Original Article

The Use of Plaque Score Measurements to Assess Changes in Atherosclerotic Plaque Burden Induced by Lipid-Lowering Therapy Over Time: The METEOR Study

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Aim: To evaluate whether plaque scoring measurements are able to track changes in atherosclerotic plaque burden over time and to study whether this is affected by lipid-lowering therapy.

Methods: Data used were from METEOR (Measuring Effects on Intima-Media Thickness: an Evaluation Of Rosuvastatin), a randomized controlled trial of rosuvastatin 40 mg among 984 low-risk patients with modest carotid intima-media thickening (CIMT). In this analysis, duplicate ultrasound images from 12 carotid sites were collected at the baseline and end of the study from 495 European patients and were evaluated for plaque presence and severity. Plaques were scored from near and far walls of the 12 sites (0 = none; 1 = minimal; 2 = moderate; 3 = severe) and plaque scores (PS) were combined into two summary measures for each examination. The MeanMaxPS is the mean over the 12 carotid sites of the maximum score at each site and the MaxMaxPS reflects the most severe lesion at any site.

Results: Baseline MeanMaxPS and MaxMaxPS were 0.31 (SD: 0.20) and 1.15 (SD: 0.51), respectively. Changes in MeanMaxPS and MaxMaxPS significantly differed between rosuvastatin and placebo (mean difference: -0.03 [SE: 0.01; $p=0.016$] and -0.09 [SE: 0.04; $p=0.027$], respectively). In contrast to rosuvastatin, which demonstrated no change from the baseline, placebo showed significant progression in MeanMaxPS and MaxMaxPS ($p=0.002$; both).

Conclusion: The plaque-scoring method proved capable of assessing the change in atherosclerotic plaque burden over time and proved useful to evaluate lipid-lowering in asymptomatic individuals with a low risk of cardiovascular disease and subclinical atherosclerosis.

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Key words; Plaque score, B-mode ultrasound, Atherosclerosis, Clinical trial, Statin

Introduction

Cardiovascular disease is a clinical manifestation

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of atherosclerosis, a chronic and progressive disease of the arterial wall that is the major cause of disability and death in both low and high income countries. Lipid-lowering strategies, in particular statin treatment, together with lifestyle changes, have been shown to slow or even reverse the development of atherosclerosis¹. Carotid intima-media thickness (CIMT), as assessed using B-mode ultrasound, is a subclinical marker of atherosclerosis and changes in CIMT over time are commonly used in clinical trials

to evaluate the cardiovascular effects of pharmaceutical interventions^{2,3}).

As for CIMT, the presence of atherosclerotic plaque in the carotid artery has consistently been associated with cardiovascular risk factors and with prevalent and incident vascular events⁴⁻¹⁵. Moreover, measurement of changes in plaque volume may be of value in assessing changes in atherosclerotic burden over time, as some studies have found a stronger association with vascular events for plaques than for CIMT^{4, 5, 7, 11, 13}. Because CIMT and atherosclerotic plaques reflect different stages of the atherosclerotic process¹⁶, it would be of value to determine the ability of ultrasound-detected carotid plaque burden to measure changes in atherosclerotic plaque burden over time.

Recent studies using carotid magnetic resonance imaging (MRI) and coronary intravascular ultrasound (IVUS) suggested that plaque volume is affected in a beneficial manner through lipid lowering¹⁷⁻²⁰. These imaging modalities are rather expensive and are subsequently not easily applicable for large groups of individuals; however, B-mode ultrasound could be used to examine the presence and severity of atherosclerotic plaques in a safe, relatively inexpensive, simple, reliable, and reproducible manner. A simple and inexpensive measure to assess atherosclerotic plaque burden might be of great value in clinical research to study the effects of interventions and clinical practice as a screening tool for the severity of atherosclerotic disease. Studies evaluating the changes in atherosclerotic plaque burden over time with cheaper and simpler ultrasound methods, however, have not been reported. Therefore, we set out to study the ability of an easily applicable plaque-scoring method to assess changes in plaque size and severity, attenuated by lipid-lowering therapy, over time.

