Stroke

CLINICAL TRIAL

Rosuvastatin Slows Progression of Carotid Intima-Media Thickness: The METEOR-China Randomized Controlled Study

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BACKGROUND: Atherosclerosis is the leading cause of cardiovascular disease worldwide, including in China. Primary prevention, through lipid-lowering, could avert development of atherosclerosis. Carotid intima-media thickness (CIMT) is a well-validated measure of atherosclerosis used in intervention studies as the primary outcome and alternative end point for cardiovascular disease events.

METHODS: This randomized, double-blind, placebo-controlled, multicenter, parallel-group study assessed the effects of rosuvastatin 20 mg/d compared with placebo on progression of CIMT over 104 weeks in Chinese people with subclinical atherosclerosis. The primary end point was the annualized rate of change in mean of the maximum CIMT measurements taken 7× over the study period from each of 12 carotid artery sites (near and far walls of the right and left common carotid artery, carotid bulb, and internal carotid artery). Secondary end points included CIMT changes at different artery sites and lipid-parameter changes. Safety was also assessed.

RESULTS: Participants were randomized (1:1) to receive rosuvastatin (n=272) or placebo (n=271). Baseline characteristics were well balanced between groups. The change in mean of the maximum CIMT of the 12 carotid sites was 0.0038 mm/y (95% CI, −0.0023–0.0100) for the rosuvastatin group versus 0.0142 mm/y (95% CI, 0.0080–0.0204) for the placebo group, with a difference of −0.0103 mm/y (95% CI, −0.0191 to −0.0016; *P*=0.020). For the CIMT secondary end points, the results were generally consistent with the primary end point. There were clinically relevant improvements in lipid parameters with rosuvastatin. We observed an adverse-event profile consistent with the known safety profile of rosuvastatin.

CONCLUSIONS: Rosuvastatin 20 mg/d significantly reduced the progression of CIMT over 2 years in Chinese adults with subclinical atherosclerosis and was well tolerated.

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Key Words: atherosclerosis ■ carotid intima-media thickness ■ China ■ dyslipidemia ■ primary prevention

Atherosclerosis is the leading cause of cardiovascular disease (CVD),[1] and atherosclerotic CVD is the principal source of mortality globally.[2] Compared with higher-income countries, lower- and middle-income countries have higher rates of major CVD events and death from cardiovascular causes.[3] The incidence and

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Nonstandard Abbreviations and Acronyms

AE	adverse event
CCA	common carotid artery
CIMT	carotid intima-media thickness
CVD	cardiovascular disease
HDL-C	high-density lipoprotein cholesterol
ICA	internal carotid artery
LDL-C	low-density lipoprotein cholesterol
MeanMax	mean of the maximum
METEOR	Measuring Effects on Intima-Media Thickness: An Evaluation of Rosuvastatin

prevalence of CVD in China likely will increase rapidly in the future because of the large and expanding population, rising life expectancy, and unfavorable risk-factor levels.[4] Approximately one-third of Chinese adults aged ≥40 years have carotid atherosclerotic plaques, with the prevalence increasing with age.[5] In addition to lifestyle interventions and blood pressure lowering,[6] an important part of preventing atherosclerosis development and subsequent CVD events involves managing elevated cholesterol levels, primarily with statins.[7,8] Most evidence for the beneficial effects of statins on atherosclerosis development derives from non-Asian populations. Genetic differences could account for variations in statin pharmacokinetics between Asians and Westerners.[9] Accordingly, because of a higher drug exposure, Asians might achieve similar benefits from statins at lower dosages.[9] The global METEOR study (Measuring Effects on Intima-Media Thickness: An Evaluation of Rosuvastatin), which did not include participants from China, showed that 40 mg/d rosuvastatin treatment was associated with significant reductions in the rate of maximum carotid intima-media thickness (CIMT) progression over 2 years in middle-aged people with mild to moderate subclinical atherosclerosis.[10] The purpose of the present study, METEOR-China, is to expand the evidence base for rosuvastatin treatment of CVD in Chinese people, using the highest approved dose (20 mg/d) in China. We evaluated atherosclerosis progression, as estimated by CIMT measurements, with rosuvastatin or placebo treatment in asymptomatic Chinese people.

METHODS

This study complies with the AstraZeneca's transparency policy at www.astrazenecaclinicaltrials.com. Anonymized data and materials are available at ClinicalTrials.gov.

Study Design

METEOR-China was preregistered at ClinicalTrials.gov. METEOR-China was a multicenter (25 sites in China; Table S1), randomized, double-blind, placebo-controlled, parallel-group study evaluating the effects of 104 weeks' treatment with rosuvastatin 20 mg/d on CIMT progression in Chinese adults (men aged ≥45 and <70 years or women aged ≥55 and <70 years) with subclinical atherosclerosis.

Participants were enrolled by investigators after assessing eligibility. Randomization was 1:1 using block size 4, stratified by ischemic CVD risk (<5% or 5%–<10%), and allocation was completed sequentially via an interactive web/voice-response system. The study intervention was labeled using a unique kit identification number, which was linked to the randomization scheme. Participants, investigators, study-site personnel, CIMT technicians, and sponsor personnel involved with data review and analyses remained blinded to study treatment throughout the study. The study consisted of 13 visits: 3 screening, 1 baseline, and 9 treatment visits (Figure 1).

