Original Article

Journal of INTERNAL MEDICINE

doi: 10.1111/j.1365-2796.2009.02073.x

Intensive lipid lowering may reduce progression of carotid atherosclerosis within 12 months of treatment: the METEOR study

M. L. Bots[1], M. K. Palmer[2], S. Dogan[1], Y. Plantinga[1], J. S. Raichlen[3], G. W. Evans[4], D. H. O'Leary[5], D. E. Grobbee[1] & J. R. Crouse III[4] on behalf of the METEOR Study Group*

From the [1]Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, The Netherlands; [2]Keele University, Staffordshire, UK; [3]AstraZeneca, Wilmington, DE; [4]Division of Public Health Sciences, Wake Forest University, Winston Salem, NC; and [5]Caritas Carney Hospital, Boston, MA, USA

Abstract. Bots ML, Palmer MK, Dogan S, Plantinga Y, Raichlen JS, Evans GW, O'Leary DH, Grobbee DE, Crouse JR III, on behalf of the METEOR Study Group (University Medical Center Utrecht, Utrecht, The Netherlands; Keele University, Staffordshire, UK; AstraZeneca, DE; Wake Forest University, Winston Salem, NC; and Caritas Carney Hospital, Boston, MA; USA). Intensive lipid lowering may reduce progression of carotid atherosclerosis within 12 months of treatment: the METEOR study. *J Intern Med* 2009; **265**: 698–707.

Background. In several statin trials, vascular event rates for treatment groups begin to separate 1 year after commencement of treatment. For atherosclerosis progression, the temporal sequence of the effect has not been defined. We used data from the Measuring Effects on intima media Thickness: an Evaluation Of Rosuvastatin (METEOR) trial to determine the earliest time point at which significant differences in atherosclerosis progression rates could be detected after initiation of statin therapy.

Methods. The METEOR trial was a double-blind, randomized placebo-controlled trial that studied the effect of LDL-C lowering with 40 mg rosuvastatin on the rate of change of carotid intima media thickness (CIMT) measured by B-mode ultrasound amongst 984 low risk subjects. Ultrasound assessments were made at baseline and every 6 months up to 2 years.

Results. Rosuvastatin treatment was associated with a 49% reduction in LDL-C-C, a 34% reduction in total cholesterol, an 8.0% increase in HDL-C and a 16% reduction in triglycerides (all $P < 0.0001$ compared with placebo). The difference in rate of mean maximum CIMT progression between the rosuvastatin and placebo groups (based on near and far wall measurements from both left and right common carotid and internal carotid segments and carotid bifurcation) was not statistically significant after 6 months (0.0023 mm year^{-1} and 0.0106 mm year^{-1}, respectively $P = 0.34$). After 12 months, CIMT progression rates were significantly different between the groups: 0.0032 mm year^{-1} and 0.0133 mm year^{-1} in the rosuvastatin-treated and placebo-treated groups, respectively ($P = 0.049$). This divergence grew with further follow-up: −0.0009 mm year^{-1} and 0.0131 mm year^{-1} after 18 months ($P < 0.001$) and −0.0014 mm year^{-1} and 0.0131 mm year^{-1} after 24 months of treatment ($P < 0.001$). Results were stronger for the mean common CIMT progression (based on near and far wall measurements from both left and right common carotid segments).

Conclusion. Aggressive LDL-C lowering seems to exert its beneficial effect on atherosclerosis progression during the first 12 months of treatment. This parallels the timing of event reduction seen in clinical trials and suggests that the efficacy of lipid lowering treatment on CIMT progression can be evaluated in trials with a duration of 1 year, given sufficient sample size, high precision of measurements and a treatment effect comparable to that seen in METEOR.

*The METEOR study group listed in the appendix

 © 2009 Blackwell Publishing Ltd

Trial Registration: Clinicaltrials.gov identifier: NCT00225589.

Keywords: atherosclerosis, prevention, statin, trial, ultrasound, vascular disease.

Introduction

Results from observational studies across a variety of populations indicate a continuous positive relationship between LDL-C and risk of coronary heart disease [1]. The use of 3-hydroxy-3-methylglutaryl-lowering co-enzyme A (HMG-CoA) inhibitors (statins) results in considerable reduction of LDL-C [2]. Furthermore, randomized controlled trials have consistently shown that statins reduce the risk of coronary heart disease [3]. This risk reduction has been demonstrated in a wide range of populations and patient groups and its magnitude appears to be proportional to the absolute reduction in LDL-C [4]. However, it is not clear how rapidly benefits emerge after initiation of statin therapy. Some trials report no benefit within the first year, and others report rapid benefit. A recent meta analysis, based on over 90 000 individual patients participating in randomized controlled trials of statins, indicated a significant 14% reduction in major vascular events within the first year of treatment [4]. In addition, a recently published randomized controlled trial amongst 17 802 low risk subjects with elevated C-reactive protein levels showed a benefit of lipid lowering on clinical events already after 12 months of treatment [5].