Methods

Study Population

The rationale, design, and main findings of METEOR have been reported in detail previously^{21, 22}. In essence, METEOR was a randomized, double-blind, placebo-controlled trial among 984 individuals from Europe and North America. Main inclusion criteria were: age 45-70 years (male) or 55-70 years (female); screening low-density lipoprotein cholesterol (LDL-C) 3.1 to <4.9 mmol/L (120 to <190 mg/dL) for those with only age as a coronary heart disease (CHD) risk factor, or 3.1 to <4.1 mmol/L (120 to <160 mg/dL) for individuals with ≥ 2 CHD risk factors and a 10-year Framingham risk of <10%, and at least 1 maximum CIMT measurement ≥ 1.2 mm and no

measurement ≥ 3.5 mm from 2 separate ultrasound examinations.

The main objective of METEOR was to assess the impact of rosuvastatin 40 mg daily versus placebo on the 2-year rate of change in CIMT. Eligible participants were randomized to either rosuvastatin or placebo in the ratio of rosuvastatin 5: placebo 2. Duplicate carotid ultrasound examinations were performed at baseline and at the end of the study 2 years later. Single examinations were performed at 6-month intervals as detailed elsewhere²³.

Here, we report the post-hoc analysis of temporal changes in plaque presence and severity in a subset of METEOR participants. For logistic reasons and to facilitate reproducibility studies, this analysis was limited to European METEOR participants that completed 24 months of follow-up on study medications with duplicate ultrasound examinations at the baseline and end of the study ($n=495$).

Carotid Ultrasound Imaging

For each participant examination, ultrasound images were collected from 12 well-defined arterial sites ($2 \times 2 \times 3$): the near and far walls of the right and left common carotid arteries, bifurcation, and the internal carotid artery. For each of the 12 wall sites, images were collected from 5 circumferential angles separated by 30° using Meijer's Carotid Arc²¹. For the bifurcation and internal carotid artery, near and far wall sites were imaged separately, but for the common carotid artery, near and far wall sites were imaged simultaneously to allow measurement of lumen diameter. A complete ultrasound examination therefore consists of 50 images (20 bifurcation images, 20 internal carotid images, and 10 common carotid images). The entire ultrasound examination was recorded on super VHS videotapes and recordings for the European participants were sent to the core laboratory at the University Medical Center Utrecht, the Netherlands.

The primary endpoint of the METEOR study was the annualized rate of change in the mean of the maximum (MeanMax) CIMT measurements based on all scans performed during the 2-year study period from each of the 12 carotid artery sites. The maximum CIMT at each of the 12 sites is defined as the largest measurement derived from five interrogation angles, each one 30° different from the adjacent angle.

Plaque Assessment

For the present analyses, images from the 5 circumferential angles from 12 arterial sites were scored for the presence and severity of plaques using a 4 level

Fig. 1. Score of carotid plaques on B-mode ultrasound images. CIMT, carotid intima-media thickness.

A: Score 0: No plaque: No plaque and no CIMT thickening.

B: Score 1: Minimal (small focal) plaque: Minimal, uni/multifocal thickening of the intima-media layer. There is no to minimal diameter reduction of the lumen.

C: Score 2: Moderate plaque: There is a uni/multifocal thickening present that is easily seen. There is minimal to moderate lumen diameter reduction.

D: Score 3: Severe plaque: There is abundant plaque formation present that is always associated with moderate to significant diameter reduction.

rating scale: 0=no plaque, 1=minimal plaque, 2=moderate plaque, and 3=severe plaque. **Fig. 1** provides image examples of the classification of the plaques.

The categories of moderate and severe plaques were generally consistent with the Mannheim definition²⁴⁾ of plaque as a focal structure that encroaches into the arterial lumen or demonstrates a thickness >1.5 mm. When more than 1 plaque was present on a single image, only the most severe plaque was evaluated. Scoring was based solely on the size and appearance of the plaque without further quantification.