The study was performed in accordance with the Declaration of Helsinki and the principles of the International Council for Harmonisation/Good Clinical Practice. Ethics approval was obtained from the local institutional review boards. All participants provided written informed consent. METEOR-China complied with Chinese regulatory requirements by generating data from Chinese people. In accordance with the 2007 China Adult Dyslipidemia Management Guidelines,[11] use of placebo in low-risk participants in METEOR-China was considered ethical. The publication follows the CONSORT guidelines (Consolidated Standards of Reporting Trials) for reporting parallel-group randomized trials (Table S2).[12]

Study Population

Classification of ischemic CVD risk was based on the 2007 China Adult Dyslipidemia Management Guidelines, in which the risks of coronary heart disease and ischemic stroke were integrated into a single model, and Chinese prevalence characteristics were considered.[11] Key inclusion and exclusion criteria are listed in the Supplemental Material.

Study Interventions

Patients received 20 mg rosuvastatin or placebo tablets matching in appearance and labeling, once daily, at the same time each day for 104 weeks.

Efficacy End Points

The primary end point was the annualized rate of change in mean of the maximum (MeanMax) CIMT measurements from each of the 12 carotid artery sites (near and far walls of the right and left common carotid artery [CCA], carotid bulb, and internal carotid artery [ICA]) based on all scans performed during the 104-week study period. Assessment of the MeanMax CIMT from 12 segments is most frequently applied in studies of this design[13] and is based on evidence that aggregating data across a larger number of vessel segments increases the reliability of longitudinal measurements.[14–17]

Secondary end points were (1) the annualized rate of change in the MeanMax CIMT of the near and far walls of the right and left CCA, carotid bulb, or ICA; (2) the annualized rate of change in the mean of the mean CIMT of the near and far walls of the right and left CCA; and (3) the percentage change from baseline in LDL-C (low-density lipoprotein cholesterol), total cholesterol, HDL-C (high-density lipoprotein cholesterol),

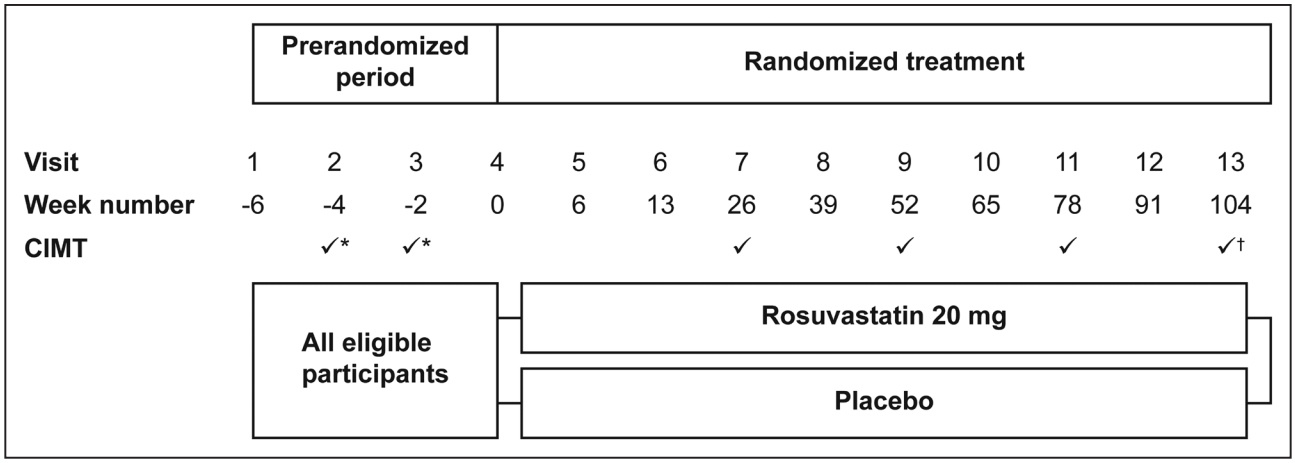

Figure 1. Study flow chart.
CIMT indicates carotid intima-media thickness. *Intima-media thickness (IMT) measurements at visit 2 (wk −4) and visit 3 (wk −2) were to meet inclusion criteria of maximum IMT ≥1.2 mm and <3.5 mm at any location in the carotid ultrasound scans. †Final IMT procedures were to be scheduled before discontinuation of study treatment. The second and final IMT procedure was to occur at or before visit 13 (wk 104), at the time of discontinuation of the study treatment. The 2 IMT procedures for visit 13 were to be performed on different days when possible.

triglycerides, non–HDL-C, apoB, apo AI, non–HDL-C/HDL-C, and apoB/apo AI.

Safety End Points

Safety assessments included adverse events (AEs); serious AEs; AEs leading to discontinuation; changes in clinical laboratory analyses (chemistry, hematology, and urinalysis), vital signs, 12-lead electrocardiograms; and physical examinations. All AEs, including serious AEs, were collected from the time of informed consent provision throughout the treatment period and within 10 days post last dose of the study drug. Clinically significant abnormal laboratory values, vital signs, or other physical examination findings were recorded as AEs. Electrocardiograms were taken at baseline and at study end.

