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Carotid Plaque Assessment

A Bumpy Road to Improved Risk Prediction

We congratulate Nambi et al. (1) on their study of improved prediction of coronary heart disease (CHD) risk by including the information on carotid plaque presence in the ARIC (Atherosclerosis Risk In Communities) study. Inclusion of plaque in the risk prediction model reclassified over 10% of individuals into the higher risk category beyond the levels of carotid intima-media thickness (CIMT) and traditional risk factors. The study is significant because the ARIC investigators acknowledge that small, nonstenotic carotid plaque might be a different phenotype of atherosclerosis, carrying an important contribution to the vascular risk beyond CIMT. Plaque presence was defined if 2 of the following 3 criteria were met: CIMT >1.5 mm, abnormal wall shape, and abnormal wall texture. This is a somewhat novel approach, because Dr. Ward A. Riley (a reputable CIMT and ARIC investigator who unfortunately is no longer with us) believed that "whatever is between intima and media represents CIMT" (Dr. Ward A. Riley, personal communication, 2001). In the recent CIMT meta-analysis (2) very little is mentioned regarding the difference between CIMT and plaque and the prognostic importance of carotid plaque. Carotid plaque is a distinctive phenotype of atherosclerosis, most likely is not a simple continuum of CIMT progression, and predicts stroke and CHD risk better than CIMT (3).

Interestingly, the ARIC investigators report that slightly more subjects were reclassified to a lower risk group (approximately 12%) than to a higher risk group (approximately 11%) after adding CIMT and plaque information. No one was reclassified from the low-risk group (<5% estimated 10-year CHD risk) to the high-risk group (>20% estimated 10-year CHD risk). In the NOMAS (Northern Manhattan Study)—a prospective, multi-ethnic, urban, population-based cohort—the presence of small, nonstenotic carotid plaque reclassified 44% of the low-risk individuals (<10% estimated 10-year CHD risk) to the intermediate-risk category (10% to 20% estimated 10-year risk) (4). In addition, approximately 12% of subjects in a lower risk category had a 10-year estimated risk of 25%, which reclassified these individuals to high risk (>20% estimated 10-year risk). None of the individuals was reclassified to a lower risk category after adding information on plaque presence—as opposed to ARIC. The NOMAS results are, however, hardly ever cited, possibly because they appeared in *Neurology*, a journal mostly neglected by non-neurologists. Therefore, "the intriguing hypothesis" raised by Stein and Johnson in the Editorial Comment (5) that "carotid ultrasound could be used to identify persons at lower than apparent risk who might be candidates for *less* intensive interventions" might be simply rejected if data from NOMAS and others (6) are considered.

Nevertheless, less intensive intervention should not be advised according to ultrasound imaging data for individuals otherwise estimated at intermediate-to-high vascular risk on the basis of traditional vascular risk factors. We believe these individuals should be treated aggressively, irrespective of a possible lower risk according to the information obtained by the levels of biomarkers, either imaging or soluble.

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doi:10.1016/j.jacc.2010.04.051

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Reply

We thank Drs. Rohatgi and Berry and Rundek and Salameh for their interest in our communication regarding the use of carotid intima media thickness (CIMT) and plaque to improve coronary heart disease (CHD) risk prediction in the ARIC (Atherosclerosis Risk In Communities) study (1).

It is important to note that our study tested whether CIMT and plaque can help better predict CHD risk, but it does not have the ability to offer guidance on treatment strategies on the basis of such a risk prediction scheme. Therefore, we completely agree with Drs. Rundek and Salameh that, on the basis of our data alone, one should not decide on decreasing interventions. However, we feel that such a strategy should be prospectively tested, as has been suggested by Drs. Stein and Johnson in the editorial that accompanied our publication (2). Drs. Rundek and Salameh also discuss their excellent contribution from the NOMAS (Northern Manhattan Study) (3), in which they examined the value of adding plaque to the Framingham risk prediction score (FRS). However, some important facts/differences need to be considered.

