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TRIAL DESIGN

Measuring Effects on Intima Media Thickness: An Evaluation of Rosuvastatin in Subclinical Atherosclerosis—The Rationale and Methodology of the METEOR Study

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***Summary. Background*: Increased carotid intima media thickness (IMT) is associated with established coronary heart disease (CHD) and is a marker of atherosclerosis. Statins are an effective treatment for dyslipidaemia, and have been shown to retard progression or promote carotid IMT regression in patients at high risk of CHD. Rosuvastatin is a highly efficacious statin, and the Measuring Effects on intima media Thickness: an Evaluation Of Rosuvastatin (METEOR) study is designed to assess the impact of rosuvastatin on carotid IMT progression in low risk subjects with signs of subclinical atherosclerosis.**

***Methods*: In this randomised, parallel-group study, asymptomatic subjects at low risk of cardiovascular disease, but with evidence of atherosclerosis (defined as carotid IMT $\geq$1.2 mm and $<$3.5 mm), will receive rosuvastatin (40 mg/day) or placebo for 104 weeks. The study will enrol 840 European and US subjects randomised 5:2 between rosuvastatin and placebo. The primary end point will be the change in carotid IMT from baseline to study end, measured using B-mode ultrasonography. Other efficacy end points include changes in the serum lipid profile and C-reactive protein. Safety parameters will also be assessed.**

***Conclusion*: The METEOR study will evaluate whether long-term rosuvastatin treatment promotes regression, or slows progression, of subclinical atherosclerosis in asymptomatic subjects at low risk of cardiovascular disease.**

***Key Words*. asymptomatic atherosclerosis, B-mode ultrasound, carotid, intima media thickness, statins**

Introduction

Atherosclerosis is a progressive disease that is associated with many cardiovascular complications, including coronary heart disease (CHD) and stroke, which are major causes of morbidity and mortality. Atherosclerosis may, however, remain asymptomatic for many years, with sudden death being its first clinical manifestation [1]. Furthermore, most cardiovascular events (>60%) occur in the three-quarters of subjects classified as being at 'low-to-intermediate risk' of CHD, according to current Framingham risk assessment criteria [2]. The early detection and treatment of subclinical atherosclerosis is therefore of great importance.

Elevated low-density lipoprotein cholesterol (LDL-C) levels are a major CHD risk factor [3,4], and the 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase inhibitors, or statins, are known for their efficacy in reducing LDL-C. Atorvastatin, lovastatin, simvastatin, pravastatin and fluvastatin have been shown to reduce LDL-C by 24–60% [5]. A number of key trials have demonstrated the benefits of statins on the risk of CHD and cardiovascular mortality [6–13]. As a result, statins are first-line therapy in CHD patients and those at high risk of developing CHD, as recommended by European [14] and US (National Cholesterol Education Program Adult Treatment Panel III [NCEP ATP III]) guidelines [15].

Several reports have also demonstrated the beneficial effects of statins on intima media thickness (IMT) of the carotid artery, a marker of atherosclerosis. Statins have been shown to delay progression, or even cause regression, of carotid IMT in patients with established CHD [16–18]. Furthermore, other studies have demonstrated that this beneficial effect extends to 'low-risk' asymptomatic patients with subclinical indications of atherosclerosis [19–21]. The initiation of statin therapy

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early in the progression of atherosclerosis may therefore delay or perhaps prevent the onset of CHD.

More recently, the Atorvastatin versus Simvastatin Atherosclerosis Progression (ASAP) study examined the effect of aggressive versus conventional lipid lowering on atherosclerosis progression in familial hypercholesterolaemia (FH) [22]. High-dose atorvastatin (80 mg) reduced LDL-C by 50% (on-treatment LDL-C of 150 mg/dl), and produced a significant regression in carotid IMT. Simvastatin 40 mg reduced LDL-C by less (40%, on-treatment LDL-C of 186 mg/dl) and did not result in regression [22]. Similarly, in the ARterial Biology for the Investigation of the Treatment Effects of Reducing cholesterol (ARBITER) study, atorvastatin 80 mg produced regression of carotid IMT and reduced LDL-C by 49% whereas pravastatin 40 mg stabilised progression and reduced LDL-C by 27% (76 mg/dl versus 110 mg/dl) [23]. These data suggest that greater LDL-C reductions with more intensive statin therapy (i.e. use of a higher dose and/or a more efficacious statin) may result in greater carotid IMT reductions, but non-lipid actions of statins may also be important. Beneficial effects on change of IMT over time may be expected with rosuvastatin, a well-tolerated and efficacious statin, which is capable of lowering LDL-C by 63% at 40 mg and has other benefits across the lipid profile [24].