Plaque Endpoint

For each individual, 2 summary plaque scores (PS) were constructed for each of the 4 examinations. The MeanMaxPS was the mean over the 12 carotid sites of the maximum score at each site. The single maximum PS (MaxMaxPS) was the most severe lesion

at any of the 12 sites on an ultrasound examination. For each PS, participant-specific change scores were calculated by subtracting the average of the 2 baseline examinations from the average of the 2 end of study examinations.

Reproducibility

Six readers previously certified to collect CIMT measurements in the METEOR study were trained and certified in the plaque-scoring method. Certification was achieved in 2 steps and required an estimated within-reader Intraclass Correlation Coefficient (ICC) of 0.80 or above based on repeat readings. Readers started with a repeat reading set of 52 randomly selected B-mode images where an ICC was estimated using the results from the repeat image evaluations. When the ICC was satisfactory, readers started with a repeat reading of a set of 21 participant scans where the ICC was based on the repeated MeanMaxPlaque

Score of each participant.

For each participant, all 4 scans (duplicate baseline and duplicate end-of-study scans) were read in batch fashion, with scans read in random order by a single reader blinded to the treatment allocation over a brief period of time to minimize any potential reader drift in plaque scores.

Statistical Analysis

All 495 European patients completing 24 months of follow-up on study medications with duplicate ultrasound examinations at the baseline and end of the study were included in these analyses. Baseline characteristics were reported as the means and standard deviations or percentages. The ICC was used to assess the reproducibility of the plaque assessment between duplicate baseline and duplicate end-of-study visits. Two-sample *t*-tests were used to compare changes in plaque over time between the treatment groups. In addition, paired *t*-tests were used to determine whether plaque scores in end-of-study examinations differed from those at the baseline within the treatment groups.

To examine the consistency of treatment effects on changes in plaque scores across subgroups, we used a series of multiple linear regression models. Each model included an indicator variable for the treatment group and subgroup under consideration as well as a term for the 2-way interaction between these factors. The following baseline factors were considered as subgroups and examined in dividually: age, sex, body mass index, alcohol use, current smoking, hypertension, family history of premature coronary artery disease, Framingham risk score, high-density lipoprotein cholesterol (HDL-C), LDL-C, creatinine clearance, MeanMaxCMT, and MaxMaxPS. Cut-off points were, in case of continuous variables, based on the population median.

Spearman correlation coefficients were used to examine the relation between changes in the plaque score and CMT. Since rosuvastatin may have different effects on changes in the plaque score than in CMT, only participants from the placebo group were used for this analyses. Differences in baseline characteristics and the rate of change of MeanMaxCMT in participants with and without progression in MeanMaxPS were examined. MeanMaxPS had progressed when the end-of-study MeanMaxPS was higher than the baseline MeanMaxPS. Also, the proportional change in MaxMaxPS between duplicate baseline and end-of-study examinations was evaluated by constructing cross tabs. The proportion of participants with a higher or lower MaxMaxPS at the end of the

study when compared to baseline MaxMaxPS was calculated and the difference between treatment allocations was evaluated.

All statistical analyses were performed using SPSS 15.0. Two-sided significance levels of 5% and 95% confidence intervals (CI) were used for statistical inference.

Results

Consistent with the 5:2 randomization scheme for the METEOR trial, these analyses included 343 patients randomized to the rosuvastatin group and 152 randomized to the placebo group. Baseline characteristics of these patients were generally balanced between the 2 treatment groups, although placebo patients were slightly more likely to have hypertension (**Table 1**).

Across all carotid sites and angles rated for the duplicate baseline examinations, 6.7% of the participants had no plaques, 93.3% had at least 1 minimal plaque, 21.1% had at least 1 moderate plaque, and 2.7% had at least 1 severe plaque. Participants in both groups had at baseline on average three carotid sites with a plaque (SD: 2.0). The mean plaque scores in the total population at baseline were 0.31 (SD: 0.2) for the MeanMaxPS and 1.15 (SD: 0.51) for the MaxMaxPS.

