ApoA-1	148.8 (28.7)

Apo = apolipoprotein; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; SD = standard deviation; TG = triglycerides.

high triglycerides >200 mg/dL plus non-HDL-C > 130 mg/dL with low HDL-C [<40 mg/dL]) and acute coronary syndromes.

More recently, there have been reports of suboptimal achievement of the combined LDL-C and non-HDL-C goal in hypertriglyceridemic and high-risk patients [10,11]. This may be partly due to lack of awareness of the non-HDL-C goal [10,12], but there may also be variability in the effectiveness of different lipid-lowering treatments on non-HDL-C.

The aim of the present analysis was to evaluate whether there are differences between statins in their ability to help patients to reach combined LDL-C and non-HDL-C goals using the VOYAGER (an indi-Vidual patient data meta-analysis Of statin therapY in At risk Groups: Effects of rosuvastatin, atorvastatin and simvastatin) meta-analysis database.

2. Methods

2.1. Study design

VOYAGER is an individual patient data meta-analysis including 32,258 patients from 37 clinical trials. The patients included and methods have been reported previously [13]. Only studies of fixed-dose comparisons of rosuvastatin with either simvastatin or atorvastatin that also recorded lipid parameters at baseline and on therapy for individual patients were included in the database.

All lipid parameters were quantified on samples collected in the fasting state. Cholesterol and triglyceride quantitation was determined by enzymatic assay. LDL-C was calculated using the Friedewald equation for patients with triglycerides ≤400 mg/dL and measured by quantification for those with triglycerides >400 mg/dL. HDL-C was quantified after the precipitation of apolipoprotein (Apo) B-containing lipoproteins. Levels of non-HDL-C were calculated by the subtraction of HDL-C from total cholesterol. ApoB levels at baseline were quantified by immunonephelometry.

2.2. Objective

The objective of this analysis was to determine the percentage of patients from the VOYAGER database reaching combined goals of LDL-C and non-HDL-C <100 and <130 mg/dL and <70 and <100 mg/dL, respectively, during treatment with simvastatin 10, 20, 40, and 80 mg, atorvastatin 10, 20, 40, and 80 mg, or rosuvastatin 10, 20, and 40 mg.

2.3. Statistical analysis

Least squares mean percentage change in LDL-C and non-HDL-C for each statin and dose was obtained from a mixed effects model.

For dual goal achievement, paired comparisons were made between each dose of rosuvastatin and the same or higher milligram doses of simvastatin or atorvastatin, with logistic regression models utilizing only studies directly comparing the pair of treatments by randomized design. All analyses were performed on the total VOYAGER population. Because some studies included forced titration, there were a total of 35,093 patient exposures to individual statin doses among the 32,258 patients included in the database. Each model had fixed effects for trial and treatment (two levels) and estimated the odds ratio for achieving the combined goals. Odds ratios are displayed in forest plots for rosuvastatin versus atorvastatin, and rosuvastatin versus simvastatin, with 95% confidence intervals.

3. Results

3.1. Patients

Baseline characteristics and lipid parameters of the patients included in the analysis are shown in Table 1.

3.2. LDL-C and non-HDL-C reductions

Least squares mean (LSM) reductions in LDL-C and non-HDL-C for each statin dose in this patient population are shown in Table 2.

For some statins and doses, LSM reductions in LDL-C and non-HDL-C were greater in females and in patients older than 65 years. Some of these effects reached statistical significance, but they were small (<2.4%), and not consistent across statins and doses. Atherogenic dyslipidemia status had no effect on the LSM reductions in LDL-C and non-HDL-C.

3.3. Combined goal of LDL-C <100 mg/dL and non-HDL-C <130 mg/dL

The percentages of patients reaching the combined goal of LDL-C <100 mg/dL and non-HDL-C <130 mg/dL are shown in Fig. 1. Fig. 2 shows paired comparisons of each dose of rosuvastatin with an equal or higher dose of atorvastatin or simvastatin, including only those studies that directly randomized patients to the treatments being compared. Each dose of rosuvastatin brought significantly more patients to the combined goal than the same or double dose of atorvastatin (all

Table 2
Least squares mean percentage change from baseline in LDL-C and non-HDL-C.