The principal objective of the Measuring Effects on intima media Thickness: an Evaluation Of Rosuvastatin (METEOR) study is to compare the effects of intensive rosuvastatin (40 mg) therapy with placebo on carotid IMT progression, using B-mode ultrasonography, following 2 years of treatment in 'low-risk' asymptomatic subjects. The hypothesis is that rosuvastatin will induce regression, or slow progression, of atherosclerosis (monitored by change in carotid IMT over time) compared with placebo. It is important that the study is capable of detecting whether rosuvastatin can induce regression, as well as delay progression. Therefore, the study will use a hierarchical model and a novel two-stage analysis to evaluate statistically whether changes in carotid IMT indicate a slowing of progression or a regression of carotid IMT with rosuvastatin. A further objective will be to assess the safety of long-term, intensive rosuvastatin therapy in these patients, and several safety parameters will be evaluated.

METEOR Study Design

The METEOR study is a randomised, double-blind, placebo controlled, international, multicentre, parallel-group study involving 30 US and European IMT laboratories and two specialised Ultrasound Reading Centres for IMT measurement. Subjects will be screened for eligibility during a 6-week run-in period that will include three clinic visits (Fig. 1, Table 1). At visit 4, subjects will be randomised in a 5:2 ratio to receive either rosuvastatin 40 mg or placebo once daily for 104 weeks (Fig. 1). During the study, participants will visit the clinic nine further times. The study will be conducted according to the principles of Good Clinical Practice (GCP) and local regulations. All subjects participating in the study will be required to sign an informed consent form that has been approved by the Institutional Review Board or Independent Ethics Committee. A Steering Committee has been appointed to review compliance with the study procedures and (blinded) adverse effects, in accordance with the scientific, ethical and regulatory requirements.

Study end points

The primary end point for the METEOR study is the change from baseline (visit 4) to the end of treatment (visit 13) in the mean of the maximum (MeanMax) IMT (i.e. the mean of 12 maximum IMT measurements made in pre-defined segments of the anterior [near] and posterior [far] walls of the right and left common carotid

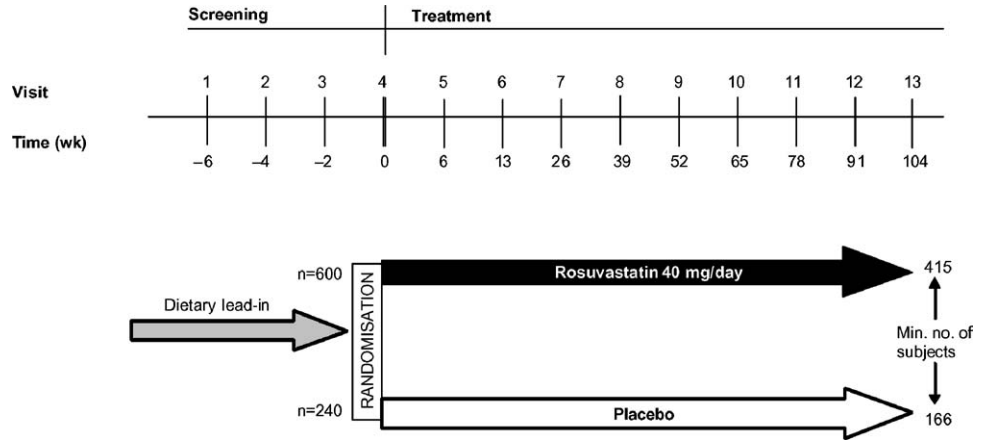

Fig. 1. *Flow chart of the METEOR study.*

Table 1. *METEOR efficacy and safety parameter assessment schedule*

	Screening			Treatment									
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13
Week	–6	–4	–2	0	6	13	26	39	52	65	78	91	104
Efficacy													
IMT		▲[1]	▲[1]				▲		▲		▲		▲▲[2]
Serum lipid profile	▲			▲		▲				▲			▲
Apo A-I and Apo B				▲									▲
CRP				▲									▲
Safety													
Vital signs	▲			▲	▲	▲		▲		▲		▲	▲
Adverse events		▲	▲	▲	▲	▲	▲	▲	▲	▲	▲	▲	▲
Concomitant medications	▲			▲	▲	▲	▲	▲	▲	▲	▲	▲	▲
ECG				▲									▲
Chemistry panel	▲			▲	▲	▲		▲		▲		▲	▲
Haematology				▲									▲
Urine sample				▲	▲	▲		▲		▲		▲	▲