Part of the beneficial effect of LDL-C lowering on coronary heart disease (CHD) risk has been attributed to its influence on atherosclerosis progression. Indeed, several randomized controlled trials have shown that statins lead to reduced progression, or even regression, of atherosclerosis [6–11]. For atherosclerosis progression, the temporal sequence of the beneficial effect has not yet been defined. This is partly because, in trials using quantitative coronary angiograms or coronary intravascular ultrasound (IVUS) as tools to assess atherosclerosis progression, follow-up measurements were generally obtained 18 or 24 months after the start of the study [7–9]. Also, trials using magnetic resonance imaging (MRI) to assess atherosclerosis progression over time used repeated measurement after 18 months [10]. In contrast, in several lipid lowering trials where ultrasound-assessed carotid intima-media thickness (CIMT) was used as indicator of atherosclerosis progression, atherosclerosis was evaluated at baseline and every 6 months over a period of 2 or 3 years [11–15]. These CIMT trials allow assessment of the temporal sequence of statin effects on atherosclerosis progression more precisely. Using data from one of these trials, the Measuring Effects on intima media Thickness: an Evaluation Of Rosuvastatin (METEOR) study [16], we sought to determine the earliest time point after initiation of statin therapy at which significant differences in atherosclerosis progression rates could be detected.

Methods

The rationale, design and main findings of the METEOR study have been detailed elsewhere [15, 16]. In short METEOR was a 2-year, double-blind, placebo-controlled trial that compared rosuvastatin 40 mg with placebo treatment in middle-aged asymptomatic subjects with moderately elevated cholesterol and low risk of cardiovascular disease according to the National Cholesterol Educational Program Adult Treatment Panel III criteria (0–1 risk factor or ≥2 risk factors with a 10-year CHD risk <10%). The study was conducted in accordance with the ethical principles in the Declaration of Helsinki, the International Conference on Harmonization of Good Clinical Practice guidelines, and appropriate regulatory requirements. The study protocol was approved by the appropriate Institutional Review Board and/or Independent Ethics Committee at each site. All participants provided written informed consent. Main inclusion criteria were: age 45–70 years (male) or 55–70 years (female); screening LDL-C-C 120–190 mg dL^{-1} (3.1–4.9 mmol L^{-1}) for those with only age as a CHD risk factor, or 120–160 mg dL^{-1} (3.1–4.1 mmol L^{-1}) for individuals with two or more CHD

risk factors and a 10-year risk of CHD events <10%; HDL-C ≤ 60 mg dL^{-1} (1.6 mmol L^{-1}); TG <500 mg dL^{-1} (5.7 mmol L^{-1}); and at least one maximum CIMT measurement >1.2 mm and no measurement ≥3.5 mm from two separate ultrasound examinations. This lower boundary for CIMT measurement actually identifies subjects with relatively thick walls compared with the general population. Thus, clinically these participants were at 'low risk', although their IMT indicated the presence of subclinical atherosclerosis. Eligible participants were randomized to either the placebo or rosuvastatin groups in blocks of seven (five rosuvastatin, two placebo) at each clinical site.

Carotid ultrasound examinations were performed twice before randomization, once each at 6, 12 and 18 months after randomization, and then twice at the end of 24 months of study treatment. At each visit sonographers obtained standardized longitudinal B-mode images of the left and right and near and far walls of the three segments of the carotid artery, as detailed elsewhere [16]. The common carotid artery (CCA) was defined as the segment extending from 10 to 20 mm proximal to the tip of the flow divider. The carotid bifurcation was defined as the segment beginning at the tip of the flow divider and extending 10 mm proximal. The internal carotid artery (ICA) was defined as the segment beginning at the tip of the flow divider and extending 10 mm distally. Meijer's Carotid Arc® (Bio-Imaging Technologies, Leiden, the Netherlands) was used to image the artery at prespecified angles [17]. All ultrasound scans were read with Image Pro® software (Meyer Medical Ultrasound, Utrecht, the Netherlands) using a uniform reading protocol that ensured standardized settings across reading stations and core laboratories. The image boundaries were marked manually. For CIMT measurements, trailing edges were traced on the near wall boundaries and leading edges on the far wall boundaries. Measurements were performed on images from selected predefined angles: for the right carotid artery – 60, 90, 120, 150 and 180 degrees on the Meijer's Carotid Arc; for the left carotid artery – 300, 270, 240, 210 and 180 degrees. For the near and far walls of the right and left carotid bifurcation and ICA, measurements were made only of the maximum CIMT at all selected angles. For the CCA, measurements were made of both the mean and maximum CIMT of each wall at all selected angles. All readers completed a uniform training program. A single reader read all seven scans in random order and in a batch fashion after each individual had finished the study. Reproducibility of the measurement was excellent [15, 16].