CIMT Assessments

CIMT assessment occurred in duplicate at baseline and at the end of the study, with single assessments at the 26-, 52-, and 78-week visits. Images were made of the near and far walls of the CCA, the carotid bulb, and the ICA sites in the right and left carotid arteries. The ultrasound acquisition protocol complied with the Mannheim consensus[18] and was similar to that used in the global METEOR study,[19] with ability to obtain as much information on CIMT as possible, using a semi-automatic reading system (Artery Management System). The standard protocol required each of these 12 artery sites to be imaged from 3 predefined interrogation angles using the Meijer Carotid Arc, each of which differed from the adjacent orientation by 30° of angulation. For each of the 12 carotid artery sites scanned at each visit, the 3 images and clips were recorded at the 3 interrogation angles for measurement of the minimum, mean, and maximum CIMT for a specific angle in that site. The maximum CIMT measured from the 3 interrogation angles was to be entered as the Max CIMT value for that arterial site. This process was to be repeated for the 12 carotid arterial sites including the near and far walls of the CCA, the carotid bulb, and the ICA sites in the right and left carotid arteries. Additionally, the means of the CIMT measurements of the 4 CCA sites over the 3 interrogation angles were to be recorded as the Mean CIMT values for each of the 4 sites (near and far walls of the right and left CCA). Batch reading of all the 7 scans (2 before and 5 after randomization) of a given participant was conducted by the same reader over a short period of time for each randomized and treated participant upon completion of (or premature discontinuation from) the 2-year treatment to reduce reader variability and eliminate reader drift. Only batch-read CIMT data were used for the statistical efficacy analysis. Using uniform ultrasound imaging systems (X-Porte, FUJIFILM Sonosite, Inc, Bothell, Seattle, WA) across all the CIMT centers, the sonographers digitally recorded carotid ultrasound images and sent them to the Ward A. Riley Ultrasound Center, Wake Forest School of Medicine, Winston-Salem, or the Vascular Imaging Center of the UMC Utrecht, Utrecht, the Netherlands, for centralized evaluation using the standardized CIMT reading software (AMS II, Gothenburg, Sweden). All sonographers and readers participated in a uniform training and certification program executed by faculty members of both the core labs. Data from duplicate baseline and end of study measurements were used for quality assurance and control.

Laboratory Measurements

Samples were taken for analysis of serum lipids, hematology, urinalysis, and clinical chemistry parameters. Fasting lipid and lipoprotein levels, and chemistry panel, were measured at baseline, week 6, week 13, week 39, week 65, week 91, and week 104. Apolipoprotein levels, hematology, and urinalysis were measured at baseline and at the end of the study. All laboratory analyses, except for urine pregnancy tests, were performed by a central laboratory.

Statistical Analysis

Sample Size Considerations

With 207 participants per group, there would be 90% power to detect a difference of −10.6 µm/y in the change in the MeanMax CIMT of 12 vessel segments over a 104-week study period at an SD of 33.28 µm/y and a 0.05 2-sided significance level. Adjusting for an 18% drop-out rate (based on the global METEOR study[10]) ≈506 participants were to be randomized.

All analyses were conducted by originally assigned groups prespecified in the protocol.

Data Analysis

Three analysis sets were used for data analysis: the intention-to-treat population, consisting of all randomized participants; the per-protocol population: a subset of the intention-to-treat population that included participants without any important protocol deviations and analyzed according to the treatment received; and the safety analysis set: all participants who took at least one dose of rosuvastatin or placebo. The intention-to-treat population was the primary efficacy analysis population. A multilevel, linear mixed-effects model was used for the primary analysis to assess the difference in the mean annualized rate of change in the MeanMax CIMT of 12 carotid artery sites between the rosuvastatin and placebo treatment groups over 104 weeks.[10] The model fitted regression lines based on data availability with linear assumption of CIMT change over time.[10] Imputation on missing CIMT data was not implemented, as this was deemed unnecessary in a prior CIMT study.[20] Safety parameters were summarized using the safety analysis set. Extent of exposure was calculated as the duration from the date of first dose to the date of last dose in days.

SAS version 9.4 (SAS Institute, Inc, Cary, NC) was used for all statistical analyses.

RESULTS

The first participant was enrolled on September 17, 2015, and the last participant visit was on January 29, 2019. A total of 3166 people were enrolled and 543 were randomized (rosuvastatin: 272; placebo: 271). Figure 2 shows participants' disposition.

Baseline characteristics were similar between rosuvastatin- and placebo-treated participants (Table 1). The overall mean age was 59.4 years; there was a slight preponderance of women (n=304, 56%). The extent of exposure was similar between the treatment groups; mean duration was 611.8 days for rosuvastatin and 613.8 days for placebo.

Efficacy

In the rosuvastatin group, 272 participants had CIMT scans at weeks −2 and −4, 234 at week 26, 223 at week 52, 212 at week 78, and 211 and 209 participants at week 104 visits 1 and 2, compared with 271, 231, 219, 207, 205, and 205 participants in the placebo group, respectively. The CIMT data of CCA sites had relatively higher completion rates than bulb sites. The ICA sites had lower, yet still rather high, completion rates. During the treatment period, the completion rate varied from 83.9% at week 104 (visit 1) for the ICA right near wall to higher than 99.0% for most visits in other carotid artery sites in the placebo group. Completion ranged from 86.3% at week 78 for the ICA right near wall to greater than 99.0% for most visits in other carotid artery sites in the rosuvastatin group.