IMT: intima media thickness; Apo A-I: apolipoprotein A-I; Apo B: apolipoprotein B; CRP: C-reactive protein; ECG: electrocardiogram.
[1]Must meet inclusion criterion of maximum IMT ≥1.2 and <3.5 mm at this visit.
[2]A second IMT will be performed within 2 weeks of the IMT procedure completed for the final visit.

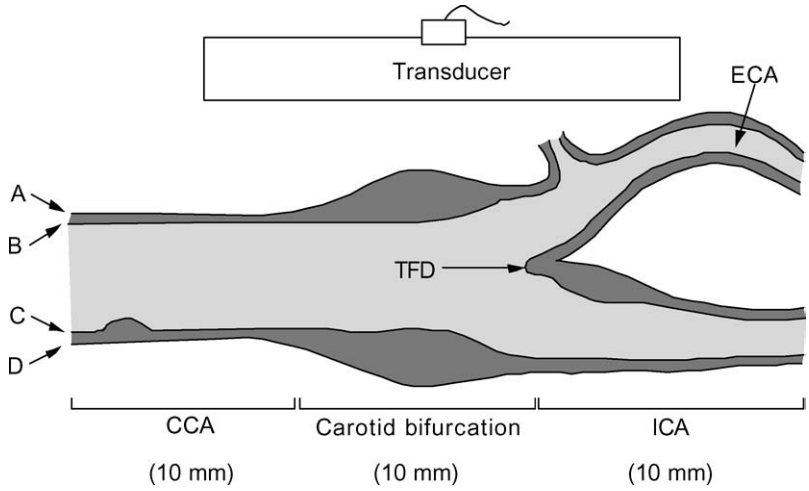

Fig. 2. *Schematic of the left carotid artery in longitudinal section. A and D represent the border of the media and adventitia; B and C represent the border of the intima and arterial lumen. The distance between A and B represents the intima media thickness (IMT) of the anterior wall, whereas the distance between C and D represents the IMT of the posterior wall. CCA: common carotid artery; ECA: external carotid artery; ICA: internal carotid artery; TFD: tip of the flow divider.*

artery [CCA], carotid bifurcation and internal carotid artery [ICA] combined [Fig. 2]). Secondary end points include: change from baseline to end of treatment in the MeanMax IMT of the right and left CCA, carotid bifurcation and ICA independently, and the mean IMT of the near and far walls of the right and left CCA. Other secondary end points include: change from baseline to study end in LDL-C, total cholesterol, high-density lipoprotein cholesterol (HDL-C) and non-HDL-C components, non-HDL-C:HDL-C ratio, triglyceride, apolipoprotein (Apo) A-I or Apo B levels and the Apo B:Apo A-I ratio. Change in C-reactive protein (CRP) level from baseline to study end will also be measured.

Ultrasound and IMT measurements

Longitudinal B-mode images will be obtained in six well-defined wall segments in both the right and left carotid arteries (Fig. 2). The segments are defined as: the near and far walls of the arterial segment extending from 10 mm to 20 mm proximal to the tip of the flow divider (TFD) into the CCA; the near and far walls of the carotid bifurcation extending 10 mm proximal to the TFD; and the near and far walls of the proximal 10 mm of the ICA (Fig. 2). A METEOR study ultrasound examination will start with an exploratory transverse and longitudinal scan of the right carotid artery to familiarise the sonographer and reader with the participant's

