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EDITORIAL COMMENT

From Risk Factors to Clinical Disease

New Opportunities and Challenges for Cardiovascular Risk Prediction*

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Cardiovascular risk prediction is one of the major challenges of modern medicine and understanding the role of risk factors on the development of cardiovascular diseases has been a milestone of preventive medicine. However, the transition from risk factors to overt disease is mediated by the complex interplay between preclinical lesions and triggers that accelerate the evolution of atherosclerotic plaques (1). In the last years, several markers of preclinical cardiovascular disease have been proposed to refine the identification of subjects at higher risk to be enrolled in more aggressive prevention programs. The evidence that atherosclerosis is a widespread process in the arterial tree and that the recognition of the presence of the disease in an arterial segment correlates with the involvement of other districts focused the attention to the carotid artery as a target for the assessment of preclinical disease.

Noninvasive carotid artery interrogation by ultrasonography and, more recently, by magnetic resonance imaging (MRI) offers the opportunity to observe the arterial wall in its evolution from normal anatomy to advanced atherothrombotic lesions. In the past years, the thickness of the intima-media complex (IMT) of the carotid arterial wall has been proposed as a marker of preclinical atherosclerosis. However, when compared with the clinical risk scores in a comprehensive metanalysis, the additional information in risk reclassification provided by carotid IMT resulted in only marginal contribution (2). Several issues are probably involved in the explanation of the poor performance of IMT in cardiovascular risk prediction/reclassification. The first, and maybe the most important, is the fact the IMT is not only a measure of early atherosclerosis but also of smooth muscle hypertrophy/hyperplasia. In a seminal study, Roman et al. (3) showed a parallel increase of IMT and left ventricular wall thickness in hypertensive patients demonstrating that wall stress stimulates the increase of the muscular layer of the intima-media complex. Conversely, the bulging of the intimal layer due to lipid accumulation during atherosclerotic plaque development is determined by a different pathophysiological process. Accordingly, plaque prevalence but not IMT is modified by hypercholesterolemia if IMT measurements are taken in plaque-free areas (4). Thus, strictly speaking, IMT and atherosclerosis should be kept separate. Obviously, any atherosclerotic plaque is, in origin, a focal "thickening of the intima-media complex." However, measuring and averaging IMT in a wide carotid segment including focal areas of thickening (which is how most ultrasonographic devices provide this measurement) probably results in a sort of "mixing of apples with pears," limiting the accuracy and prognostic value of this approach. Focusing on carotid plaque characteristics could thus provide more reliable information on the evolution of the atherosclerotic process and the risk of subsequent cardiovascular events.

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In this issue of the *Journal*, Bos et al. (5) associated carotid plaque composition with incident strokes and coronary heart disease (CHD) in a large population

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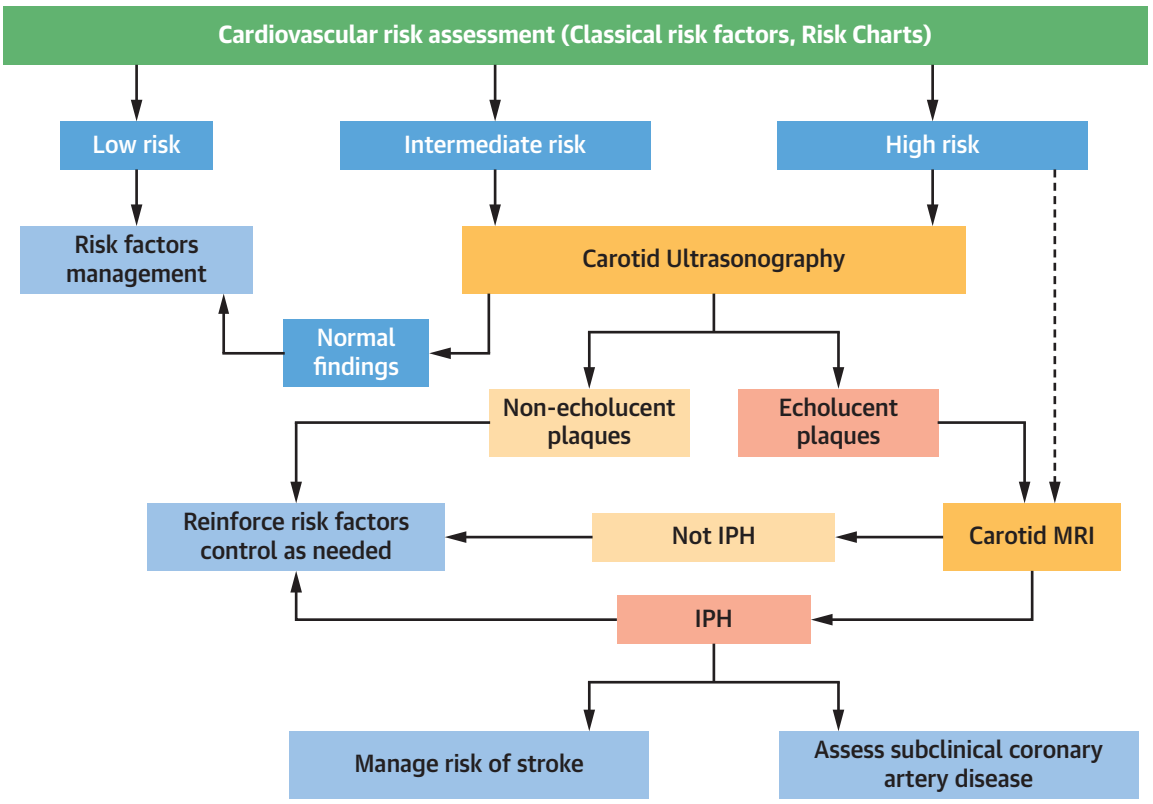
FIGURE 1 **Proposed Algorithm for Cardiovascular Risk Stratification and Patient Management**