Reproducibility based on measurements from duplicate baseline ultrasound assessments was better for MeanMaxPS than for MaxMaxPS. Analysis of the ICC showed 0.71 for MeanMaxPS and 0.61 for MaxMaxPS. Results for end-of-study visits were 0.78 for MeanMaxPS and 0.71 for MaxMaxPS.

In European participants (the study population for this analysis), rosuvastatin 40 mg was associated with a 49% reduction in LDL-C and an 8% increase in HDL-C, whereas participants in the placebo group showed no change in LDL-C and a 2% increase in HDL-C after 2 years of follow-up ($p < .001$ for rosuvastatin compared with placebo for both changes).

Participants receiving rosuvastatin had on average 3 carotid sites with a plaque after two years of follow-up, whereas those in the placebo group had plaques at 4 sites (SD: 2.0 both). Plaque scores and changes in plaque scores over time are shown in **Table 2**. The MeanMaxPS at baseline was on average 0.30 (SE 0.01) for the rosuvastatin group and 0.31 (SE 0.02) for the placebo group. At the end of the study, the MeanMaxPS was 0.31 (SE: 0.01) for the rosuvastatin group and 0.35 (SE: 0.02) for the placebo group. The MaxMaxPS at baseline was 1.16 (SE: 0.03) in the rosuvastatin group and 1.14 (SE: 0.04) in the placebo group.

Table 1. Baseline characteristics of the studied population

	Overall (<i>n</i> = 495)	Rosuvastatin (<i>n</i> = 343)	Placebo (<i>n</i> = 152)
Age, mean (SD)	56 (6)	56 (6)	57 (6)
Sex male (%)	64	62	67
Body Mass Index, mean (SD)	27 (4)	26 (4)	27 (3)
Current alcohol use (%)	66	65	69
Current smoking (%)	4	4	5
Hypertension (%)	21	19	25
Family history of premature CHD (%)*	8	8	9
Framingham total score, mean (SD)	13 (3)	13 (3)	13 (3)
HDL-C (mmol/L), mean (SD)	1.30 (0.23)	1.30 (0.23)	1.32 (0.23)
LDL-C (mmol/L), mean (SD)	3.99 (0.65)	3.99 (0.65)	3.99 (0.62)
Creatinine clearance (mL/min), mean (SD)	101 (23)	101 (24)	101 (20)

To convert HDL-C and LDL-C from mmol/L to mg/dL, multiply by 38.6.

*Defined as CHD in a first-degree male relative younger than 55 years or in a first-degree female relative younger than 65 years. SD, standard deviation; CHD, coronary heart disease; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

Table 2. Plaque scores and changes in plaque scores over time

	Mean plaque score (SE)							<i>p</i> -value		
	Baseline		End of study		Change in over time			Rosuvastatin vs. Placebo	Within group vs. no change	
	Rosuvastatin	Placebo	Rosuvastatin	Placebo	Rosuvastatin	Placebo	Difference		Rosuvastatin	Placebo
MeanMaxPS	0.30 (0.01)	0.31 (0.02)	0.31 (0.01)	0.35 (0.02)	0.005 (0.01)	0.035 (0.01)	−0.030 (0.01)	0.016	0.42	0.002
MaxMaxPS	1.16 (0.03)	1.14 (0.04)	1.17 (0.03)	1.24 (0.04)	0.015 (0.02)	0.102 (0.03)	−0.087 (0.04)	0.027	0.51	0.002
MeanMax CIMT					0.003 (0.002)	0.015 (0.003)	−0.014 (0.003)	<0.001	0.85	<0.001

SE, standard error; MeanMaxPS, mean over the 12 carotid segments of the maximum score in each segment (range 0–3); MaxMaxPS, single maximum plaque score of each of the 12 carotid segments (range 0–3); MeanMaxCIMT, mean of the maximum carotid intima-media thickness of each of the 12 carotid segments.