anatomy. During the transverse scan, the 'optimal angle of interrogation (OAI)', i.e. the view that best displays the TFD and 'Y' appearance of the two arteries in a single longitudinal image, will be determined. The sonographer will then acquire a longitudinal image at the OAI and position the TFD on a vertical marker line on the image. Following the exploratory scans, the 12 defined segments will be examined longitudinally. For the CCA, the sonographer will select an image showing both near and far wall boundaries at the OAI. Images will also be selected at 60, 90, 120, 150 and 180 degrees marked on the Meijer's Arc® when scanning the right carotid artery, and at 300, 270, 240, 210 and 180 degrees when scanning the left carotid artery. Selected images will be maintained for at least five cardiac cycles. The same approach will be used for the carotid bifurcation and the ICA. However, for the carotid bifurcation and ICA, no attempt will be made to determine the OAI, but rather the near and far wall boundaries will be scanned separately to improve the ability to align each wall horizontally in these segments. A complete METEOR scan will yield 52 images (6 right and 6 left CCA, 10 right and 10 left bifurcation and 10 right and 10 left ICA images) from which carotid IMT can be measured.

In the METEOR study, several high-resolution ultrasound systems will be used (Acuson Sequoia® 512, Acuson Sequoia® 256, SONOLINE® Antares [all Siemens Medical Solutions, CA, USA], HDI 5000 [Phillips Medical Systems, MA, USA] and LOGIQ [GE Medical Systems, WI, USA]), which have been approved by a quality control centre. All staff involved in B-mode ultrasonography will undergo a standardised training and certification programme to ensure accuracy and consistency of measurements and techniques between study centres. The images obtained will be stored on SVHS videotape and will be sent to one of two specialised Ultrasound Reading Centres in Europe (University Medical Centre, Utrecht, Netherlands) and the USA (Wake Forest University School of Medicine, Winston-Salem, NC) for measurement of carotid IMT.

For measurement of MeanMax IMT, the maximum IMT in each of the 12 segments is defined as the largest measurement derived from five interrogation angles, each one 30 degrees different to the adjacent angle. Assessment of the MeanMax from 12 segments is most frequently applied in studies of this design [25], and is based on evidence that aggregating data across a larger number of vessel segments increases the reliability of longitudinal (i.e. change over time) measurements [26]. IMT measurements will be made at randomisation (in duplicate), 26-week intervals during treatment, and the end of the study (in duplicate). The same angles will be used for interrogation at follow-up as at baseline, and the maximum wall thickness at each segment will be quantified, although the angle that defines the maximum wall thickness for any segment at follow-up may be different from that which was used at baseline.

Table 2. *Inclusion and exclusion criteria for the METEOR study*

Inclusions
One or more maximum IMT measurements of ≥1.2 and <3.5 mm (assessed at both visits 2 and 3)
Aged 45–70 years (male) or 55–70 years (female)
Asymptomatic for any atherosclerosis-related disease
Fasting LDL-C levels of ≥120 mg/dl (3.1 mmol/l) and <160 mg/dl (4.1 mmol/l) at visit 1 (−6 weeks) (for subjects with ≥2 risk factors and a 10-year CHD risk of <10%)
Fasting LDL-C levels of ≥120 mg/dl (3.1 mmol/l) and <190 mg/dl (4.9 mmol/l) at visit 1 (for subjects with no additional CHD risk factor other than age)
HDL-C ≤60 mg/dl (1.6 mmol/l) and triglyceride levels of <500 mg/dl (5.65 mmol/l)
Exclusions
Pharmacological lipid-lowering therapies (statins, fibrates, bile acid binding resins, niacin or its analogues at doses >400 mg) in the 12 months before the first visit
Clinical evidence of coronary artery disease, angina, MI or other peripheral atherosclerotic disease
Revascularisation procedures
10-year CHD risk of ≥10%
Diabetes mellitus, uncontrolled hypertension or familial hypercholesterolaemia
Serum creatinine levels of >2 mg/dl (177 μmol/l) during screening

IMT: intima media thickness; LDL-C: low-density lipoprotein cholesterol; CHD: coronary heart disease; HDL-C: high-density lipoprotein cholesterol; MI: myocardial infarction.