	Least squares mean (SE) % change from baseline										
	ATV 10 mg	ATV 20 mg	ATV 40 mg	ATV 80 mg	RSV 10 mg	RSV 20 mg	RSV 40 mg	SIM 10 mg	SIM 20 mg	SIM 40 mg	SIM 80 mg
No. of patients	7677	3607	1100	1853	11,437	2886	2463	165	2885	542	478
LDL-C	−35.9	−42.1	−46.4	−50.5	−44.5	−50.1	−54.9	−27.8	−33.3	−39.4	−45.3
Non-HDL-C	−33.4	−38.9	−42.7	−47.0	−40.8	−45.7	−50.2	−25.4	−30.6	−35.8	−41.0

ATV = atorvastatin; LDL-C = low-density lipoprotein cholesterol; non-HDL-C = non-high-density lipoprotein cholesterol; RSV = rosuvastatin; SIM = simvastatin.

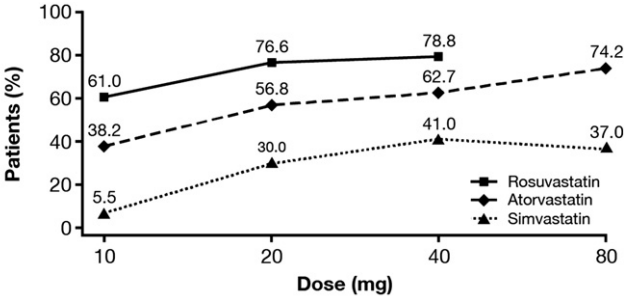

Fig. 1. Percentages of patients achieving both low-density lipoprotein cholesterol <100 mg/dL and non-high-density lipoprotein cholesterol <130 mg/dL goals.

$p < 0.001$); atorvastatin 80 mg was significantly superior to rosuvastatin 10 mg ($p < 0.001$) (Fig. 2a).

Likewise, each dose of rosuvastatin helped significantly more patients to reach the combined goal than any dose of simvastatin (all $p < 0.001$), with the exception of rosuvastatin 10 mg versus simvastatin 80 mg (p = non-significant [NS]) (Fig. 2b).

Interaction tests showed that the results applied equally whether patients were considered high-risk or not. The percentages of patients reaching the individual goals of LDL-C <100 mg/dL or non-HDL-C <130 mg/dL with each dose of rosuvastatin, simvastatin, or atorvastatin are shown in Table 3.

3.4. Combined goal of LDL-C <70 mg/dL and non-HDL-C <100 mg/dL

The percentages of patients reaching the lower combined goal of LDL-C <70 mg/dL and non-HDL-C <100 mg/dL are shown in Fig. 3.

