Editorial

Vascular Biomarkers in Cardiovascular Risk Prediction: The Central Role of the Cardiologist

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Key words: **Vascular biomarkers, risk prediction, cardiovascular risk.**

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Cardiovascular disease remains the leading cause of death in the western world, a fact that underscores the importance of cardiovascular prevention strategies (primary and secondary prevention). The success of preventive measures in primary prevention depends mainly on the accurate identification of individuals who are at considerable risk for future cardiovascular events, in order to implement the appropriate therapies to reduce the occurrence of such events. Traditionally, risk prediction has been based on the identification of classical risk factors such as hypertension, diabetes mellitus, dyslipidemia, smoking, etc. However, it soon became obvious that atherosclerosis, the major substrate for cardiovascular events, is not the result of a single factor but rather the interaction of several risk factors. This led to the use of tools that assess the global cardiovascular risk of individuals and guide the use and intensity of therapies according to that risk.[1-4]

Risk scores (i.e. multifactorial cardiovascular risk estimators), although widely used for cardiovascular risk stratification in the general population, have several inherent limitations that are related to the differences between the populations used to derive and validate these models and the populations to which they are applied: i.e. underestimation or overestimation of risk in specific subgroups. Risk scores estimate a population-based risk rather than quantifying the risk for each individual.[1,2] Furthermore, a significant part of the population is designated as intermediate risk, indicating that it is not clear whether aggressive prevention may be useful. Nevertheless, it is this group of patients who experience the largest number of cardiovascular events. Thus, there is an important need for new ways to improve the information obtained from traditional risk assessment, so that preventive measures can be applied to those who are the most likely to experience events.[2,5]

The use of biomarkers to improve traditional cardiovascular risk prediction has attracted considerable attention. Literally hundreds of circulating, genetic, imaging, and vascular biomarkers have been proposed in the cardiovascular literature. A few have been evaluated comprehensively and have shown a small or modest improvement in risk discrimination individually, usually with a weak value in the reclassification of patients at intermediate risk.[5] Detection of coronary artery calcium (CAC) by electron beam computed tomography or multidetector computed tomography is likely to be the most useful biomarker to improve risk assessment among individuals who are found to be at intermediate risk after traditional global risk assessment. Coronary calcifications indicate coronary artery atherosclerosis and correlate with the extent of total plaque burden; CAC may be quantified

using the Agatston score. The use of CAC over risk factors has been shown to improve the discrimination and reclassification of intermediate-risk individuals with high accuracy.[1,2,5] Although its use is recommended in recent European and American guidelines for primary cardiovascular prevention (class IIa and IIb, respectively; level of evidence, LOE B),[1,2] CAC is the most expensive imaging method and involves exposure to radiation.

Biomarkers assessing the structure and/or function of the peripheral vasculature (i.e. vascular biomarkers) allow for a "snapshot" of cardiovascular health to be taken in time and may serve as surrogates of the total cardiovascular risk burden. Significant advantages of these modalities are the low cost, patient safety, and the wide availability and high reproducibility of the indices measured. Vascular biomarkers that have been considered to be helpful in risk stratification and cardiovascular prognosis include ankle–brachial index, carotid intima–media thickness and plaques, and aortic pulse wave velocity.[1,2,5-7]

The ankle–brachial index (ABI) is a simple, noninvasive measure that provides information about the presence of significant stenosis between the aorta and the distal leg arteries and establishes the diagnosis of peripheral artery disease. An abnormal ABI (<0.9) also serves as a biomarker of overall cardiovascular risk, because individuals with peripheral arterial disease usually have atherosclerosis in other arterial beds as well. Assessment of ABI requires a (handheld) continuous wave Doppler device and a manual blood pressure cuff. In this respect, it is one of the least expensive and most available methods for detecting atherosclerosis and stratifying cardiovascular risk.[1,2] An ABI <0.9 has been associated with an approximate doubling of the risk of cardiovascular mortality and coronary events, independently of traditional risk factors. Furthermore, the addition of ABI to cardiovascular risk factors has been shown to be related to a modest improvement in risk discrimination and reclassification in intermediate risk patients, especially in women.[5] Accordingly, ABI is recommended by both European and American guidelines (class IIa and IIb respectively, LOE B)[1,2] for risk stratification in intermediate-risk patients as a part of cardiovascular prevention, as well as for the detection of peripheral artery disease in asymptomatic hypertensive (class IIa, LOE B)[6] and diabetic patients (class I, LOE C).[7]