In order to understand the various CIMT measurements a short simplified description is given. For each individual a mean maximum CIMT was estimated for each visit. First, a maximum CIMT value for each of the 12 segments was estimated based on the five angle specific measurements. Next, the maximum CIMT measurements of the 12 segments were averaged to obtain one mean maximum CIMT for each individual. All estimates of all visits were modelled as described in the data analysis paragraph to assess the rate of progression. For the maximum CIMT values of the carotid bifurcation, a similar approach was used where only the angle specific measurements performed at the near and far wall of the left and right carotid bifurcation were used. The CIMT estimate for the internal carotid artery was obtained in the same way. For the mean common CIMT estimate, we took the mean CIMT value over a 10 mm distance of all angle specific measurements of the near and far wall of the right and left common carotid artery, and averaged those. For the far wall common CIMT estimate, we restricted ourselves to mean CIMT measurement over a 10 mm segment of the angle specific measurements performed at the far wall of the left and right carotid artery.

Data analysis

Carotid intima-media thickness (CIMT) data were analysed according to the intention-to-treat (ITT) principle in all individuals with a baseline reading and at least one postbaseline CIMT reading. For the present analysis the endpoints were (i) rate of change in maximum CIMT based on all scans performed over the study period from each of the 12 carotid artery sites (near and far walls of the right and left CCA, carotid bulb and ICA) and (ii) rate of change in mean common CIMT for the near and far walls of the right

and left CCA and (iii) rate of change in mean common CIMT based on only the far walls of the right and left CCA.

To study treatment effects on CIMT progression a multi-level, repeated measures, linear mixed-effects model was used as described earlier [15]. Levels used for the data were subject, and carotid artery site within subject; the repeated measure was time. The model was specified in terms of fixed effects for carotid artery site, age, sex, reader, ultrasound machine, randomized-treatment group, time and the interaction of randomized-treatment group and time. Time was defined as the interval from date of randomization to date of CIMT measurement. To assess linearity of changes in CIMT values across the study measurements, time-squared terms were included in the model. Random effects within the model were intercepts and slopes for both subjects and sites-within-subjects.

To study the time sequence of the difference in CIMT progression rates between treatments, CIMT progression rates were estimated based on baseline and 6 month measurements only, on baseline, 6 month and 12 month assessments only, on baseline, 6 month, 12 month and 18 month assessments only, and on the full dataset up to assessments at 24 months. Furthermore, based on the findings in this study, sample size estimations were performed to define the size needed for a trial when CIMT measurements were done up to 6 months, up to 12 months, up to 18 months, or up to 24 months after baseline.

Results

The general characteristics of the study population are given in Table 1, by treatment assignment. Characteristics were similar between the two treatment arms. Rosuvastatin treatment was associated with a 49% reduction in LDL-C-C, a 34% reduction in TC, an

Table 1 General characteristics of the Measuring Effects on intima media Thickness: an Evaluation Of Rosuvastatin (METEOR) study populations by treatment group

	Rosuvastatin (n = 702)	Placebo (n = 282)
Age (SD), years	57 (6.2)	57 (6.0)
Men, n (%)	421 (60)	167 (59)
Race n (% Caucasian)	659 (94)	268 (95)
Body mass index (SD), kg m^{-2}	27.1 (4.0)	27.5 (4.0)
Systolic blood pressure, mmHg (SD)[a]	124 (13.4)	125 (13.6)
Diastolic blood pressure, mmHg (SD)[a]	77 (8.2)	78 (8.5)
Hypertension (≥140/90 mmHg or antihypertensive medication)	138 (20)	58 (21)
Fasting blood glucose, mg dL^{-1}(SD)[a]	95 (0.68)	97 (0.80)
Total cholesterol, mg dL^{-1} [mean (SD)][b]	229 (29)	230 (28)
LDL-cholesterol, mg dL^{-1} [mean (SD)][b]	154 (24)	154 (24)
HDL-cholesterol, mg dL^{-1} [mean (SD)][b]	49.7 (9.0)	49.0 (9.2)
Triglycerides, mg dL^{-1}	126 (64.3)	134 (67.8)
Family history of premature CHD[c]	65 (9)	31 (11)
Smoking (during the previous month)	22 (3)	16 (6)
MeanMax[d] of all 12 CIMT sites, mm [mean (SD)][b]	1.15 (0.19)	1.17 (0.20)
MeanMean of the CCA, mm [mean (SD)][b]	0.76 (0.12)	0.76 (0.12)

CCA, common carotid artery; CIMT, carotid intima media thickness; CHD, coronary heart disease; SD, standard deviation.
[a]Values based on randomized safety population (n = 700 rosuvastatin, n = 281 placebo). [b]Values based on intention-to-treat (ITT) population (n = 624 rosuvastatin, n = 252 placebo). [c]Defined as CHD in a first-degree male relative <55 years old or in a first-degree female relative <65 years old.

8.0% increase in HDL-C, and a 16% reduction in TG (all $P < 0.0001$ compared with placebo) [14].