At the end of the study, the average MaxMaxPS was 1.17 (SE: 0.03) for participants randomized to rosuvastatin and 1.24 (SE: 0.04) for participants randomized to placebo. Changes in the rosuvastatin group for MeanMaxPS and MaxMaxPS were small and not significantly different from zero (mean change + SE was 0.005 + 0.007 for MeanMaxPS and 0.015 + 0.022 for MaxMaxPS). For the placebo group, changes were larger and represented significant progression (0.035 + 0.011 for the MeanMaxPS and 0.102 + 0.033 for the MaxMaxPS). Two-sample *t*-test for differences PS change over time between the treatment arms showed that PS progression in the placebo group was significantly greater than in the rosuvastatin group for both parameters (*p* = 0.016 for MeanMaxPS and *p* = 0.027

for MaxMaxPS). With the exception of a larger benefit in the change in the maximum plaque score in older subjects, we found no significant differences in treatment effects between subgroups based on age, sex and CVD risk factors (Table 3).

Fig. 2 shows the positive correlation between the rate of change in MeanMaxPS and change in MeanMaxCIMT over time in the placebo group (Spearman *r* = 0.477). The Spearman correlation coefficient between changes in MaxMaxPS and MeanMaxCIMT was 0.277.

The characteristics of participants based on the progression of MeanMaxPS and treatment allocation are shown in Table 4. The rate of change in CIMT was positive in participants who showed progression

Table 3. Stratified analyses on baseline characteristics and changes in plaque scores over time

Characteristic	Cut-off point	MeanMaxPS		MaxMaxPS	
		Difference (R-P) in change from baseline to 2 years, mean (95%CI)	<i>p</i> -value*	Difference (R-P) in change from baseline to 2 years, mean (95%CI)	<i>p</i> -value*
Age	< 56	-0.03 (-0.06-0.00)	0.77	-0.01 (-0.10-0.09)	0.04
	≥ 56	-0.03 (-0.07-0.01)		-0.17 (-0.29-0.05)	
Sex	Male	-0.03 (-0.06-0.00)	0.85	-0.07 (-0.16-0.02)	0.43
	Female	-0.03 (-0.08-0.01)		-0.13 (-0.28-0.01)	
Body Mass Index	< 25	-0.04 (-0.09-0.00)	0.42	-0.07 (-0.21-0.08)	0.71
	≥ 25	-0.02 (-0.05-0.01)		-0.10 (-0.19-0.00)	
Alcohol use	No	-0.03 (-0.07-0.02)	0.93	-0.11 (-0.25-0.03)	0.68
	Yes	-0.03 (-0.06-0.00)		-0.08 (-0.17-0.02)	
Smoking	No	-0.03 (-0.06-0.01)	0.21	-0.09 (-0.17-0.01)	0.70
	Yes	0.04 (-0.12-0.20)		-0.02 (-0.53-0.51)	
Hypertension	No	-0.03 (-0.06-0.00)	0.67	-0.10 (-0.19-0.01)	0.68
	Yes	-0.02 (-0.07-0.03)		-0.06 (-0.22-0.10)	
Family history of premature CHD [†]	No	-0.02 (-0.05-0.00)	0.12	-0.08 (-0.16-0.00)	0.56
	Yes	-0.09 (-0.17-0.01)		-0.16 (-0.42-0.09)	
Framingham total score	< 13	-0.02 (-0.07-0.04)	0.87	-0.11 (-0.27-0.05)	0.30
	≥ 13	-0.01 (-0.07-0.05)		0.02 (-0.18-0.22)	
HDL-C	< 1.30 mmol/L	-0.04 (-0.07-0.00)	0.57	-0.06 (-0.17-0.04)	0.54
	≥ 1.30 mmol/L	-0.02 (-0.06-0.01)		-0.11 (-0.23-0.01)	
LDL-C	< 4.00 mmol/L	-0.03 (-0.06-0.01)	0.68	-0.08 (-0.18-0.03)	0.82
	≥ 4.00 mmol/L	-0.04 (-0.07-0.00)		-0.10 (-0.21-0.02)	
Creatinine clearance	< 100 mL/min	-0.01 (-0.05-0.03)	0.09	0.01 (-0.12-0.13)	0.09
	≥ 100 mL/min	-0.05 (-0.08-0.02)		-0.14 (-0.25-0.03)	
Baseline MeanMaxCIMT	< 1.11 mm	-0.05 (-0.08-0.02)	0.25	-0.06 (-0.18-0.06)	0.62
	≥ 1.11 mm	-0.02 (0.05-0.02)		-0.10 (-0.21-0.01)	
Baseline MaxMaxPS	≤ 1	-0.03 (-0.06-0.01)	0.89	-0.09 (-0.17-0.01)	0.98
	> 1	-0.03 (-0.09-0.04)		-0.09 (-0.28-0.10)	

