Effect of Rosuvastatin on the Echolucency of the Common Carotid Intima-Media in Low-Risk Individuals: The METEOR Trial

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Background: The echolucency of the carotid intima-media is related to increased cardiovascular risk factor levels, morbidity, and mortality. The aim of this study was to assess the effect of statins on the echolucency of the common carotid intima-media in a low-risk population.

Methods: Data from the Measuring Effects on Intima-Media Thickness: An Evaluation of Rosuvastatin study were used. Ultrasound images from the far walls of the left and right common carotid arteries were used for evaluation of the echolucency of the carotid intima-media, measured by grayscale median (GSM). Low GSM values reflect echolucent structures, whereas high values reflect echogenic structures. The primary end point was the difference in the annual rate of change in GSM between rosuvastatin and placebo.

Results: Two-year change in GSM did not significantly differ between rosuvastatin and placebo in the total population, with a mean difference in the rate of change in GSM of 1.13 (95% confidence interval, −1.00 to 3.25). The effect of rosuvastatin differed across quintiles of baseline GSM values (*P* for interaction = .01). In the lowest quintile (n = 175) (i.e., in those with the most echolucent intima-media), the difference in the rate of change in GSM between rosuvastatin and placebo was 4.18 (95% confidence interval, −0.23 to 8.58). Increases in GSM were significantly related to decreasing low-density lipoprotein cholesterol levels in the lowest quintile (β = 0.76; 95% confidence interval, 0.26 to 1.25).

Conclusions: Treatment with rosuvastatin did not affect the echolucency of the arterial wall in all low-risk individuals. However, a potential effect of rosuvastatin on the echolucency of the common carotid intima-media is most likely to be found in individuals with echolucent arterial walls at baseline. (J Am Soc Echocardiogr 2012;25:1120-7.)

Keywords: Echolucency, carotid artery, B-mode ultrasound, statin therapy, randomized controlled trial

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Abbreviations

CI = Confidence interval

CIMT = Carotid intima-media thickness

CRP = C-reactive protein

CV = Cardiovascular

GSM = Grayscale median

HDL = High-density lipoprotein

LDL = Low-density lipoprotein

METEOR = Measuring Effects on Intima-Media Thickness: An Evaluation of Rosuvastatin

Atherosclerosis is a chronic and progressive disease that may result in the formation of atherosclerotic plaque lesions in the arterial wall. Although atherosclerosis is a lifelong process, the disease remains asymptomatic for decades. However, once atherosclerosis becomes symptomatic, it often manifests as a major cardiovascular (CV) event such as myocardial infarction, stroke, or sudden death. Atherosclerotic plaques leading to CV events (i.e., vulnerable plaques) may not necessarily be the biggest or most stenotic plaques but primarily have vulnerable content.[1,2] Autopsy and imaging studies have shown that vulnerable plaques are characterized by a large lipid-rich necrotic core, a thin fibrous cap, and a high macrophage content.[3,4]

Plaque content can be measured noninvasively using B-mode ultrasound. On these images, echolucent plaques are lipid rich and hold less collagen, whereas echogenic plaques are more stable and have higher contents of fibrous tissue and calcification.[4,5] Echolucent plaques have been associated with CV risk factors and with a higher risk for CV events than echogenic plaques in both symptomatic and asymptomatic individuals.[6-11]

A disadvantage of plaque assessment is that it can be performed only in individuals with overt plaques and not in earlier stages of atherosclerosis. Carotid intima-media thickness (CIMT) is a measure of atherosclerosis that could be used in all stages of the disease process, and measurement of the echolucency of the carotid intima-media may be performed in individuals in whom plaques are absent. We recently showed in a sample of elderly individuals with a high prevalence of plaque that the echolucency of the common carotid intima-media was closely related to plaque echolucency.[12] Also, an echolucent common carotid intima-media is associated with a threefold increased risk for all-cause mortality and an eightfold increased risk for CV mortality compared with an echogenic common carotid intima-media in elderly men.[13] Therefore, examination of the echolucency of the carotid intima-media might be of use to determine CV risk.