In Table 2 the CIMT progression rates based on different CIMT assessments are given by treatment group. The difference in rate of maximum CIMT progression between the rosuvastatin and placebo groups was not statistically significant 6 months after baseline (0.0023 mm year^{-1} and 0.0106 mm year^{-1}, respectively $P = 0.34$). After 12 months, CIMT progression rates were significantly different between groups: 0.0032 mm year^{-1} and 0.0133 mm year^{-1} ($P = 0.049$). This divergence grew and statistical significance increased with further follow-up: −0.0009 mm year^{-1} and 0.0131 mm year^{-1} after 18 months ($P < 0.001$) and −0.0014 mm year^{-1} and 0.0131 mm year^{-1} after 24 months of treatment ($P < 0.001$). Results were similar for common CIMT progression when based on the combined near and far wall measurements or when based on the far wall measurements only (Table 2). We found a strong and highly statistically significant difference in mean common CIMT progression between the two treatments 12 months after initiation of statin therapy. Similar trends toward increasing

Table 2 Carotid intima media thickness (CIMT) progression by time after baseline, for the rosuvastatin groups and the placebo group and differences in CIMT progression between treatments[a]

	CIMT progression (mm year^{-1})		Difference in progression between treatment groups (mm year^{-1})	*P*-value for the difference
	Rosuvastatin	Placebo		
Mean maximum CIMT (near and far wall combined)				
6 months	0.0023	0.0106	−0.0083	0.34
12 months	0.0032	0.0133	−0.0101	0.049
18 months	−0.0009	0.0131	−0.0140	<0.001
All time points	−0.0014	0.0131	−0.0145	<0.001
Mean common CIMT (near and far wall combined)				
6 months	−0.0005	0.0050	−0.0056	0.29
12 months	−0.0011	0.0062	−0.0073	0.013
18 months	−0.0012	0.0084	−0.0097	<0.001
All time points	0.0004	0.0089	−0.0085	<0.001
Mean common CIMT (far wall only)				
6 months	−0.0014	0.0025	−0.0039	0.51
12 months	−0.0040	0.0056	−0.0096	0.004
18 months	−0.0037	0.0065	−0.0102	<0.001
All time points	−0.0023	0.0064	−0.0087	<0.001
Maximum CIMT carotid bifurcation				
6 months	0.0009	0.0028	−0.0020	0.91
12 months	0.0005	0.0177	−0.0172	0.068
18 months	−0.0038	0.0152	−0.0190	0.004
All time points	−0.0040	0.0172	−0.0212	<0.001
Maximum CIMT internal carotid artery				
6 months	0.0042	0.0317	−0.0275	0.12
12 months	0.0102	0.0192	−0.0089	0.33
18 months	0.0045	0.0140	−0.0094	0.13
All time points	0.0039	0.0145	−0.0105	0.023

A later time point also includes the earlier time points for calculation the rate of change.
[a]Progression estimates are based on data from duplicate baseline scans, intermediate scans every 6 months, and duplicate end of study scans, as appropriate.

differences over time were found when examining CIMT progression in the carotid bifurcation and CIMT progression in the ICA, but because of more variance in the measurements, the findings did not reach statistical significance at 12 months.

Based on the METEOR design (i.e. duplicate baseline and end of study scans with intermediate scans every 6 months as appropriate and reading of the scans in a batch fashion), and on the METEOR main findings (i.e. an expected difference in mean maximum CIMT progression rates of 0.0145 mm $year^{-1}$), a similar study with 1 : 1 randomization would have 90% power to show a difference between treatments arms at the $P < 0.05$ level with a total number of 115 subjects per arm in a 2 year study, 175/arm in a 1.5 year study, 355/arm in a 1 year study, or 1285/arm in a 6 month study. These estimates do not include drop-outs. Total number of subjects in treatment arms based on mean common CIMT measurements only, with an expected difference in mean common CIMT of −0.0085 mm $year^{-1}$ would be 100 subjects/arm in a 2 year study, 155/arm in a 1.5 year study, 325/arm in a 1 year study, or 1215/arm in a 6 month study.

Discussion

The Lipid Research Clinics (LRC) trial, one of the first to test the cholesterol hypothesis, suggested that cholesterol lowering therapy took at least 2 years to exert its effect on event reduction [18, 19]. Subsequently, data from the Scandinavian Simvastatin Survival Study amongst patients with coronary heart disease suggested that a statin that lowered LDL-C by 35% began to exert its effect on event reduction between 1 and 2 years after treatment initiation [20]. The recent results from the Justification for the Use of Statins in Primary Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) trial amongst apparently healthy men and women with LDL-C levels of less than 130 mg dL^{-1} (3.4 mmol L^{-1}) and high-sensitivity C-reactive protein levels of 2.0 mg L^{-1}or higher showed that a 50% LDL-C reduction and a 37% high-sensitivity C-reactive protein level reduction, began to exert its effect on event reduction already at 12 months [5]. As the occurrence of an event is an interplay between atherosclerotic abnormalities and a variety of factors that trigger the event to occur, statin use may affect both processes in a different manner and in a different time window. We focussed on the time course of initiation of effects of aggressive lipid lowering therapy on atherosclerosis progression in humans. This may come from studies where repeated assessments of atherosclerosis progression have been performed. Trials using imaging modalities for atherosclerosis progression, such as IVUS or MRI, mostly have only two measurements with at least an 18 month period between the assessments [6–10]. At present, availability of longitudinal repeated data seems to be restricted to randomized controlled trials of statins using change in CIMT over time as indicator of atherosclerosis progression, as in several of these trials CIMT assessments were done every 6 months after baseline [11–15]. A basic assumption in these analyses is that change in CIMT over time is a linear phenomenon in statin and no-statin users. Based on existing data and exploratory analyses using the METEOR data [15], this assumption seems to be holding [12–14]. Of all the lipid lowering trials using CIMT progression, none have specifically addressed the subject of this communication: i.e. the earliest time to benefit of lipid lowering therapy on CIMT progression. Although in several CIMT trials information on timing of treatment effect can be retrieved from the published reports, it should be noted that some CIMT trials had a duration of 12 months only [21–23]. Others, although designed as 2–4 year intervention studies, had only a first re-measurement at 18–24 months [24–27]. Other reports are too restricted to extract information on potential early treatment effects [27–32].

