Editorial: Early cardiovascular structural and functional abnormalities as a guide to future morbid events

Juhani S. Koskinen[1,2,3,4] and Olli T. Raitakari[1,2,5]

[1] Research Center of Applied and Preventive Cardiovascular Medicine, University of Turku, Finland

[2] Centre for Population Health Research, University of Turku and Turku University Hospital, Finland

[3] Division of Medicine, Turku University Hospital, Finland

[4] Department of Medicine, Satakunta Central Hospital, Finland

[5] Department of Clinical Physiology and Nuclear Medicine, University of Turku, Finland

Atherosclerosis is a process that develops slowly over the lifespan and therefore has a long preclinical phase prior to the onset of symptomatic cardiovascular disease outcomes, such as myocardial, cerebral or peripheral ischemic syndromes. The major traditional risk factors of atherosclerosis, such as high levels of apolipoprotein B containing lipoproteins, elevated blood pressure and smoking, have been discovered already decades ago. Effective reduction of these risk factors by life-style modifications and drugs, such as statins and blood pressure medications, slows the progression of atherosclerosis and may even lead to its regression.[1,2] Despite the progress made in deciphering the causes of atherosclerosis and its management, however, the cardiovascular syndromes remain a major cause of morbidity and mortality worldwide.[3]

In many cases, the atherosclerotic process goes undetected for too long and preventive measures, if initiated at all, are inadequate and/or come too late. In attempting to identify individuals at increased risk for cardiovascular events, the current guidelines recommend using risk calculators, such as the Framingham or SCORE models.[4] These algorithms use traditional

risk factors that epidemiologic studies have identified as predictors of future cardiovascular events. Typically, they are used to estimate cardiovascular risk over a short period of time from 5 to 10 years. Therefore, these risk algorithms may fail to identify high-risk individuals, especially women and young men, who have a low short-term risk, but a substantial lifetime risk for cardiovascular morbidity.[5] In theory, direct measures of structural and functional properties of the vascular tree should give more accurate information of the actual burden of atherosclerosis than do the traditional risk markers. Thus, theoretically, the rates of cardiovascular events could be significantly reduced by accurately identifying individuals who have signs of preclinical atherosclerosis and by providing them with effective preventive interventions.

At present, most of the methods available to measure arterial structural and functional properties have not been tested as screening tools in cardiovascular risk assessment. The most extensive research evidence is available for computed tomography scanning for coronary artery calcium deposits and carotid artery ultrasound scanning for atherosclerotic plaques.[6] Both imaging techniques provide information that can improve the algorithms based on traditional risk factors in predicting clinical cardiovascular outcomes.[6] For example, Bittencourt et al.[7] recently demonstrated in the MESA Study that the absence of coronary artery calcium is associated with a low incidence of cardiovascular events, even in individuals in whom lipid-lowering therapy is recommended based on the SCORE model. However, imaging techniques, as well as other tests for measuring arterial changes, are recommended for reclassification purposes only to refine the cardiovascular risk estimates given by the risk calculators.[4] Thus, at present the evaluation of future cardiovascular risk is still based on traditional risk algorithms, as the value and interpretation of additional functional and structural tests is not completely clear. Therefore, there is a considerable and continued research interest to develop

and evaluate diagnostic tools for detecting and monitoring early vascular disease in asymptomatic subjects.

In this issue of *European Journal of Preventive Cardiology*, Duprez et al.[8] evaluated the predictive value of a battery of ten non-invasive tests on the future risk of cardiovascular events. Their study included 1,442 initially asymptomatic self-referred middle-aged adults (mean age 53 years), who were followed-up for a median of 9 years for cardiovascular morbidity and mortality. These individuals underwent a standard protocol consisting of a series of tests that assessed the functional and structural health of the large conduit arteries, the small pre-capillary arteries and the left ventricle, thus involving a wide range of cardiovascular systems. The test pattern included resting and exercise blood pressure, small and large artery elasticity (derived from a radial pulse contour analysis), retinal photography, urine test for microalbumin/creatinine ratio, carotid ultrasound for wall thickness and plaques, electrocardiogram, cardiac ultrasound for left ventricular structure and function, and a blood test for assessment of N-terminal Pro-B-type natriuretic peptide. A disease score was calculated based on these tests and the population was categorized into tertiles.

A total of 102 participants experienced an adverse event: six (0.16 events per 100 patient-years) in the lowest tertile; 36 (0.86 events per 100 patient-years) in the middle tertile; and 60 (1.3 events per 100 patient-years) in the highest tertile. Furthermore, the authors calculated hazard ratios for the cardiovascular event using the lowest tertile as the reference group yielding hazard ratios of 5.4 (95% confidence intervals (CI) 2.3-12.9) and 8.3 (95% CI 3.6-19.2), the 2nd and 3rd tertiles, respectively. Risk assessment using the Framingham risk score also predicted cardiovascular events but the prediction was improved by adding the disease score information.

However, disease score and the Framingham risk score were often discordant in recognizing individuals in need of treatment.

From these results, the investigators concluded that assessing the biological disease process in the arteries and heart of asymptomatic adults provides a guide to the risk for a future cardiovascular morbid event. These data suggest that in asymptomatic adults, the absence of non-invasively assessed functional and structural cardiovascular abnormalities identifies individuals at a very low risk for future morbid events. One limitation of the study was that the population included was self-referred and concerned about their health. Therefore, the results might be biased by selective attendance. However, Grønhøj et al.[9] recently observed no selection towards healthy people in a coronary artery calcium screening study among middle-aged men and women free of cardiovascular disease. They found lower socioeconomic status in non-participants than in participants, but no differences in cardiovascular health.

The links between structural and functional properties of arteries and cardiovascular morbidity have been demonstrated by several methods.[4] However, the lack of extensive long-term studies has so far slowed down the introduction of these methods for cardiovascular risk assessment. There are several concerns regarding the available methods. Most methods are lacking clear thresholds for classifying individuals as high-risk. Additionally, there is no data on the cost-effectiveness. This issue is particularly relevant to the coronary artery calcium imaging. Lower cost of carotid ultrasound would favor its use as a primary imaging technique in risk assessment. However, the interpretation of carotid plaque finding is not straightforward; the plaque prevalence increases with age and there are no age- and sex-specific thresholds for plaque classification. In addition, the measurement of carotid intima-media thickness has been

criticized: measurement techniques may involve variation; and intima-media thickness may be a sign of medial hypertrophy rather than atherosclerotic process. Finally, it is presently scientifically unproven whether individuals defined as high-risk based on arterial changes would benefit from enhanced prevention – although common sense says this could be the case. At least, the diagnosis of preclinical atherosclerosis would expect to improve the adherence to preventive measures such as healthy lifestyles and medications.

Studies exploring the role of tests that assess the structural and functional properties of the vascular tree in attempt to find the best ways to identify high-risk individuals that could benefit from early treatment, similar to the present study by Duprez et al.,[8] are important and should be encouraged. Such studies are needed to pave the way to the future, where instead of measuring cardiovascular risk factors, physicians could use tools to measure and monitor the actual disease process, vascular atherosclerosis, to assess the individual risk for disease outcomes and to optimize preventive treatment. To achieve this, larger studies with a longer follow-up should be conducted to determine whether and which structural and functional tests can be used as primary indicators to guide treatment decisions. However, already today, these methods could be more widely used to support clinical decision-making, or at least motivate high-risk patients for treatment interventions. As Cohn and Duprez stated in 2008: "The time has come to enter a new era in which we focus on early disease rather than risk factors."[10] Perhaps this era will begin in the new decade.

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