Study population

Eligibility and treatment withdrawal. Inclusion and exclusion criteria for the METEOR study are summarised in Table 2. The specified subject age ranges have been chosen due to concerns that the minimum carotid IMT required would be difficult to obtain in subjects younger than 45 years, and that age-related increases in IMT would be more apparent in those older than age 70. For inclusion, subjects must be asymptomatic for any arterial disease or diabetes and must have either: LDL-C ≥120 mg/dl (3.1 mmol/l) and <160 mg/dl (4.1 mmol/l) with a 10-year CHD risk of <10%, or LDL-C ≥120 mg/dl (3.1 mmol/l) and <190 mg/dl (4.9 mmol/l) with no additional CHD risk factor other than age, and have a maximum carotid IMT between 1.2 mm and <3.5 mm in any of the 12 segments. Exclusion criteria include the use of pharmacological lipid-lowering therapies in the 12 months before the first visit, FH, and elevated serum creatinine levels during the screening period. Subjects will be withdrawn from treatment or assessment for any of the following reasons: treatment non-compliance (assessed at visits 5–13), indications of elevated liver/muscle toxicity (including elevated concentrations of liver enzymes [3 × upper limits of normal (ULN)], increased

creatine kinase levels [10 × ULN] with muscle pain/weakness) or the occurrence of an adverse event that warrants treatment discontinuation.

Concomitant medication. Concomitant medication may be given, barring a conflict with exclusion criteria. Potent immunosuppressants will not be permitted. A bile acid sequestrant will be added to the treatment regimen under the following circumstances: placebo group, if LDL-C levels are ≥190 mg/dl (4.9 mmol/l) on two consecutive visits (in subjects with only age as a risk factor) or if LDL-C levels are ≥160 mg/dl (4.1 mmol/l) on two consecutive visits (in subjects with a <10% risk of CHD over 10 years); rosuvastatin group, if LDL-C levels are ≥100 mg/dl (2.56 mmol/l) on two consecutive visits. Investigators will be informed only that a bile acid sequestrant should be added, and actual LDL-C levels will remain concealed.

Laboratory analyses

Blood samples will be taken at specific visits for analysis of serum lipid, haematology, clinical chemistry (such as creatine kinase, creatinine, alanine/aspartate aminotransferase, alkaline phosphatase, total bilirubin, albumin, fasting blood glucose) and CRP. Urine samples will also be taken at specific visits for urinalysis (Table 1). The samples will be sent immediately for analysis to one of two central standardised laboratories in Europe (Covance Central Laboratory Services, Geneva, Switzerland) and in the USA (Covance Central Laboratory Services, IN).

Safety assessments

An evaluation of the long-term safety of rosuvastatin treatment will be made from the incidence of adverse events (serious or otherwise) and from abnormal safety data collected during the study. Regular assessments of vital signs and body weight will be made during the study to detect any sudden change in condition. Electrocardiogram (ECG) recordings will be taken at randomisation and at study end. Frequency and severity of adverse events will be recorded by means of a standard question put to the subject at each visit ("How have you felt since the last visit?"), and investigators will be asked to rate the severity of any adverse event as mild (awareness of symptom, but easily tolerated), moderate (discomfort sufficient to interfere with normal activities) or severe (incapacitating, with inability to perform normal activities).

Data analysis

Efficacy. For analysis of the efficacy of rosuvastatin treatment in slowing progression or causing regression of carotid IMT, a hierarchical mixed effects model (HMEM) will be employed. The primary end point (i.e. change in carotid IMT from randomisation to week 104) is derived from the HMEM by means of an estimate statement. Data will be held hierarchically as subject, vessel segments within subject, and measurements over time within subjects. The model will include random effects for subject and time since randomisation, and fixed effects for carotid segment (12 levels), treatment group (2 levels), clinical centre, core laboratory (US versus Europe), ultrasound reader and a treatment by time interaction. All analyses will be made using SAS PROC MIXED [27] and Type III sums of squares.

Statistical analysis of the primary end point data involves a novel two-stage design. In stage 1 of the analysis, a between-group comparison of the change in MeanMax carotid IMT in the rosuvastatin- and placebo-treated groups from randomisation to week 104 will be made. If this analysis shows a statistically significant difference ($p < 0.05$) that is favourable to the active treatment group, then the indication will be that rosuvastatin has *at least slowed the progression* of IMT. If such a difference is found, stage 2 will be carried out as a within-group comparison for the rosuvastatin-treated group only, to assess whether the active treatment has caused *regression* of the carotid IMT, and not simply delayed progression. Regression will be inferred if the treatment group mean end of treatment IMT is significantly ($p < 0.05$) less than baseline. Patients will be categorised according to whether they regress or do not regress.