In the Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol (ARBITER) trial, where 161 high risk patients were randomized to pravastatin (40 mg) or atorvastatin (80 mg), no difference in common CIMT progression was found at 6 months, but a significant difference was reported at 12 months [21]. Unfortunately, no information on 18 months or 24 months CIMT progression was collected to substantiate the 12 month finding.

Furthermore, the observed difference in CIMT progression constituted one of the largest found in the trials performed so far. In atorvastatin versus simvastatin and atherosclerosis progression (ASAP), 325 mainly untreated patients with familial hypercholesterolemia were randomized to simvastatin (40 mg) or atorvastatin (80 mg) [33]. From that report, the mean maximum and mean common CIMT progression rates appear to be significantly different after 1 year of treatment, and this was more pronounced after 2 years. However, the precise estimates and statistical evaluations were not presented. In the MARS study, where 188 patients with angiographically documented CHD were randomized to lovastatin or placebo on top of a diet, there was a clear divergence of the common CIMT after 6 months and 12 months, which further extended during the next 3 years in a linear fashion [34]. Unfortunately, the publication does not provide information on CIMT progression rates and their precision. The examination of high risk patients in the above mentioned studies provides a population in whom the extent of disease and the potential to demonstrate changes due to different therapeutic interventions may be greater than that anticipated for lower risk patients, as studied in METEOR. Yet, the results from these high risk population studies are in line with our findings, i.e. a benefit of aggressive lipid lowering on atherosclerosis progression within 12 months. Importantly, we expand the evidence into an asymptomatic population at reasonably low CHD risk. Our findings are applicable to populations in which, based on general characteristics such as age, gender, previous medical history, smoking, weight, blood pressure and lipid levels, similar CIMT progression rate may be expected.

One assumption of our results is that increased CIMT reflects atherosclerosis elsewhere in the arterial system. This issue has been addressed in several studies and reviews. An increased CIMT has been shown to be related to increased prevalence of carotid plaques in the carotid artery, to increased atherosclerosis in the abdominal aorta, to atherosclerosis in the coronary arteries and to atherosclerosis in the arteries of the lower extremities [35–39]. Apart from the relation with atherosclerosis, an increased CIMT is related to an increased risk of future symptomatic atherosclerotic events [40, 41].

The data presented in this report may have important implications for the design of new lipid modifying treatments, in particular when investigators want to have an early indication of benefit of their treatment before embarking on a larger, more costly morbidity and mortality trial. Trials using imaging to assess progression of atherosclerosis as the primary endpoint have been proposed for this purpose as such trials can be performed in a smaller number of subjects and generally are of shorter duration. The present analysis shows that for trials that assess the efficacy of lipid modifying treatment on mean common or mean maximum CIMT progression, a duration of 12 months may be sufficient, given appropriate sample size, high precision of measurements and a treatment effect comparable to that seen in the METEOR trial.

In conclusion, aggressive LDL-C lowering with rosuvastatin seems to exert its beneficial effect on atherosclerosis during the first 12 months of treatment. This parallels the timing of event rate reduction seen in some clinical trials in which other statins were used, and is in line with the observation on event reduction seen in the JUPITER trial. The finding suggests that in trials on the efficacy of lipid lowering treatment on CIMT progression, a duration of 12 months may be adequate, given sufficient sample size, high precision of measurements and treatment effect.

Conflict of interest statement

Dr Bots has received study grants for studies on CIMT and/or honoraria for professional input on CIMT issues from AstraZeneca, Organon, Pfizer, Servier and Unilever. *Dr Crouse* has received grant or salary support from Merck, Merck-Schering Plough, Pfizer, AstraZeneca and Kos Pharmaceuticals. He has delivered lectures for Merck, Merck-Schering Plough, Pfizer, AstraZeneca, Abbott and Kos Pharmaceuticals. *Dr Grobbee* has received grant support from, and delivered lectures for, Pfizer, AstraZeneca, Organon, Servier and Merck. *Dr O'Leary* serves as a consultant to Sanofi-Aventis. He owns stock in Medpace, Inc.

Mr. Evans has received grant support and honoraria from AstraZeneca, Organon and Pfizer, and has served as a consultant for AstraZeneca and Pfizer. Dr Palmer is a former employee and current consultant to AstraZeneca. Dr Raichlen is an employee of AstraZeneca. *Drs Dogan* and *Plantinga* have no disclosures.