The changes in the MeanMax CIMT of the 12 carotid artery sites were 0.0038 mm/y (95% CI, −0.0023 to 0.0100) in the rosuvastatin group and 0.0142 mm/y (95% CI, 0.0080–0.0204) in the placebo group. For the primary end point, the difference in the annualized rate of change in the MeanMax CIMT of the 12 carotid artery sites between rosuvastatin- and placebo-treated participants was statistically significant at −0.0103 mm/y (95% CI, −0.0191 to −0.0016; P=0.020; Figure 3, Figure 4, Table 2). Within the rosuvastatin 20 mg group, the estimated annualized CIMT change rates were 0.0030 mm/y and 0.0029 mm/y in participants with change from baseline or on-treatment LDL-C less than the mean, whereas the corresponding rates were 0.0060 mm/y and 0.0056 mm/y from participants with change from baseline or on-treatment LDL-C greater than or equal to the mean (Table S3). The results indicate that the participants in the rosuvastatin 20 mg group with more LDL-C reduction during the study period were likely to have slower CIMT progression than participants in the placebo group.

For the CIMT secondary end points (Figure 3, Table 2), rosuvastatin slowed the progression of CIMT compared with placebo, as evidenced by a significant difference in the annualized rate of change in the MeanMax CIMT of the CCA sites (mean difference, −0.0110 mm/y [95% CI, −0.0197 to −0.0024]; P=0.013) and the mean of the mean CIMT of the CCA sites (mean difference, −0.0086 mm/y [95% CI, −0.0139 to −0.0032]; P=0.002). Rosuvastatin treatment also showed favorable effects on the annualized rate of change of the MeanMax CIMT of the carotid bulb and ICA sites, although the differences compared with placebo did not reach statistical significance (mean difference, −0.0162 mm/y [95% CI, −0.0339 to 0.0015]; P=0.073 and −0.0043 mm/y [95% CI, −0.0183 to 0.0097]; P=0.547, respectively). The per-protocol analyses showed results in accordance with those of the intention-to-treat analyses for both primary and secondary end points (Figure S1).

For lipid secondary end points, the difference between the rosuvastatin and placebo groups in the percent change from baseline was −39.5% for LDL-C, −25.5% for total cholesterol, 3.7% for HDL-C, −18.4% for TG, −33.8% for non–HDL-C, and −33.9% for non–HDL-C/HDL-C, based on time-weighted averages. Table S4 shows an analysis of percentage change from baseline to final visit in lipid, lipoprotein, and Apo values, which were all significant (P<0.001 for all except apo AI [P=0.047]).

Subgroup analyses showed that the treatment effect on CIMT was consistent across subgroups by age, sex, body mass index, ischemic CVD risk category, and smoking status, but not for a history of hypertension (Table S5). Similarly, the treatment effect was generally consistent across subgroups of baseline lipids, lipoproteins, and apolipoproteins (data not shown).

Safety

In the rosuvastatin group, 84.6% of participants had at least one AE during the study compared with 77.6% in