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September 21, 2010:1065–70

Anytime a new marker is added to a risk prediction schema, individuals will have to be (re)classified into higher- and lower-risk groups. It is this reclassification that allows us to evaluate the utility of the marker, including its ability to discriminate between those who have disease and those who do not have disease. For example, in our analysis, values were coded for the presence or absence of plaque and for the CIMT group (i.e., <25th percentile, 25th to 75th percentile, and >75th percentile), and then this was added to the traditional risk scores to get the new predicted risk. Having no plaque and a CIMT <25th percentile is favorable and might result in an individual remaining in the same risk group or being reclassified to a lower-risk group. This would depend on the contribution of the traditional risk factors to the individual's risk. Therefore, we are not clear as to how no one was reclassified to a lower-risk group in Dr. Rundek's analysis. Furthermore, in the other analysis cited by them, Bard et al. (4) evaluated individuals with "intermediate FRS" (6% to 19%, 10-year predicted CHD risk in their analysis) and described that adding CIMT and plaque area reclassified individuals to both "high"- and "low"-risk groups. However, this analysis could not test whether the reclassification was accurate, because they did not have incident CHD event data.

Another difference between our analysis and Dr. Rundek's analysis was that stroke was included as an end point in her analysis, and 121 of the 319 events were strokes. Although there is a Framingham cardiovascular disease risk score that includes stroke as an end point, the CHD FRS does not include stroke as an end point. The risk score used by Dr. Rundek in her analysis seems to be the CHD risk score and hence might not have been able to adequately predict risk when stroke was included as an end point.

Drs. Rohatgi and Berry discuss our presentation of the net reclassification index (NRI) statistic and suggest that the information provided is insufficient to evaluate the clinical utility of the test. We disagree. First, NRI is only 1 of many test statistics that are required (and presented in our paper) to evaluate clinical utility of a risk predictor. Second, we believe that both upward (to a higher-risk group) and downward (to a lower-risk group) reclassification is clinically relevant. The format of reclassification we have presented has been used by others as well (5). However, we agree that the format they request is another valid and informative way to present the data and have presented the same in Table 1 here.

For the calculation of "clinical NRI," 5% to 20% was considered as 1 risk group, and reclassification to >20% risk was considered an upward reclassification, whereas reclassification to <5% risk was considered a downward reclassification. Incidentally, if we used 10% to 20% as the intermediate-risk group, the clinical NRI was 18.2%.

We disagree with Drs. Rohatgi and Berry that treatment changes can only result when an individual is reclassified to >20%, because Adult Treatment Panel III clearly identifies "optional" goals for both high-risk and intermediate-risk individuals. However, as previously noted, our main effort was to evaluate the ability of CIMT and plaque in improving risk prediction and not to direct therapy, which should be tested formally.

Finally, FRS has been developed for both "hard CHD" and "total CHD" end points. We included all CHD end points except angina to be able to compare the NRI with other markers such as high-sensitivity C-reactive protein (5). In fact, Pencina et al. (6), in the example they provided in their original description of NRI, included angina and coronary insufficiency in evaluating the additive effects of high-density lipoprotein cholesterol in CHD risk prediction. If we used only hard CHD end points, the NRI for the overall group, men and women was 5.0%, 8.6%, and 5.3%, whereas the clinical NRI was 14.0%, 16.4%, and 16.5%, respectively.

Table 1 Net Reclassification Index and Clinical Net Reclassification Indices Among Those With and Without Incident Coronary Heart Disease Events

Population	Reclassification Index Among Those With Events	Reclassification Index Among Those Without Events	Net Reclassification Index
Men	3.2%	5.7%	8.9%
Women	9.6%	0.1%	9.8%
Overall	7.6%	2.3%	9.9%

	Clinical Reclassification Index Among Those With Events	Clinical Reclassification Index Among Those Without Events	Clinical Net Reclassification Index
Men	9.5%	6.8%	16.4%
Women	9.7%	15.6%	25.4%
Overall	10.4%	11.3%	21.7%

We also would like to point out an error we noted in Table 5 of our paper (1). The value in the last row (i.e., Kaplan-Meier estimates for "All") of Table 5 under the column "10% to 20%" should read "13" and not "3" as listed. We regret this error.

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doi:10.1016/j.jacc.2010.06.013

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