Acknowledgements

The authors would like to thank Helena Melezinkova, MD, AstraZeneca, who monitored adverse events in Europe, and Joseph Neubauer, AstraZeneca, who provided administrative support of the trial and study supervision.

The authors would like to thank all the METEOR investigators and the individuals involved in this study: *Belgium:* Marcelo Goldstein, Anderlecht; Jan Staessen, Leuven; Guy Marchal, Leuven. *Czech Republic:* Ales Linhart, Prague. *Finland:* Jukka T. Salonen, Kuopio. *France:* Alain Simon, Paris Cedex; Patrick Audouy, Paris; Charles Baranes, Paris; Jean-Philippe Brugnaux, Paris; Eric Chabaud, Ivry sur Seine; Daniel Delbecq, Paris; Jean Claude Mouchet, Meudon; Andre Sebbah, Paris; Gilles Bertrand, Metz; Marcel Frohn, Moutiers; Jean-Luc Jacques, Mars la Tour; Dominique Richter, Jarney; Jean-Louis Doubet, Thionville; Philippe Martin, Yutz; Alain Prochasson, Metz; Eric De Ste Lorette, Paris; Jean-Claude Ingrand, Les Lilas; Denis Smila, Yerres; Genevieve Arcizet, Bangolet; Pascal Didi, Paris; Albert Cohen, Les Lilas; Mohamed Oulmekki, Drancy; Karima Allouache, Bangolet; Serge Kownator, Thionville. *Germany:* Raimund Erbel, Essen; Clemens Von Shacky, Munich. *Norway:* Leiv Ose, Oslo; Knut Risberg, Skedsmokorset; Andreas Tandberg, Bekkestua; Olyvind Aabo, Oslo; Jon Christensen, Oslo; Anne C. Poole, Oslo; David Russell, Oslo. *The Netherlands:* Annette Bak, Utrecht; Jan Jonker, Rotterdam. *United States:* Thomas W. Littlejohn, Winston-Salem, NC; David M. Capuzzi, Philadelphia, PA; John Morgan, Philadelphia, PA; Robert Davidson, Los Angeles, CA; Michael Davidson, Chicago, IL; Alan Hirsch, Minneapolis, MN; Stephen Glasser, Minneapolis, MN; Leslie Miller, Minneapolis, MN; Daniel Duprez, Minneapolis, MN; Donald Hunninghake, Minneapolis, MN; Robert Knopp, Seattle, WA; Christie Ballantyne, Houston, TX; William Insull, Houston, TX; Daniel Edmundowicz, Pittsburgh, PA; Alan Gradman, Pittsburgh, PA; Neville Bittar, Madison, WI; Laurence Yellen, San Diego, CA; David Cameron, Kirkland, WA; Evan Stein, Cincinnati, OH; Eli Roth, Cincinnati, OH; Tasneem Z Naqvi, Los Angeles, CA; Cecil Farrington, Salisbury, NC; Bernard Mizok, Chicago, IL; Zane P Osborne, Chicago, IL; Monica Perlman, La Jolla, CA; Margaret Drehobl, San Diego, CA; Dean Kereiakes, Cincinnati, OH; Norman M. Lunde, Brooklyn Center, MN; Stephen Pomeranz, Cincinnati, OH; Steven Feinstein, Chicago, IL; Charles McCollum, Houston, TX; James Stein, Madison, WI; Laurence Needleman, Philadelphia, PA; Kim Sutton-Tyrell, Pittsburgh, PA; Shirley Otis, La Jolla, CA; Kirk Beach, Seattle, WA.

CIMT core laboratory United States: Wake Forest University School of Medicine, Winston-Salem, USA. Gregory Evans, MA; Ward Riley, PhD (co-chairs). CIMT core laboratory Europe: Vascular Imaging Center, Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, The Netherlands. Anne-Marie Bos; Michiel Bots, MD, PhD (co-chair); Corine van Everdingen; Marrij Geurtsen; Frank Leus; Corry Loffveld; Rudy Meijer, MSc; Dicky Mooiweer-Bogaerdt; Karin Nijssen (co-chair), BSc, Hannie Noordzij; Anneke Rutgers; Els Stooker; Brigitte van der Vlist; Lucienne van der Vlist; Arthur Waterschoot; Elise Wineke.

We would also like to thank Covance Central Laboratory Services, Inc., 8211 SciCor Drive, Indianapolis, IN 46214-2985, USA, and Covance Central Laboratory Services, SA, Rue Moise-Marcinhes 7, 1217 Meyrin, Geneva, Switzerland.

Funding and the role of the sponsor

The METEOR study was funded by AstraZeneca. The sponsor participated in discussions regarding the design and conduct of the study and provided logistical support during the trial. Collection management and analysis of the data were performed by the

sponsor and the contract research organization under contract with the sponsor. The manuscript was prepared by the author group. The sponsor was permitted to review the manuscript and suggest changes, but the final approval of content was exclusively retained by the authors.