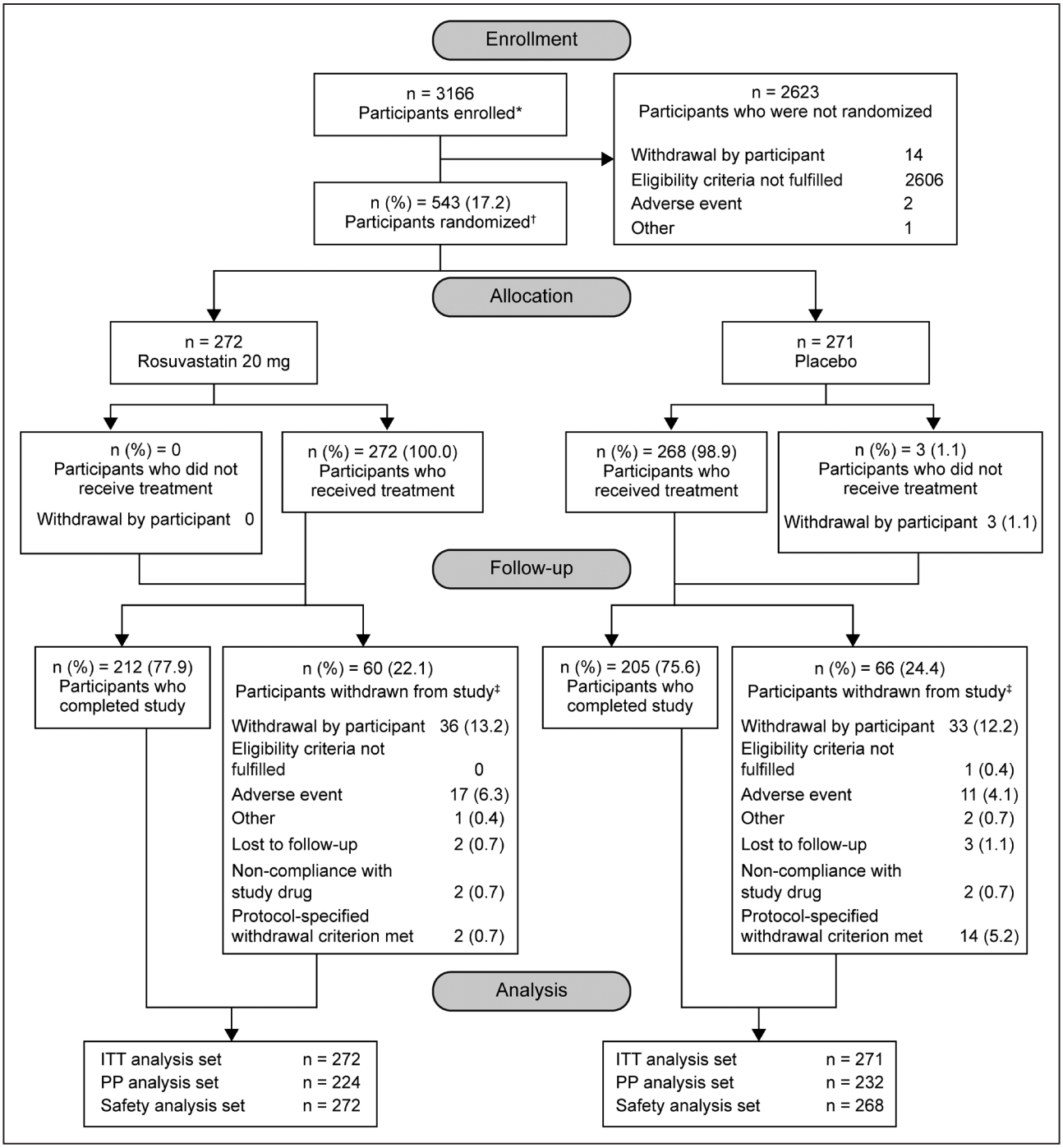

Figure 2. CONSORT participant flow diagram.
The denominator for calculating all other percentages is the number of participants randomized in each treatment group and overall total. The intention-to-treat (ITT) population consisted of all randomized participants. The per-protocol (PP) analysis set is a subset of the ITT population that includes participants without any important protocol deviations that may affect the study outcome significantly or the interpretability of the study results. The safety analysis set consists of all participants who took at least one dose of the investigational product or placebo. n indicates number of participants. *Informed consent received. †The denominator for calculating percentage is the number of participants enrolled. ‡Includes participants withdrawn before receiving treatment.

the placebo group. The majority of AEs were mild (82.4% in the rosuvastatin group and 74.6% in the placebo group) and considered by the investigator to be unrelated to study treatment. AEs leading to discontinuation were reported by 10.3% of participants in the rosuvastatin group compared with 9.3% in the placebo group (Table S6). The incidence of diabetes mellitus was numerically higher in the rosuvastatin group (3.3%) compared with the placebo group (0.4%). The most commonly reported AEs by preferred term were nasopharyngitis

Table 1. Baseline Characteristics (ITT Analysis Set)

Characteristic	Rosuvastatin 20 mg/d; N=272	Placebo; N=271
Age, y, mean (SD)	59.0 (5.2)	59.7 (5.0)
<65 y, n (%)	234 (86.0)	227 (83.8)
≥65 y, n (%)	38 (14.0)	44 (16.2)
Women, n (%)	146 (53.7)	158 (58.3)
Body mass index, mean, kg/m² (SD)	25.0 (2.6)	24.7 (2.7)
Nicotine use, current, n (%)	52 (19.1)	40 (14.8)
Alcohol use, current, n (%)	42 (15.4)	42 (15.5)
CrCl, mL/min, mean (SD)	92.5 (19.0)	88.1 (19.9)
CrCl at baseline, n (%)*		
Normal	205 (75.4)	166 (61.3)
Mild impairment	66 (24.3)	103 (38.0)
Moderate impairment	1 (0.4)	2 (0.7)
Severe impairment	0	0
Hypertension, n (%)	57 (21.0)	68 (25.1)
LDL-C, mg/dL, mean (SD)	135.0 (22.5)	137.9 (24.4)
Fasting blood glucose ≥110 mg/dL (≥6.11 mmol/L)	40 (14.7)	30 (11.1)
10-y ICVD risk, n (%)—eCRF†		
<5%	196 (72.3)	195 (72.8)
≥5% to <10%	75 (27.7)	73 (27.2)
Mean of maximum CIMT, mean (SD), mm‡		
12 Carotid artery sites	1.11 (0.17)	1.10 (0.18)
Common carotid artery sites	1.06 (0.18)	1.04 (0.17)
Carotid bulb sites	1.35 (0.27)	1.34 (0.27)
Internal carotid artery sites	0.90 (0.22)	0.90 (0.24)
Mean of mean CIMT, mean (SD), mm		
Common carotid artery sites	0.78 (0.12)	0.77 (0.11)

Baseline is defined as the last result obtained before the first dose of study treatment (or last result obtained before randomization if the participant did not receive any study treatment). CIMT indicates carotid intima-media thickness; CrCl, creatinine clearance; eCRF, electronic case report file; ICVD, ischemic cardiovascular disease; ITT, intention-to-treat; and LDL-C, low-density lipoprotein cholesterol.

*Normal: creatinine clearance >80 mL/min; mild impairment: creatinine clearance of 50 to ≤80 mL/min; moderate impairment: creatinine clearance of 30 to <50 mL/min; severe impairment: creatinine clearance of <30 mL/min.