Expected changes in carotid IMT following treatment with placebo or rosuvastatin were calculated from existing data. For example, the Asymptomatic Carotid Artery Progression Study (ACAPS) recruited patients with a similar LDL-C range (130–189 mg/dl) as the METEOR study and demonstrated that a carotid IMT reduction of 0.009 mm/year was associated with a reduction in cardiovascular events [19]. Based upon this and other studies, the carotid IMT in METEOR is expected to increase by 0.012 (SD 0.058) mm/year with placebo treatment, and is expected to decrease by at least 0.008 (SD 0.058) mm/year with rosuvastatin treatment [19,21,22,26,28,29]. These expected changes in carotid IMT have enabled the calculation of the numbers of subjects necessary to make statistically meaningful conclusions. As a result, an estimated 415 and 166 evaluable subjects will be required in the rosuvastatin and placebo groups, respectively, and will provide sufficient data for each stage of analysis. The inclusion of 166 placebo-treated subjects will allow 90% power in detecting, at stage 1, a between-group difference in the primary end point of 0.02 mm/year (assuming that carotid IMT increases by 0.012 [SD 0.058] mm/year in the placebo group). The 415 subjects in the rosuvastatin group will allow 80% power in detecting a carotid IMT regression of 0.008 (SD 0.058) mm/year. These numbers thus provide the 5:2 ratio by which subjects will receive rosuvastatin or placebo treatment, respectively. Assuming a 30% post-randomisation dropout rate, 840 randomised subjects

(rosuvastatin: 600; placebo: 240) will be required to achieve the minimum number of evaluable subjects (581).

Treatment efficacy will be assessed based upon intention-to-treat (ITT) and per-protocol (PP) populations. For the primary end point, the principal analysis will be conducted in the ITT population, while a further analysis will be carried out in the PP population. The ITT population is defined as randomised patients who receive at least one dose of trial medication and have a pre-randomisation and at least one post-randomisation IMT value. Data for patients in this population who withdraw prematurely from the study will be included in the analysis up to time of withdrawal. Groups for comparison will be defined by treatment randomly allocated. The PP population will exclude ITT subjects considered by the study physician and statistician to have shown non-compliance with the study drug or procedures, dietary non-compliance or the use of prohibited drugs during the study. In the event that some patients do not receive the treatment randomly assigned, the PP analysis will compare groups defined by treatment (rosuvastatin or placebo) actually received.

Summary statistics for IMT values will be shown by centre (or grouped centres if numbers are small) to determine the consistency of treatment effect between centres. Heterogeneity tests between centres will be conducted at the 0.01 level of statistical significance. Similar summary statistics will be employed to detect any differences between the US and European reading centres, and also between individual readers.

For the secondary carotid IMT end points (i.e. the MeanMax IMT of the CCA, ICA and carotid bifurcation separately), the HMEM will be used to estimate the effect of treatment from randomisation to week 104, in the same manner as the primary end point. The principal analyses will be made in the ITT population, while secondary analyses will be made in the PP population. For other measurements of efficacy, such as lipid parameters or CRP, an analysis of covariance (ANCOVA) will be employed to detect significant differences between treatment groups in the ITT population.

Safety. Safety analyses will be conducted on the pre-randomisation screened population (all subjects who gave written informed consent) and the randomisation population ($\geq$1 dose of trial medication, $\geq$1 safety assessment). Safety data (vital signs, haematology and clinical chemistry) will be summarised using descriptive statistics at each visit at which they are measured. For analysis, adverse events will be categorised as: (1) being reported during the 6-week pre-randomisation screening phase or (2) treatment emergent (either ongoing from the screening phase and worsening during the treatment phase, or starting within the treatment phase). ECG and urinalysis data will be listed only and not analysed statistically.