References

1 Prospective Studies Collaboration, Lewington S, Whitlock G *et al.* Blood cholesterol and vascular mortality by age, sex, and blood pressure: a meta-analysis of individual data from 61 prospective studies with 55,000 vascular deaths. *Lancet* 2007; **370:** 1829–39.

2 Jones PH, Davidson MH, Stein EA *et al.* Comparison of the efficacy and safety of rosuvastatin versus atorvastatin, simvastatin, and pravastatin across doses (STELLAR Trial). *Am J Cardiol* 2003; **92:** 152–60.

3 Law MR, Wald NJ, Rudnicka AR. Quantifying effect of statins on low density lipoprotein cholesterol, ischaemic heart disease, and stroke: systematic review and meta-analysis. *BMJ* 2003; **326:** 1423.

4 Baigent C, Keech A, Kearney PM *et al.* Cholesterol Treatment Trialists' (CTT) Collaborators. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomized trials of statins. *Lancet* 2005; **366:** 1267–78.

5 Ridker PM, Danielson E, Fonseca FA *et al.* Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *N Engl J Med* 2008; **359:** 2195–207.

6 Revkin JH, Shear CL, Pouleur HG, Ryder SW, Orloff DG. Biomarkers in the prevention and treatment of atherosclerosis: need, validation, and future. *Pharmacol Rev* 2007; **59:** 40–53.

7 Brown BG, Zhao XQ, Sacco DE, Albers JJ. Lipid lowering and plaque regression. New insights into prevention of plaque disruption and clinical events in coronary disease. *Circulation* 1993; **87:** 1781–91.

8 Rodriguez-Granillo GA, Agostoni P, Garcia-Garcia HM *et al.* Meta-analysis of the studies assessing temporal changes in coronary plaque volume using intravascular ultrasound. *Am J Cardiol* 2007; **99:** 5–10.

9 Nicholls SJ, Sipahi I, Schoenhagen P, Crowe T, Tuzcu EM, Nissen SE. Application of intravascular ultrasound in anti-atherosclerotic drug development. *Nat Rev Drug Discov* 2006; **5:** 485–92.

10 Corti MR. Noninvasive imaging of atherosclerotic vessels by MRI for clinical assessment of the effectiveness of therapy. *Pharmacology therpaeutice* 2006; **110:** 57–70.

11 Grobbee DE, Bots ML. Statin treatment and progression of atherosclerotic plaque burden. *Drugs* 2003; **63:** 893–911.

12 Kastelein JJ, van Leuven SI, Burgess L *et al.* Effect of Torcetrapib on carotid atherosclerosis in familial hypercholesterolemia. *N Engl J Med* 2007; **356:** 1620–30.

13 Bots ML, Visseren FJ, Evans GW *et al.* Torcetrapib and carotid intima-media thickness in mixed dyslipidaemia (Radiance II): a randomised double-blind trial. *Lancet* 2007; **370:** 153–60.

14 Kastelein JJ, Akdim F, Stroes ES *et al.* Simvastatin with or without ezetimibe in familial hypercholesterolemia. *N Engl J Med* 2008; **358:** 1431–43.

15 Crouse JR III, Raichlen JS, Riley WA *et al.* Effect of Rosuvastatin on progression of carotid intima-media thickness in low-risk individuals with subclinical atherosclerosis: the METEOR trial. *JAMA* 2007; **297:** 1344–53.

16 Crouse JR III, Grobbee DE, O'Leary DH *et al.* Carotid intima-media thickness in low-risk individuals with asymptomatic atherosclerosis: baseline data from the METEOR study. *Curr Med Res Opin* 2007; **23:** 641–8.

17 Oren A, Vos LE, Uiterwaal CS, Grobbee DE, Bots ML. Cardiovascular risk factors and increased carotid intima-media thickness in healthy young adults: the Atherosclerosis Risk in Young Adults (ARYA) study. *Arch Intern Med* 2003; **163:** 1787–92.

18 The Lipid Research Clinics Coronary Primary Prevention Trial results. II. The relationship of reduction in incidence of coronary heart disease to cholesterol lowering. *JAMA* 1984; **251:** 365–74.

19 The Lipid Research Clinics Coronary Primary Prevention Trial results. I. Reduction in incidence of coronary heart disease. *JAMA* 1984; **251:** 351–64.

20 Scandinavian Simivastatin Survival Study Group. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simivastatin Survival Study (4S). *Lancet* 1994; **344:** 1383–9.

21 Taylor AJ, Kent SM, Flaherty PJ, Coyle LC, Markwood TT, Vernalis MN. ARBITER: Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol: a randomized trial comparing the effects of atorvastatin and pravastatin on carotid intima medial thickness. *Circulation* 2002; **106:** 2055–60.

22 Taylor AJ, Sullenberger LE, Lee HJ, Lee JK, Grace KA. Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol (ARBITER) 2: a double-blind, placebo-controlled study of extended-release niacin on atherosclerosis progression in secondary prevention patients treated with statins. *Circulation* 2004; **110:** 3512–7.

23 Taylor AJ, Lee HJ, Sullenberger LE. The effect of 24 months of combination statin and extended-release niacin on carotid intima-media thickness: ARBITER 3. *Curr Med Res Opin* 2006; **22:** 2243–50.