To convert HDL-C and LDL-C from mmol/L to mg/dL, multiply by 38.6.

**P*-value of interaction term between treatment allocation and characteristics in a multivariate linear regression model with treatment allocation and baseline characteristics as independent variables; [†] Defined as CHD in a first-degree male relative younger than 55 years or in a first-degree female relative younger than 65 years.

R, rosuvastatin; P, placebo; CI, confidence interval; MeanMaxPS, mean over the 12 carotid segments of the maximum score in each segment (range 0-3); MaxMaxPS, single maximum plaque score of each of the 12 carotid segments (range 0-3); CHD, coronary heart disease; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MeanMaxCIMT, mean of the maximum carotid intima-media thickness of each of the 12 carotid segments.

in MeanMaxPS (Rosuvastatin: +0.002 (SE: 0.001); Placebo: +0.007 (SE: 0.001)) and negative in participants without progression in MeanMaxPS (Rosuvastatin: -0.008 (SE: 0.001); Placebo: -0.002 (SE: 0.001)).

Table 5 shows the proportion of participants with a higher, lower, or equal MaxMaxPS at the end of the study when compared to the baseline. The MaxMaxPS increased in 21.3% of the participants randomized to rosuvastatin and in 25.0% of the participants randomized to placebo. MaxMaxPS

decreased in 17.2% of the participants randomized to rosuvastatin and in 9.2% of the participants randomized to placebo. The *p*-value of the chi-squared test for differences between groups was 0.006.

Discussion

The present study shows the ability of a simple plaque-scoring method to track changes in atherosclerotic plaque burden over time and to detect the effect of intensive lipid-lowering therapies. Assessment of

changes in atherosclerotic plaque might be useful in trials examining the early effects of new treatments for atherosclerosis.

Our findings with the plaque-scoring method are in agreement with previous studies that showed a beneficial effect of statin therapy on changes in plaque burden over time^{17-20, 25-29}; however, these studies used more expensive and complex imaging modalities to demonstrate a treatment effect. Corti *et al.* used MRI to demonstrate a dose-independent decrease in carotid and aortic plaque burden and an increase in the luminal area after 2 years of simvastatin therapy^{27, 28}. Also using MRI, the ORION trial found no significant change in the overall carotid lesion size over 2 years of treatment with rosuvastatin in 33 subjects, but did find a significant decrease in the lipid-rich/necrotic-core component of the plaques²⁰. Attenuation of the rate of change in coronary plaque burden was found in the REVERSAL¹⁷ and ESTABLISH¹⁹ trials which assessed the effect of atorvastatin using IVUS. In addition, the ASTEROID trial evaluated the effect of rosuvastatin on coronary atherosclerosis. After 2 years of treatment, the median atheroma volume in the most diseased 10-mm subsegment decreased by 9.1% by IVUS¹⁸, and quantitative coronary angiography showed a significant reduction of coronary stenoses²⁶. Also, the JAPAN-ACS study showed that the use

Fig. 2. Relationship between change in MeanMaxPS and change in MeanMaxCIMT (Spearman correlation = 0.48). MeanMaxCIMT, mean of the maximum carotid intima-media thickness of each of the 12 carotid segments; MeanMaxPS, mean of the maximum plaque score (range 0-3) of each of the 12 carotid segments.