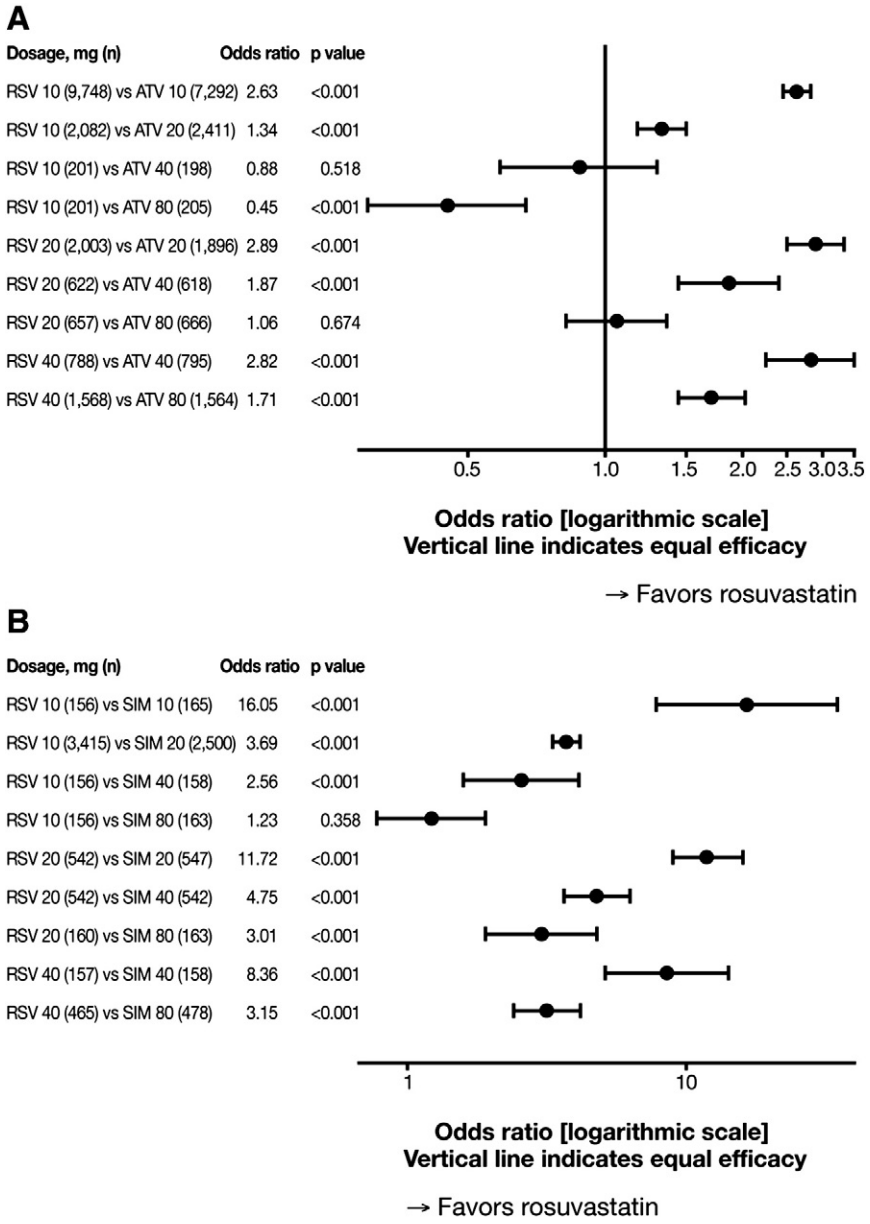

Fig. 2. Odds ratio for low-density lipoprotein cholesterol <100 mg/dL and non-high-density lipoprotein cholesterol <130 mg/dL goal achievement, with 95% confidence interval: rosuvastatin compared with equal and higher doses of (A) atorvastatin and (B) simvastatin. ATV = atorvastatin; RSV = rosuvastatin; SIM = simvastatin.

Table 3
Patients (%) achieving combined low-density lipoprotein cholesterol and non-high-density lipoprotein cholesterol goals.

Goal	ATV 10 mg	ATV 20 mg	ATV 40 mg	ATV 80 mg	RSV 10 mg	RSV 20 mg	RSV 40 mg	SIM 10 mg	SIM 20 mg	SIM 40 mg	SIM 80 mg
No. of patients	7677	3607	1100	1853	11,437	2886	2463	165	2885	542	478
LDL-C <100 mg/dL and non-HDL-C <130 mg/dL											
LDL-C <100 mg/dL	43.1	61.6	67.8	77.3	65.7	80.1	81.8	7.9	35.1	47.2	42.5
Non-HDL-C <130 mg/dL	48.6	65.0	70.4	78.8	67.8	80.9	82.5	9.7	39.3	49.3	44.8
Both	38.2	56.8	62.7	74.2	61.0	76.6	78.8	5.5	30.0	41.0	37.0
LDL-C <70 mg/dL and non-HDL-C <100 mg/dL											
LDL-C <70 mg/dL	6.1	14.5	17.7	30.8	21.8	38.0	38.9	0.0	3.7	7.6	2.9
Non-HDL-C <100 mg/dL	11.1	22.5	26.1	40.5	28.9	43.8	47.5	0.6	7.3	11.8	7.3
Both	4.9	12.3	15.5	27.6	18.6	33.6	35.1	0.0	2.8	6.3	1.7

ATV = atorvastatin; LDL-C = low-density lipoprotein cholesterol; non-HDL-C = non-high-density lipoprotein cholesterol; RSV = rosuvastatin; SIM = simvastatin.

Fig. 4 shows paired comparisons of each dose of rosuvastatin with an equal or higher dose of atorvastatin or simvastatin, including only those studies that directly randomized patients to the treatments being compared. With each dose of rosuvastatin, significantly more patients achieved this combined goal than the same or double dose of atorvastatin (all $p < 0.001$). Atorvastatin 40 mg and 80 mg brought significantly more patients to goal than rosuvastatin 10 mg ($p = 0.038$ and $p < 0.001$, respectively), with no significant difference between rosuvastatin 20 mg and atorvastatin 80 mg ($p = NS$).