†eCRF is the ICVD risk as collected on the eCRF. Four participants did not have eCRF data.

‡Baseline is defined as the MeanMax CIMT of the 12 carotid artery sites averaged over wk −4 and wk −2.

(52 participants [19.1%] in the rosuvastatin group and 56 participants [20.9%] in the placebo group) and upper respiratory tract infection (49 participants [18.0%] in the rosuvastatin and 55 participants [20.5%] in the placebo group; Table S7).

The frequency of serious AEs was 14.0% in the rosuvastatin and 12.7% in the placebo group. One participant in the placebo group died due to a serious AE of colon cancer which was considered by the investigator to be unrelated to study treatment. There were no reported cases of rhabdomyolysis in this 104-week study. Cardiovascular events were not adjudicated in METEOR-China given the anticipated low frequency in this low-risk population. In the rosuvastatin group, 15 participants (5.5%) had a potential ischemic cardiovascular AE compared with 12 participants (4.5%) in the placebo group (Table S8).

Changes in clinical safety laboratory results, vital signs, electrocardiograms, and physical examination were generally small and the number of clinically important findings was similar between treatment groups. No participants had alanine aminotransferase or aspartate aminotransferase ≥3× upper limit of normal or total bilirubin ≥2× upper limit of normal. One participant in the rosuvastatin group had blood creatine kinase increase >10× upper limit of normal. The event was considered by the investigator to be mild and unrelated to treatment, and the creatine kinase value returned to the normal range at the subsequent visit.

Reproducibility

In both duplicate baseline and end of study scans, there was strong agreement between estimates of the MeanMax CIMT from the paired scans, and the intraclass correlation coefficients of 0.87 and 0.89 for baseline and end of study duplicate measurements, respectively, fit well within the range of expected values for CIMT studies performed over the last 30 years.[21]

DISCUSSION

METEOR-China showed that treatment with rosuvastatin 20 mg/d in Chinese people with a low risk of CVD significantly slowed the progression of CIMT compared with placebo. Clinically relevant improvements in lipid parameters were demonstrated, consistent with rosuvastatin's known effect.[10,22] Rosuvastatin was well tolerated, consistent with the known safety profile.[23]

The METEOR-China results can best be compared with those of the global METEOR study.[10] The main differences between the studies are the population (Chinese only, versus no Chinese participants) and the dosage (20 mg/d [highest allowed dosage in China] versus 40 mg/d). The current study population had numerically lower baseline LDL-C, body mass index, and baseline MeanMax CIMT of the 12 carotid sites versus the participants in the global METEOR study (Table S9). However, the results of the 2 studies were similar in significantly slowing the CIMT progression versus placebo during a 2-year period (global METEOR, −0.0145 mm/y [95% CI, −0.0196 to −0.0093]; METEOR-China, −0.0103 mm/y [95% CI, −0.0191 to −0.0016]), in affecting the lipid profile, and in the frequency of AEs. Myalgia, although more commonly reported in both the intervention and placebo groups in the global METEOR study than in the METEOR-China study, was not different between the intervention