Table 4. Baseline characteristics of the studied population by treatment allocation and change in plaque score

	Rosuvastatin		Placebo	
	Progression PS (n = 168)	No PS Progression (n = 175)	Progression PS (n = 84)	No Progression PS (n = 68)
Age, mean (SD)	57 (6)	56 (6)	57 (6)	57 (7)
Sex male (%)	63	61	67	68
Body Mass Index, mean (SD)	26 (4)	27 (4)	27 (4)	27 (3)
Current alcohol use (%)	60	70	73	65
Current smoking (%)	5	3	5	6
Hypertension (%)	20	18	24	27
Family history of premature CHD (%)*	4	11	7	12
Framingham total score, mean (SD)	13 (3)	13 (4)	13 (3)	13 (3)
HDL-C (mmol/L), mean (SD)	1.30 (0.22)	1.31 (0.25)	1.32 (0.24)	1.28 (0.23)
LDL-C (mmol/L), mean (SD)	3.94 (0.61)	4.01 (0.68)	4.00 (0.63)	3.99 (0.60)
Creatinine clearance (mL/min), mean (SD)	98.73 (23.00)	102.40 (24.90)	100.01 (17.76)	101.43 (22.67)
Change in CIMT, mm (SD)	0.002 (0.007)	-0.008 (0.006)	0.007 (0.007)	-0.002 (0.008)

MeanMaxPS had progressed when the end-of-study MeanMaxPS was higher than the baseline MeanMaxPS

To convert HDL-C and LDL-C from mmol/L to mg/dL, multiply by 38.6.

* Defined as CHD in a first-degree male relative younger than 55 years or in a first-degree female relative younger than 65 years.

PS, mean of the maximum plaque score over 12 carotid segments; SD, standard deviation; CHD, coronary heart disease; HDL-C, high-density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol, CIMT, mean of the maximum carotid intima-media thickness of each of the 12 carotid segments

Table 5. Percentage of change in MaxMaxPS for rosuvastatin and placebo

		Rosuvastatin							Percentage Higher PS	Percentage Lower PS	Difference in Percentage
		MaxMaxPS end-of-study									
		0	0.5	1	1.5	2	2.5	3			
MaxMaxPS Baseline	0	0.6	1.2	0.6	0.0	0.0	0.0	0.0	21.3	17.2	4.1
	0.5	2.0	1.7	3.8	0.0	0.0	0.0	0.0			
	1	1.7	3.2	52.5	5.2	2.3	0.3	0.3			
	1.5	0.0	0.0	4.1	4.7	2.0	0.0	0.3			
	2	0.0	0.0	0.9	2.3	4.7	0.9	0.9			
	2.5	0.0	0.0	0.0	0.0	1.7	0.3	0.0			
	3	0.0	0.0	0.0	0.0	0.9	0.3	0.6			
		Placebo							Percentage Higher PS	Percentage Lower PS	Difference in Percentage
		MaxMaxPS end-of-study									
		0	0.5	1	1.5	2	2.5	3			
MaxMaxPS Baseline	0	0.7	0.7	2.6	0.0	0.0	0.0	0.0	25	9.2	15.8
	0.5	0.7	2.6	4.6	0.0	0.0	0.0	0.0			
	1	0.7	1.3	50.0	6.6	3.9	0.0	0.0			
	1.5	0.0	0.0	2.6	3.9	3.9	0.0	0.0			
	2	0.0	0.0	1.3	2.0	7.2	0.7	1.3			
	2.5	0.0	0.0	0.7	0.0	0.0	1.3	0.7			
	3	0.0	0.0	0.0	0.0	0.0	0.0	0.0			
Difference in percentage change in MaxMaxPS between rosuvastatin and placebo											- 11.7

Abbreviations: MaxMaxPS, mean of the single maximum plaque score of each of the 12 carotid segments (range 0-3) at duplicate examinations; PS, plaque score

of pitavastatin or atorvastatin in patients with acute coronary syndrome resulted in the significant regression of coronary plaque volume using IVUS^{25, 29)}.