Lipid-lowering therapies, especially statins, are widely used to reduce CV risk and events.[14-16] Although scarce, data on the effect of statins on plaque echolucency have indicated a beneficial effect.[17-19] However, it is unknown whether the echolucency of the common carotid intima-media could be decreased by statin therapy. We hypothesized that the echolucency of carotid intima-media with statin use decreases primarily in individuals with echolucent carotid intima-media. Therefore, we examined the effects of statin therapy on the rate of change in the echolucency of the common carotid intima-media in a post hoc analysis of the Measuring Effects on Intima-Media Thickness: An Evaluation of Rosuvastatin (METEOR) study.

METHODS

Study Population

We used data from the METEOR study. METEOR was a 2-year, randomized, double-blind, placebo-controlled trial in 984 individuals. The rationale, design, and main findings of METEOR have been reported in detail previously.[20,21] The main inclusion criteria were age 45 to 70 years (men) or 55 to 70 years (women) and screening low-density lipoprotein (LDL) cholesterol 120 to <190 mg/dL (3.1–4.9 mmol/L) for those with only age as a coronary heart disease risk factor and 120 to <160 mg/dL (3.1–<4.1 mmol L) for individuals with two or more coronary heart disease risk factors, a 10-year Framingham risk of <10%, at least one maximum CIMT measurement > 1.2 mm, and no measurement ≥ 3.5 mm from two separate ultrasound examinations. The main objective of METEOR was to assess the impact of rosuvastatin 40 mg/d versus placebo on the 2-year rate of change in CIMT. Eligible potential participants were randomized to either rosuvastatin or placebo in blocks of seven (five rosuvastatin, two placebo). The reason for this was that the statistical analysis of the primary end point data involved a two-stage design. In stage 1, a between-group comparison was made. If this analysis showed a statistically significant difference that favored rosuvastatin, the stage 2 analysis was performed, in which a within-group comparison for the rosuvastatin-treated group only was made. This analysis was performed to assess whether the active treatment caused a negative rate of change in CIMT rather than simply no change from baseline.

Carotid Artery Ultrasound Evaluation

Sonographers performed carotid ultrasound examinations 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 examination, images were taken from the common carotid artery, carotid bifurcation, and internal carotid artery, each providing near-wall and far-wall data for the right and left carotid arteries. For the right carotid artery, measurements were performed at 60°, 90°, 120°, 150°, and 180° and for the left carotid artery at 300°, 270°, 240°, 210°, and 180°. Images of these 12 artery segments were obtained from five different angles. Each examination potentially provided a maximum of 60 images. Sonographers were trained to provide images showing the maximum thickness of a particular site. Hence, when a plaque was located at these predefined locations, it was included in the maximum CIMT measurement. The Acuson Sequoia 512, Acuson Sequoia 256, SONOLINE Antares (Siemens Medical Solutions USA, Inc., Mountain View, CA), and HDI 5000 (Phillips Medical Systems, Andover, MA) were the ultrasound devices used in METEOR. These devices all have electrocardiographic gating and use high-resolution linear-array probes at about 7.5 MHz. All ultrasound measurements were made on end-diastolic images at the top of the R wave of the electrocardiogram.

For the present analysis, images from the left and right far wall of a single angle (left, 240° or 270°; right, 90° or 120°) from the common carotid artery were evaluated, resulting in a maximum of 14 measurements (2 × 7) per participant over the whole study duration. The choice for these carotid segments and angles was based on the results from an earlier study that showed that measurements from the far-wall measurements from the common carotid artery on one carotid angle were predictive of CV events.[13]

End Point

The primary end point was the annualized rate of change in the grayscale median (GSM) of the common CIMT on the basis of all scans performed during the 2-year study period from two carotid artery sites (the far walls of the right and left common carotid arteries). Low GSM values represent an echolucent carotid intima-media,