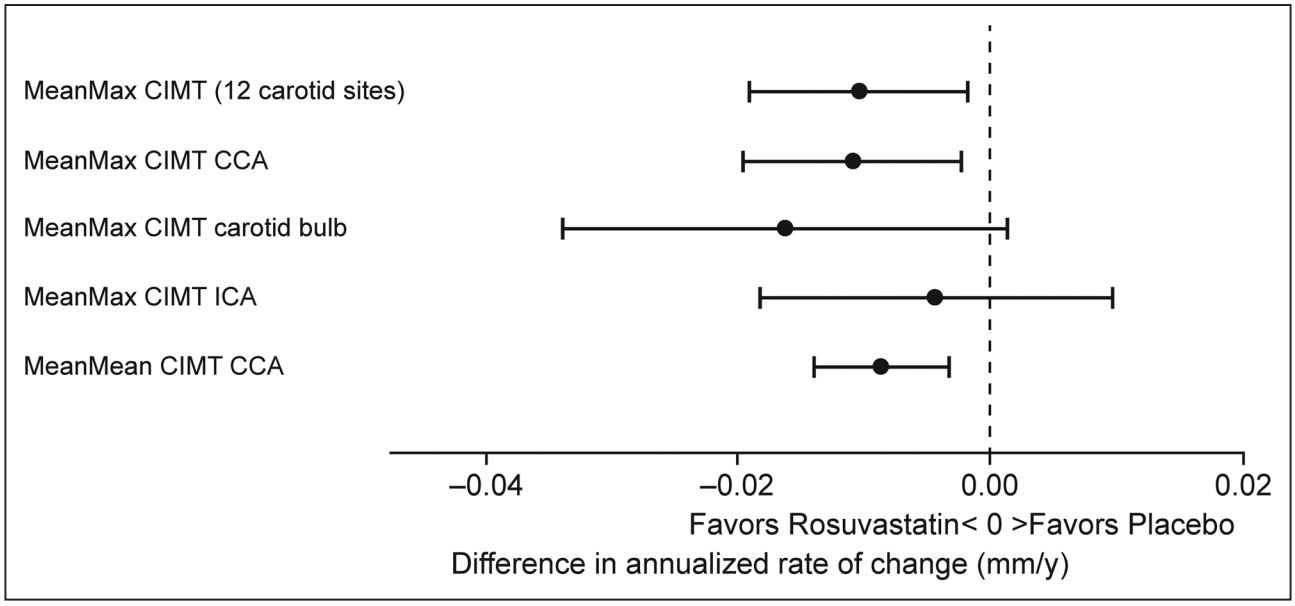

Figure 3. Difference between rosuvastatin and placebo in annualized rate of change and 95% CIs for the primary and secondary carotid intima-media thickness (CIMT) end points, mixed-effects model (intention-to-treat analysis set).
Twelve carotid sites: near and far walls of the right and left common carotid artery (CCA), carotid bulb, and the internal carotid artery (ICA). MeanMax indicates mean of the maximum; and MeanMean, mean of the mean.

and placebo groups: in the global METEOR study at 12.7% in the rosuvastatin and 12.1% in the placebo group, whereas in METEOR-China at 2.9% and 1.5%, respectively.

Findings from METEOR-China compare well with the results from existing studies on the effect of statins on CIMT progression.[21,24] It expands the evidence from White to Asian populations. The results are in agreement with the evidence reported by a meta-analysis of aggregated data from PubMed, other common databases, and Chinese databases, up to January 2013, comparing rosuvastatin with placebo or other statins on CIMT changes.[25]

Furthermore, the results from METEOR-China compare well with results from other imaging studies of rosuvastatin, such as the nonrandomized ASTEROID study (A Study to Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound-Derived Coronary Atheroma Burden), which showed regression of coronary atherosclerotic burden with rosuvastatin 40 mg/d treatment in a high-risk population,[26,27] and the double-blind randomized controlled SATURN study (Study of Coronary Atheroma by Intravascular Ultrasound: Effect of Rosuvastatin Versus Atorvastatin), which demonstrated significant regression of coronary atherosclerosis with rosuvastatin 40 mg/d.[28] The nonrandomized REACH study (Rosuvastatin Evaluation

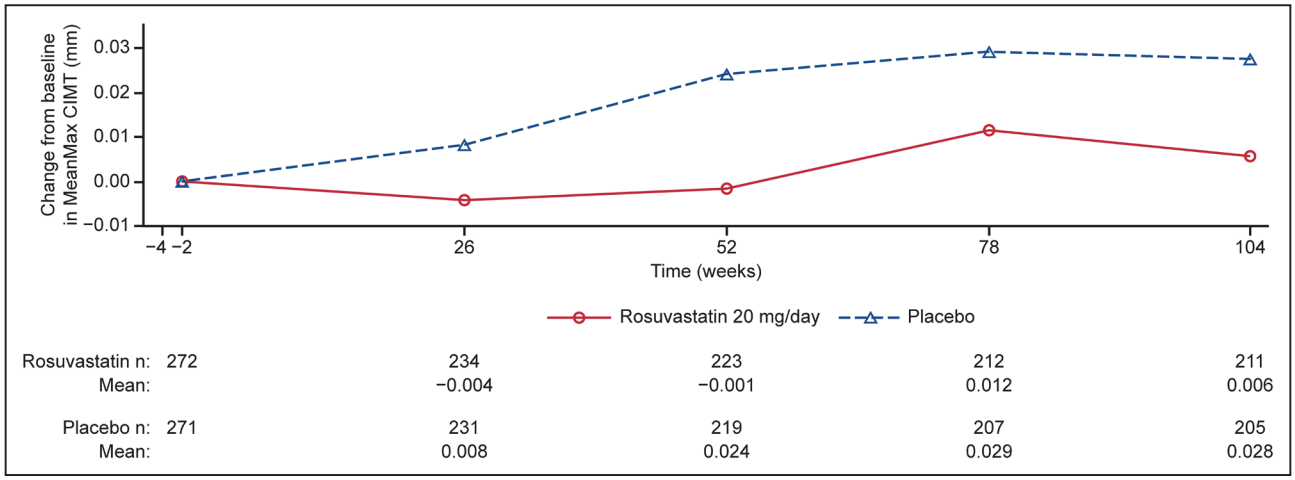

Figure 4. Change from baseline in mean of the maximum (MeanMax) carotid intima-media thickness (CIMT) of the 12 carotid artery sites, by study visit (intention-to-treat analysis set).
Baseline is defined as the MeanMax CIMT of the 12 carotid artery sites averaged over wk –4 and wk –2. Wk 104 is defined as the MeanMax CIMT of the 12 carotid artery sites averaged over wk 104 (scan 1) and wk 104 (scan 2).