The findings presented here demonstrate that rosuvastatin 40 mg attenuates atherosclerotic plaque burden, as measured using a fast and simple ultrasonic measure of carotid artery plaque burden. This adds to the previous results of the METEOR trial which showed the effect of rosuvastatin using widely accepted and validated CIMT measurements²²⁾. The ongoing Justification for Atherosclerosis Regression Treatment (JART) study will clarify the efficacy of intensive lipid-lowering therapy on changes in CIMT with rosuvastatin in Japanese with atherosclerosis³⁰⁾. Despite the widespread use of CIMT in clinical research, it has been recognized that CIMT is an imperfect measure of carotid atherosclerosis and has some limitations. First, although atherosclerosis is a disease of the intima layer, it is not possible to distinguish between thickening of the media and intima tissue layers using a CIMT measurement¹⁶⁾. Changes in CIMT may therefore be due to hypertrophy in the media layer rather than atherosclerotic changes in the intima. Plaque assessment may overcome these limita-

tions, at least in certain populations, by solely focusing on changes in the intima^{4, 5, 7, 11, 13)}; however, CIMT and plaques reflect different stages and biological aspects of atherosclerosis with different relations to clinical vascular disease and therefore may not be interchangeable¹⁶⁾. Whereas changes in CIMT could be observed in the early stages of atherosclerosis, even when no plaque was present, plaques represented more advanced stages of the disease. We showed here that rosuvastatin 40 mg causes a significant difference in a more advanced stage of atherosclerotic disease when compared to placebo.

The main advantages of using our plaque score to track changes in atherosclerotic burden over time are its simplicity and low cost when compared with more precise 3D images that could be obtained using advanced, labor intensive, and time-intensive methods. The use of a plaque-scoring method in clinical research might allow for wide-scale studies into changes in atherosclerotic plaque burden over time. In addition, plaque scoring might be useful in clinical practice as a screening tool for cardiovascular risk; however, plaque scoring first needs to be further established and validated before its extensive use. Further-

more, it is important to mention that our plaque score is a categorical variable which may be less powerful to track changes in plaque burden over time than a continuous measure. Continuous plaque measures, such as the carotid plaque area, carotid plaque volume or vessel wall value, might therefore be more efficient in terms of sample size and duration of follow-up to measure changes^{31, 32}; however, continuous plaque measures are much more expensive and time-consuming, which limits their extensive use. Additionally, we were able to track changes in atherosclerotic plaque burden over time despite this limitation.

Some possible limitations of this study need to be mentioned. First, our study was limited to European participants with duplicate measurements at baseline and at the end of the study and might have been prone to selection bias. Comparison of baseline characteristics, however, showed no differences between the participants studied in the present analysis and the European METEOR population as a whole (data not shown). Moreover, the main CIMT outcomes for the European participants were similar to those for the whole METEOR population²⁰. The rate of change in maximum CIMT in European participants for the 12 carotid sites was 0.0003 (95% CI, -0.0030-0.0036) mm/year for the rosuvastatin group versus 0.0147 (95% CI, 0.0095-0.0200) mm/year for the placebo group ($p < 0.001$).

Also, the reproducibility of plaque scores was modest, and some misclassification undoubtedly occurred; however, since sonographers and readers were blinded to the treatment allocation, we consider this misclassification as non-differential, which would result in an underestimation of the true association³³. Finally, the plaque score aggregates the presence and severity of a plaque in one score. Tissue characterization by means of measures of composition, stability, and structure of the plaques may also be of importance³⁴⁻³⁷, but could not be captured by our plaque scores.

In conclusion, the effect of intensive lipid-lowering therapy with rosuvastatin 40 mg could be detected using a simple and easily applicable plaque-scoring approach that tracks the rate of change in atherosclerotic plaque burden over time. Simple assessment of changes in atherosclerotic plaque burden might be useful in trials examining early effects of new treatments for atherosclerosis, but needs to be further established.

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