Carotid intima–media thickness (cIMT) assessed by vascular ultrasound is considered an early biomarker of subclinical atherosclerosis. A value >0.9 mm is considered abnormal, although there is a graded increase in cardiovascular risk with rising cIMT, and cIMT is age- and sex-dependent.[1] Increased cIMT has been independently associated with a higher risk for cardiac events and stroke, but its additive role over classical risk factors in the risk discrimination and reclassification of intermediate-risk individuals is still questioned.[5] CIMT measurement has several limitations due to various different non-standardized imaging and measurement protocols, particularly when one considers that sub-millimeter differences in cIMT may separate low- and high-risk groups. This may explain the controversy regarding the recommendations for cIMT: European guidelines for cardiovascular prevention recommend its use for risk stratification in moderate-risk subjects (class IIa, LOE B),[1] in contrast to the American guidelines (class III, LOE B).[2] At present, the use of cIMT appears to be limited to research settings, as one of the most commonly ascertained noninvasive vascular measures in cardiovascular epidemiology studies, and as a surrogate endpoint in randomized trials of new cardiovascular therapies. Standardization in imaging and measurement protocols currently underway is expected to improve the performance of the biomarker and lead to its implementation in everyday clinical practice.[5] Furthermore, apart from the measurement of cIMT, identification of carotid plaques (a focal structure of the inner vessel wall of at least ≥0.5 mm or >50% of the surrounding IMT, or any IMT measurement ≥1.5 mm) on carotid ultrasound has been suggested as a marker more closely related to the risk-factor burden and clinical outcomes (coronary and cerebrovascular events) than IMT alone. Plaque is a more definitive finding of structural atherosclerosis, as it always points to atheroma within the arterial wall. Based on evidence from a small number of studies, the combination of cIMT and carotid plaques may improve the prediction and reclassification of cardiovascular risk compared with either alone.[1]

Carotid–femoral pulse wave velocity (PWV), i.e. the velocity of the pulse as it travels along the aorta, remains the most commonly used noninvasive method of measuring arterial stiffness and is considered as the "gold standard" technique. PWV reflects structural remodeling in the aortic wall in response to elevated blood pressure, aging, or vascular disease. Arterial tonometry is mostly used to assess PWV; the method has been standardized and reference values

have recently been reported. A PWV >10 m/s is considered abnormal.[6,8] Multiple studies in both high-risk groups and the general population have demonstrated that increased PWV predicts cardiovascular events (nearly twofold increase in cardiovascular events, cardiovascular mortality and all-cause mortality) independently of other risk factors.[9] A few studies have suggested that the addition of aortic PWV to standard cardiovascular risk factors may modestly improve the discrimination and reclassification of cardiovascular risk, especially in intermediate-risk individuals.[5] Although there is no recommendation for the use of PWV, or any other measure of arterial stiffness, in the European or American guidelines for cardiovascular prevention,[1,2] the use of carotid–femoral PWV as an index of target organ damage in hypertensive patients has been included in the most recent guidelines for hypertension.[6]

In summary, noninvasive vascular assessment could be performed easily and at low cost in broad populations to identify asymptomatic individuals at particularly high risk for cardiovascular events. In contrast to other biochemical and genetic biomarkers, vascular biomarkers may detect signs of existing atherosclerotic disease: ABI for peripheral artery disease, carotid ultrasound for carotid atherosclerosis, and aortic PWV for arteriosclerosis. These biomarkers may thus have the advantage of improved predictive accuracy, particularly in the short to mid term, because individuals with subclinical disease may be closer to having overt clinical events compared with those who simply have a predisposition for disease. Problems associated with technical difficulties and the standardization of measurement methods do exist, but clinical research worldwide is expected to produce solutions to these problems.

Cardiologists today have the unique advantage of being familiar with most of these biomarkers. Cardiologists already have ultrasound and Doppler devices to assess the carotid arteries and ABI, and the availability of tonometry devices to assess PWV is widely increasing. Training in these methods is considered to be easy and should be part of the core cardiology training curriculum, as is the case already in a few centers in Europe. By integrating the use of vascular biomarkers, cardiologists can play a key role in the refinement of cardiovascular risk prediction in individual patients.

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