In addition, significantly more patients achieved the combined goal for every dose comparison between rosuvastatin and equal or higher doses of simvastatin (all $p \leq 0.020$), with the exception of rosuvastatin 10 mg versus simvastatin 40 mg and 80 mg ($p = NS$).

Once again, interaction tests showed that the results applied equally whether patients were considered high-risk or not. The percentages of patients reaching the individual goals of LDL-C <70 mg/dL or non-HDL-C <100 mg/dL with each dose of rosuvastatin, simvastatin, or atorvastatin are shown in Table 3.

4. Discussion

The results of this analysis suggest that treating patients with a more potent statin and at an adequate dose may be beneficial in helping patients to achieve the combined LDL-C and non-HDL-C goals recommended in several guidelines [1–3], and also in reaching each of these goals individually.

In a previous analysis from VOYAGER, increasing statin potency and dose were shown to be beneficial in terms of achievement of the European goal for high-risk patients of LDL-C <70 mg/dL or ≥50% reduction in LDL-C, with statistically significant differences between rosuvastatin and equal or double milligram doses of atorvastatin or simvastatin [14].

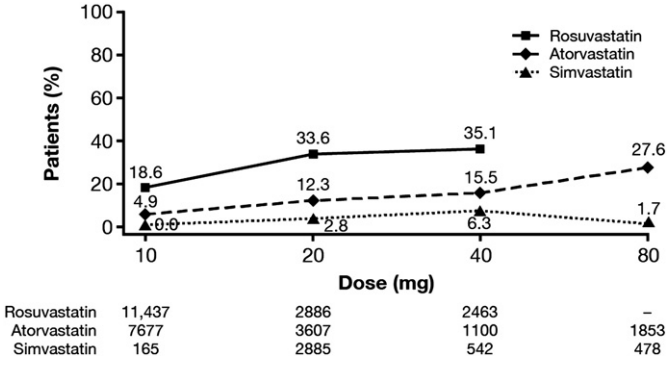

Fig. 3. Percentages of patients achieving both low-density lipoprotein cholesterol <70 mg/dL and non-high-density lipoprotein cholesterol <100 mg/dL goals.

As demonstrated in Figs. 1 and 3, it is not always easy to get patients to the suggested combined goals, especially the lower combined goal of LDL-C <70 mg/dL and non-HDL-C <100 mg/dL recommended for high-risk patients; even with the help of the highest doses of statins, a substantial number of patients do not reach the combined goals. Future studies and experience will confirm if add-on therapy with newer drugs with complementary mechanisms of action will help more patients to reach these goals, and in doing so whether they will reduce the overall risk of cardiovascular events.

Previous studies have indicated that the non-HDL-C goal may be more difficult to attain than the LDL-C goal [11,15]. In contrast, the present study showed that slightly more patients achieved the non-HDL-C goals (<130 and <100 mg/dL) than the LDL-C goals (<100 and <70 mg/dL).

LSM reductions in LDL-C and non-HDLC were slightly greater in females and in patients older than 65 years. These effects reached statistical significance because of large sample sizes, but they were small (<2.4%), not consistent across statins and doses, and therefore we feel of very limited clinical relevance.

Although the 2013 American College of Cardiology and American Heart Association guidelines differ from other recent guidelines in that they do not recommend treating patients to a specific LDL-C goal, current guidelines are uniform in that they all focus on using statin treatment to reduce LDL-C and thereby reduce cardiovascular risk [2,3,8,16]. The importance of non-HDL-C as a superior risk indicator has also been recently emphasized [8].

A limitation of the present study is that patients were not stratified according to overall cardiovascular risk or baseline triglyceride level. Another limitation of this meta-analysis is that the VOYAGER database does not hold safety or outcome data so comparisons in these respects between statins are not possible.

In conclusion, physicians' choice of statin and dose is important in helping patients achieve the recommended combined LDL-C and non-HDL-C goals.

Conflicts of interest

Dr Karlson is an employee of AstraZeneca. Dr Toth has received fees for participation in speaker's bureaus from Amarin, AstraZeneca, GSK, Kowa, and Merck; acted as a consultant for Amgen, AstraZeneca, Atherotech, Boehringer-Ingelheim, Genzyme, Kowa, Liposcience, Merck, and Novartis. Dr Palmer has received fees for statistical analysis from AstraZeneca. Prof. Barter has received speaker fees from AstraZeneca. Dr Nicholls has received research support from AstraZeneca.

