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Carotid Intima-Media Thickness and Prediction of Cardiovascular Disease

Halvor Øygarden, MD, PhD

Carotid intima-media thickness (IMT) may be measured by ultrasound, where the distance between a double-line reflex pattern representing the luminal-intimal and the medial-adventitial interfaces corresponds well with IMT measured in histological specimens.[1] Thickening of the artery wall is a hallmark of atherosclerosis. It has thus been theorized that IMT measurements could aid in the prediction of cardiovascular disease (CVD) and thereby improve CVD prediction by traditional risk factors alone. However, recommendations regarding the use of carotid IMT for CVD risk prediction are conflicting.

Several studies have shown an association between carotid IMT and future CVD events. The Kuoppio Ischaemic Heart Disease study showed 11% increased risk of myocardial infarction with each 0.1-mm incremental increase of carotid IMT.[2] In the following years, several large clinical studies like the Atherosclerosis Risk In Communities study,[3] the Cardiovascular Health Study,[4] the Rotterdam Study,[5] the Malmö Diet and Cancer Study,[6] and the Carotid Atherosclerosis Progression Study[7] produced similar results. However, little or no additional prognostic value has been found by adding carotid IMT to a traditional risk factor score, such as the Framingham Risk Score (FRS).[8–10] The contradictory results regarding the value of carotid IMT in CVD risk prediction is further portrayed by the conflicting results from 2 meta-analyses. Lorenz et al found the relative risks of CVD events increased by a factor of 1.15 for every 0.1-mm increase in carotid IMT,[11] whereas Den Ruijter et al found no meaningful addition to CVD event prediction when carotid IMT was added to conventional risk prediction models.[12]

The conflicting results are also mirrored in diverging guideline recommendations. The 2010 American Heart Association/American College of Cardiology (AHA/ACC) guidelines recommended measurements of carotid IMT for CVD risk assessment in intermediate risk asymptomatic adults as a class IIa recommendation.[13] The European Society of Hypertension/European Society of Cardiology recommends ultrasound scanning of the carotid arteries to detect vascular hypertrophy or atherosclerosis as a class IIa recommendation with level of evidence B.[14] An update of the Mannheim Carotid Intima-Media Thickness and Plaque Consensus from the advisory board of the "Watching the Risk" symposium stated that measurements of carotid IMT and plaque presence are recommended for the initial detection of CVD risk in asymptomatic patients if at intermediate risk or if risk factors were present.[15] However, in 2013, the AHA/ACC guidelines recommend against the use of carotid IMT for individual risk prediction in clinical practice.[16]

These varying study results and guideline recommendations are probably caused by differences in study design, specifically differences regarding carotid IMT measurements, such as measuring the common or internal segment and whether plaques are included or excluded from analyses, as commented in a review by Naqvi and Lee.[17]

Another hurdle when using carotid IMT for risk prediction is the large influence of age on IMT. In the current issue of *Journal of the American Heart Association*, Polak et al use an interesting approach to overcome this problem.[18] Population-based percentile values are commonly used to monitor growth in youth. They found that a similar approach, creating normative values for carotid IMT, was very suitable to compensate for the usually highly skewed distribution of the carotid IMT measurements and allow the generation of normative age-specific values. Using data from participants in The Multi-Ethnic Study of Atherosclerosis (MESA), they generated age-, sex-, and race-ethnic–specific normative values for carotid IMT and were thus able to compare 1 individual's measurement as a percentile value, while taking age, sex, and race-ethnic differences into consideration. Their main hypothesis was that an approach using a combined normative percentile score from measurements of both the common and internal carotid artery IMT combined could

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From the Department of Medicine, Sørlandet Sykehus HF, Kristiansand, Norway.

Correspondence to: Halvor Øygarden, MD, PhD, Department of Medicine, Sørlandet Sykehus HF, PB 416 Lundsiden, 4604 Kristiansand, Norway. E-mail: hoygarden@gmail.com

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improve prediction of CVD events beyond that achieved by a traditional risk factor score and, furthermore, if prediction improved independently of coronary artery calcium score, a clinical marker of atherosclerosis obtained from computed tomography scans of the coronary arteries. Coronary artery calcium is suggested to have a similar, or even superior, association with future CVD events as carotid IMT.[19]

The population investigated is enrolled in the MESA, which includes men and women aged 45 to 84 years of varying ethnic origin at 6 sites in the United States. Of the 6814 participants in MESA, 314 were excluded because of incomplete risk factor or ultrasound workup. In the resulting 6500 participants, 429 coronary events were registered during a median follow-up of 10.2 years. They found that the IMT score significantly improved prediction of events. In the multivariable Cox proportional hazards regression model, the combined IMT score showed the highest improvement by increasing the C-statistic of the base model from 0.7276 to 0.7457 ($P<0.001$). Similarly, the logistic regression model had an area under the curve of 0.7210 that increased to 0.7396 ($P<0.001$) when the combined IMT score was added to the model. The improvement in prediction achieved by including carotid IMT was still significant, although slightly attenuated, when coronary artery calcium score was included in the statistical models.

One measure of a predictive markers value in improving event prediction is called net reclassification improvement (NRI). This measure is important because it quantifies the improved accuracy of prediction when carotid IMT is added to a traditional risk prediction model. In other words, how many participants with coronary heart disease (CHD) events are correctly reclassified in a higher risk category when carotid IMT is added, and conversely, how many participants free of events are downwardly reclassified to a lower risk category. The NRI from adding the combined carotid IMT score was found to be 4.9% ($P=0.024$) overall. And, interestingly, when restricting the analysis to the intermediate risk category, they found an NRI of 11.5% when adding carotid IMT.

The take on the problem of carotid IMT as a risk factor that changes with age presented by Polak et al in the current issue is intriguing.[18] This approach significantly increased prediction of CHD events beyond a traditional FRS, even when cornary artery calcium was included in the model. This could potentially revitalize the discussion regarding carotid IMT measurements as a feasible method to improve prediction of CHD. Improving tools for identifying individuals at increased risk is important, especially regarding CHD, because effective preventive treatment is available. Improving the accuracy of risk prediction can therefore help target those most likely to benefit from preventive treatment. Conversely, correctly identifying low-risk individuals that do not need primary preventive treatment is of great interest—both for the individual that may be spared from preventive treatment and its possible side effects, and for the community, to ensure the resources put into health care are spent as efficiently as possible. The findings presented by Polak et al are a step toward refining carotid IMT measurements as an appropriate tool[18]—both by the use of normative carotid IMT scores and in finding most benefit from a combined score of the common and internal carotid IMT. Measuring carotid IMT is safe, noninvasive, and, although it requires some experience, has quite high reproducibility.

The presented method of improving CHD risk prediction may be cost efficient and should be investigated further. In addition, the normative values calculated from this MESA cohort are not universal, and efforts to generate appropriate normative values in other populations should be encouraged. Further efforts should also include individuals younger than 45 years, where the potential for primary prevention could be even greater. And although the improved prediction of CHD achieved by carotid IMT measurements in this study is promising, these findings need to be replicated for validation.

Disclosures

None.

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