Table 2. Annualized Changes From Baseline Values to the End of Treatment Period (Week 104) in CIMT for the Primary and Secondary End Points (ITT Analysis Set)

Annualized rate of change from baseline (mm/y)	Rosuvastatin 20 mg/d (N=272)		Placebo (N=271)		Comparison between groups		
	Estimated mean (SE)	95% CI	Estimated mean (SE)	95% CI	Estimated mean difference (SE)	95% CI	*P* value
Primary end point							
MeanMax CIMT of the 12 carotid artery sites	0.0038 (0.00312)	(−0.0023 to 0.0100)	0.0142 (0.00317)	(0.0080 to 0.0204)	−0.0103 (0.00445)	(−0.0191 to −0.0016)	0.020
Secondary end points							
MeanMax CIMT of the near and far walls of the right and left CCA	−0.0031 (0.00310)	(−0.0092 to 0.0030)	0.0079 (0.00315)	(0.0017 to 0.0141)	−0.0110 (0.00442)	(−0.0197 to −0.0024)	0.013
MeanMax CIMT of the near and far walls of the right and left carotid bulb	0.0067 (0.00634)	(−0.0058 to 0.0191)	0.0228 (0.00643)	(0.0102 to 0.0354)	−0.0162 (0.00903)	(−0.0339 to 0.0015)	0.073
MeanMax CIMT of the near and far walls of the right and left ICA	0.0077 (0.00502)	(−0.0022 to 0.0175)	0.0120 (0.00511)	(0.0020 to 0.0220)	−0.0043 (0.00716)	(−0.0183 to 0.0097)	0.547
MeanMean CIMT of the near and far walls of the right and left CCA	−0.0011 (0.00191)	(−0.0048 to 0.0027)	0.0075 (0.00194)	(0.0037 to 0.0113)	−0.0086 (0.00272)	(−0.0139 to −0.0032)	0.002

Comparisons of the annualized rate of change are based on a multilevel mixed-effects model which is fitted to the Max CIMT or the Mean CIMT value for each site over 104 wk with randomized treatment group, time, time-by-treatment interaction, ICVD risk stratification, carotid artery site, center, age, sex, and scan reader as fixed effects. Random effects within the model are the intercept and slope for individual participants. Time in the model is a continuous measure and is the interval in years from date of randomization to date of CIMT measurement and its effect is linear. Statistical significance of the maximum (or mean) CIMT annualized rate of change (slope) between rosuvastatin and placebo was evaluated using time-by-treatment interaction term in the model. CCA indicates common carotid artery; CIMT, carotid intima-media thickness; ICA, internal carotid artery; ICVD, ischemic cardiovascular disease; ITT, intention-to-treat; MeanMax, mean of the maximum; and MeanMean, mean of the mean.

of Atherosclerotic Chinese Patients) in 32 asymptomatic Chinese participants with carotid lipid-rich atherosclerotic plaques showed that rosuvastatin 10 mg/d resulted in rapid depletion of magnetic resonance imaging–assessed plaque lipid content after 3 months.[29]

Increased CIMT has been associated with conventional cardiovascular risk factors,[30] the presence of other localizations of atherosclerosis,[31,32] and an increased risk of myocardial infarction, stroke,[33,34] and recurrent stroke.[35] Studies performed in Asian populations showed consistent results with those found in Whites.[36,37] A recent meta-analysis from Willeit and colleagues included data from 119 randomized controlled trials involving 100 667 patients (average follow-up of 3.7 years).[38] Across all interventions, the authors estimated that interventions reducing CIMT progression by 10, 20, 30, or 40 µm/y would yield relative risks for CVD of 0.84 (95% credible interval, 0.75–0.93), 0.76 (0.67–0.85), 0.69 (0.59–0.79), or 0.63 (0.52–0.74). The degree of CVD risk reduction was predicted by the extent of interventions' effects on CIMT progression. This supports the rate of atherosclerotic progression seen in METEOR-China (−10.3 µm/y) as being clinically meaningful.

The METEOR-China results are further supported by the results from the primary prevention JUPITER trial (Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin). JUPITER, which was conducted outside of China, showed a significant reduction in a combined end point comprising myocardial infarction, stroke, or death from cardiovascular causes with rosuvastatin 20 mg/d versus placebo in 17 802 seemingly healthy participants without elevated LDL-C levels but with elevated C-reactive protein levels.[39] The global HOPE-3 trial (Heart Outcomes Prevention Evaluation-3), which included 12 705 participants of whom 3691 were Chinese, compared treatment with rosuvastatin 10 mg/d with placebo and showed superiority to placebo in diminishing cardiovascular events, with no racial differences regarding efficacy and safety.[40] METEOR-China adds to the evidence base of CIMT randomized controlled studies that showed results congruent with studies that had morbidity and mortality as outcomes.[41]

Strengths of METEOR-China are that in its design and analysis it included various features to proactively reduce measurement error and residual confounding: it involved a placebo group; included a clinically relevant Chinese population; had objective, blinded CIMT measurements analyzed by batch reading; used core laboratories for CIMT and blood samples; and provided extensive training and quality control of sonographers and readers. No attempt was made for imputing missing data since it has been shown that this does not aid in obtaining valid estimates in CIMT trials.[20] However, the results may have limited generalizability, considering the intentionally limited ethnic and racial diversity of study participants.

CONCLUSIONS

In conclusion, rosuvastatin 20 mg/d significantly reduced the progression of CIMT over 2 years in Chinese adults with subclinical atherosclerosis and was well tolerated.

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Michiel L. Bots declares no conflicts of interest, apart from being paid for his services by the organization that received the METEOR-China grant from AstraZeneca to run the study. The payment went to UMC Utrecht. Drs Karlson, Zhao, Wei, and Meng are employees of AstraZeneca. The other authors report no conflicts.

Supplemental Material

Supplemental Methods
Figure S1
Tables S1–S9

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