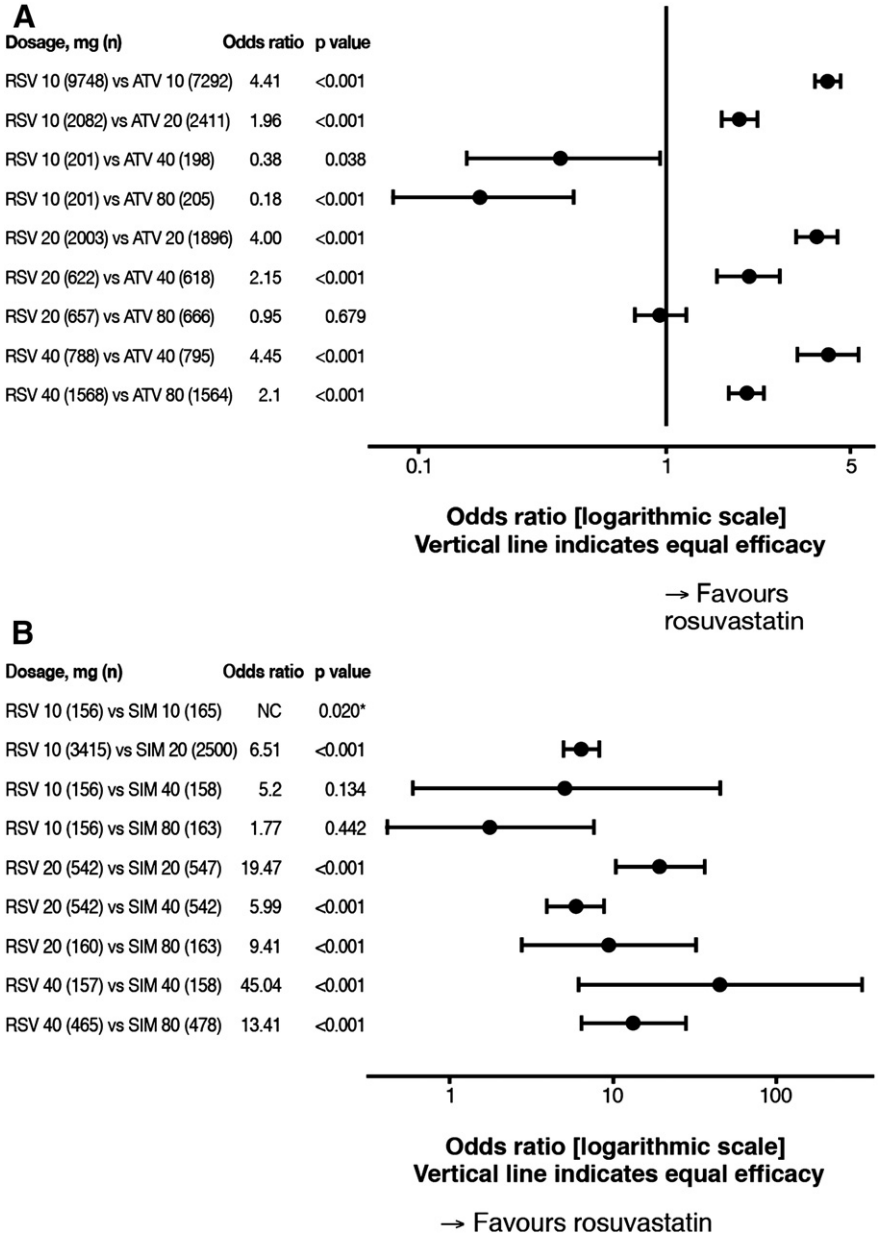

Fig. 4. Odds ratio for low-density lipoprotein cholesterol <70 mg/dL and non-high-density lipoprotein cholesterol <100 mg/dL goal achievement, with 95% confidence interval: rosuvastatin compared with equal and higher doses of (A) atorvastatin and (B) simvastatin. *Chi-square test. Odds ratio could not be calculated because target achievement was zero in the simvastatin group. ATV = atorvastatin; RSV = rosuvastatin; SIM = simvastatin.

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