Discussion

There are several reports of a beneficial effect of statins upon carotid IMT both in patients with established CHD and in asymptomatic patients with atherosclerosis [17,21,30]. In the ACAPS trial, lovastatin 20–40 mg/day reduced carotid IMT compared with placebo in subjects with asymptomatic atherosclerosis [19]. These results were supported by data from the Long-term Intervention with Pravastatin in Ischemic Disease (LIPID) 4-year atherosclerosis substudy in CHD patients, which demonstrated a mean 0.014 mm decrease in carotid IMT with pravastatin 40 mg/day, compared with a mean 0.048 mm increase with placebo [18]. The Pravastatin, Lipids and Atherosclerosis in the Carotid Arteries (PLAC-II) study showed that LDL-C reduction with pravastatin reduced the rate of arterial disease progression (measured as a change in carotid IMT), and also produced an 80% reduction in the incidence of fatal and non-fatal myocardial infarctions [16,31]. The ASAP study did not report carotid IMT regression in FH patients treated with simvastatin 40 mg, despite greater LDL-C lowering than was seen in the LIPID and ACAPS studies [22]. However, the ASAP and ARBITER studies [23] showed significant carotid IMT regression with atorvastatin 80 mg. Although the non-lipid or pleiotropic properties of statins may be an important contributory factor to their anti-atherosclerotic effects [32,33], the ASAP study suggests that a greater lipid-lowering capacity may be more favourable for atherosclerosis reduction. In addition to reducing LDL-C, statins including rosuvastatin, have beneficial effects on HDL-C and other components of the lipid profile [34]. Whatever the precise mechanism may be, aggressive rather than conventional statin therapy appears to be more effective in causing atherosclerosis regression or slowing its progression.

The METEOR study is a prospective, randomised trial designed to assess the effects of long-term treatment with rosuvastatin on carotid IMT in 'low CHD risk' patients with subclinical atherosclerosis. In addition to regular measurements of carotid IMT during the 2-year study, assessments of patient lipid profile, CRP inflammatory marker levels and a range of safety parameters will be made. A placebo control has been chosen so that the normal change in IMT can be ascertained for subjects who meet lipid entry criteria. These criteria were selected to provide a population of subjects whose low risk of cardiovascular events warrant therapeutic lifestyle changes according to the NCEP ATP III guidelines (2001) [15].

The value of a marker that demonstrates increased atherosclerosis (and thus increased CHD risk) cannot be underestimated. Increased carotid IMT is associated with the presence of atherosclerosis in other regions, such as the coronary arteries, abdominal aorta or the arteries of the lower extremities [35–37]. Furthermore, several studies have shown that increased IMT of the

carotid artery is associated with an increased risk of CHD [38–42]. Carotid IMT is therefore a valid surrogate marker for atherosclerosis and associated risk of CHD. Although there is no definitive value above which an atherosclerotic plaque occurs, it has been suggested that in most cases, a carotid IMT of >1.0–1.2 mm indicates the presence of atherosclerosis [43,44]. The value of B-mode ultrasound has been recognised by the American Heart Association Prevention Conference V Writing Group III, which indicated that carefully performed and standardised carotid ultrasound examination with IMT measurement is useful for assessing plaque progression or regression during patient follow-up [45].

B-mode ultrasound is a sensitive technique that enables the precise definition of the various boundaries required for IMT measurement, and is a valid and reliable method of ultrasonography [21,46]. Intravascular ultrasound (IVUS) and quantitative coronary angiography (QCA) are used for the measurement of atherosclerosis; however, they require highly specialised training, involve exposure to X-ray radiation and are invasive tests requiring arterial catheterisation and introduction of cannulae into the arteries being examined. Furthermore, QCA is based on luminal stenosis measurement, reducing its sensitivity for detecting plaques that do not protrude into the lumen. As ultrasonography does not rely on stenosis, it is more sensitive to early, 'angiographically silent' atherosclerosis [44,47]. Unlike IVUS or QCA, B-mode ultrasonography is a non-invasive procedure that is painless for the subject and, with a moderate degree of training and the implementation of standardised procedures, is reproducible and simple to conduct.

The METEOR study will ascertain whether rosuvastatin 40 mg significantly promotes regression, or slowing of progression, of subclinical atherosclerosis in addition to lowering serum lipid levels. The LDL-C-lowering efficacy of this dose of rosuvastatin is greater than that of atorvastatin 80 mg [24, 34] and, based on the findings of the ASAP study [22], is therefore considered likely to have a positive effect. The potential of rosuvastatin to cause regression of arterial thickening is of greatest interest, and the METEOR study has been designed to detect whether rosuvastatin induces regression as well as delay progression. The duration of the METEOR study is relatively short, and has not been designed to detect differences in clinical atherosclerotic events with rosuvastatin treatment. Therefore, no statistical analysis of any such events will be made.

The detection of carotid IMT regression, or slowing of progression, in individuals who do not have a moderate or high risk of cardiovascular disease (according to conventional risk assessment), but who demonstrate evidence of atherosclerosis, would therefore support the early implementation of statin therapy.

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