Carotid magnetic resonance imaging (MRI) *should* be considered after an ultrasonographic finding of an echolucent plaque and *could* be considered as the first step in high-risk patients. In the presence of intraplaque hemorrhage (IPH), risk of stroke should be managed and subclinical coronary artery disease should be detected.

sample derived from the Rotterdam Study with ultrasonographic evidence of IMT (5). Using a contrast medium-free high-resolution MRI protocol, they found that the most prevalent (80.6%) plaque characteristic was calcification, whereas lipid-rich necrotic core (LRNC) and intraplaque hemorrhage were less common (44.2% and 32.2%, respectively). Among these features, only intraplaque hemorrhage was associated with incident stroke (hazard ratio: 2.42; 95% confidence interval: 1.30 to 4.50) and CHD (hazard ratio: 1.95; 95% confidence interval: 1.20 to 3.14), independent of cardiovascular risk factors. Conversely, LRNC and calcification were not associated with stroke or CHD. This is not surprising because calcified plaques are usually more stable and in the time span of a research study the presence of intraplaque hemorrhage is likely more evolutive toward ulceration than a lipid-rich plaque core. It should be emphasized that these findings should be interpreted as the expression of a "vulnerable patient" instead of simply a "vulnerable plaque" and, accordingly, the incidence of CHD was almost double than stroke during follow-up. Carotid plaque characteristics detection thus provides the opportunity to better refine cardiovascular risk prediction over traditional risk factors. In a previous study conducted on 946 participants in the Multi-Ethnic Study of Atherosclerosis, Zavodni et al. (6) found that LRNC was predictive of stroke and CHD, with a statistically significant net reclassification improvement for event prediction of 7.4% and 15.8% for participants with and those without cardiovascular events, respectively (6). Of note, the net reclassification improvement for ultrasonographically-determined IMT in addition to traditional risk factors was not significant. However, the improvement of the prediction of cardiovascular events estimated by C-statistics from a model with only cardiovascular risk factors and a model including carotid plaque characteristics was modest (from 0.696 to 0.734) (6). Similar results were obtained in the larger population of the Rotterdam Study, in which the model including intraplaque hemorrhage

improved the discrimination from 0.67 to 0.70 for stroke and from 0.72 to 0.74 for CHD (5).

Is this limited discrimination improvement cost-effective? In a recent report (7), MRI was shown to be cost-effective for primary stroke prevention when applied to a simulated population that was predominantly male and older than 70 years. Similar results were reported in a previous study in which MRI was planned after an ultrasonographic finding of carotid asymptomatic plaque (8). We can suppose that cost-effectiveness could further improve if we additionally consider CHD prevention, but we need specific and well-designed studies to clarify this point. Also assuming the cost-effectiveness of carotid MRI for risk stratification and prevention of stroke and CHD, the most important limitation of a similar approach would be the availability and accessibility of MRI to the large population of intermediate to high-risk subjects. In this regard, ultrasonography remains a cheaper and more available tool for assessing atherosclerosis in relatively unselected populations. Ultrasonographic detection of plaque echolucency is a possible marker of intraplaque hemorrhage (9), although its specificity is far from being comparable with MRI. Contrast-enhanced imaging has been proposed for improving ultrasonographic intraplaque hemorrhage detection. A recent pioneering report using artificial intelligence and machine learning suggests the possibility of refining intraplaque hemorrhage recognition by ultrasonography without the use of contrast enhancement (10). Further research should confirm the reliability of this approach.

In conclusion, the long run of cardiovascular risk prediction that started with the identification of "classical" risk factors is far from over. After the introduction of carotid ultrasound, aortic stiffness measurement, and coronary calcium score, present opportunities now include MRI detection of carotid plaque characteristics. Because the presence of intraplaque hemorrhage roughly doubles the risk of coronary and cerebrovascular events, the inclusion of carotid MRI in the algorithm for risk stratification and primary prevention of cardiovascular and cerebrovascular diseases in selected populations could be reasonable and cost-effective, as a radiation-free alternative to coronary artery calcium detection by computed tomography (**Figure 1**). However, our future challenges should be also directed to improve the ultrasonographic detection of prognostically significant plaque characteristics.

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