24 Hedblad B, Wikstrand J, Janzon L, Wedel H, Berglund G. Low-dose metoprolol CR/XL and fluvastatin slow progression of carotid intima-media thickness: main results from the Beta-Blocker Cholesterol-Lowering Asymptomatic Plaque Study (BCAPS). *Circulation* 2001; **103:** 1721–6.

25 Blankenhorn DH, Selzer RH, Crawford DW *et al.* Beneficial effects of colestipol-niacin therapy on the common carotid artery. Two- and four-year reduction of intima-media thickness measured by ultrasound. *Circulation* 1993; **88:** 20–8.

26 MacMahon S, Sharpe N, Gamble G *et al.* Effects of lowering average of below-average cholesterol levels on the progression of carotid atherosclerosis: results of the LIPID atherosclerosis

substudy. LIPID Trial Research Group. *Circulation* 1998; **97:** 1784–90.
27 Furberg CD, Adams HP Jr, Applegate WB *et al.* Effect of lovastatin on early carotid atherosclerosis and cardiovascular events. Asymptomatic Carotid Artery Progression Study (ACAPS) Research Group. *Circulation* 1994; **90:** 1679–87.
28 Mercuri M, Bond MG, Sirtori CR *et al.* Pravastatin reduces carotid intima-media thickness progression in an asymptomatic hypercholesterolemic mediterranean population: the Carotid Atherosclerosis Italian Ultrasound Study. *Am J Med* 1996; **101:** 627–34.
29 Salonen R, Nyyssonen K, Porkkala E *et al.* Kuopio Atherosclerosis Prevention Study (KAPS). A population-based primary preventive trial of the effect of LDL lowering on atherosclerotic progression in carotid and femoral arteries. *Circulation* 1995; **92:** 1758–64.
30 Crouse JR III, Byington RP, Bond MG *et al.* Pravastatin, lipids, and atherosclerosis in the carotid arteries (PLAC-II). *Am J Cardiol* 1995; **75:** 455–9.
31 de Groot E, Jukema JW, van Boven AJ *et al.* Effect of pravastatin on progression and regression of coronary atherosclerosis and vessel wall changes in carotid and femoral arteries: a report from the Regression Growth Evaluation Statin Study. *Am J Cardiol* 1995; **76:** 40C–6C.
32 Beishuizen ED, van de Ree MA, Jukema JW *et al.* Two-year statin therapy does not alter the progression of intima-media thickness in patients with type 2 diabetes without manifest cardiovascular disease. *Diabetes Care* 2004; **27:** 2887–92.
33 Smilde TJ, van Wissen S, Wollersheim H, Trip MD, Kastelein JJ, Stalenhoef AF. Effect of aggressive versus conventional lipid lowering on atherosclerosis progression in familial hypercholesterolaemia (ASAP): a prospective, randomised, double-blind trial. *Lancet* 2001; **357:** 577–81.
34 Hodis HN, Mack WJ, LaBree L *et al.* Reduction in carotid arterial wall thickness using lovastatin and dietary therapy: a randomized controlled clinical trial. *Ann Intern Med* 1996; **124:** 548–56.
35 Bots ML, Hofman A, de Jong PTVM, Grobbee DE. Common carotid intima-media thickness as an indicator of atherosclerosis at other sites of the carotid artery. The Rotterdam Study. *Ann Epidemiol* 1996; **6:** 147–53.
36 Bonithon-Kopp C, Touboul PJ, Berr C *et al.* Relation of intima-media thickness to atherosclerotic plaques in carotid arteries. The Vascular Aging (EVA) Study. *Arterioscler Thromb Vasc Biol* 1996; **16:** 310–6.
37 Bots ML, Hofman A, Grobbee DE. Common carotid intima-media thickness and lower extremity arterial atherosclerosis. The Rotterdam Study. *Arterioscler Thromb.* 1994; **14:** 1885–91.
38 Bots ML, Witteman JCM, Grobbee DE. Carotid intima-media wall thickness in elderly women with and without atherosclerosis of the abdominal aorta. *Atherosclerosis* 1993; **102:** 99–105.
39 Bots ML, Baldassarre D, Simon A *et al.* Carotid intima-media thickness and coronary atherosclerosis: weak or strong relations? *Eur Heart J* 2007; **28:** 398–406.
40 Lorenz MW, Markus HS, Bots ML, Rosvall M, Sitzer M. Prediction of clinical cardiovascular events with carotid intima-media thickness. A systematic review and meta-analysis. *Circulation* 2007; **115:** 459–67.
41 Prati P, Tosetto A, Vanuzzo D *et al.* Carotid intima media thickness and plaques can predict the occurrence of ischemic cerebrovascular events. *Stroke* 2008; **39:** 2470–6.

Correspondence: M. L. Bots, University Medical Center Utrecht, Julius Center for Health Sciences and Primary Care, P.O. Box 85500, Street 6.131, Utrecht, GA 3508, The Netherlands.
(fax: +31 30 250 5485; e-mail: m.l.bots@umcutrecht.nl).