# Surrogate atherosclerotic markers and atherosclerosis risk assessments

## Vascular biology in atherogenesis

Atherosclerotic disease (stroke, acute coronary syndrome, chronic coronary artery disease, and peripheral artery disease) is the most important health problem facing the developed world. Recent advances in vascular biology have provided a better understanding of the roles of cellular adhesion and transendothelial infiltration, oxidation of low-density lipoprotein–cholesterol, macrophage and foam cell transformation, plaque rupture, platelet aggregation, and the cascade of coagulation in pathogenesis and clinical manifestation of atherothrombotic disease. Evidence-based treatments have naturally targeted thrombolytic, anticoagulant, and antiplatelet therapies. Subsequently, intensive secondary preventive measures have focused on more aggressive control of the predisposing risk factors (smoking, dyslipidaemia, hypertension, obesity, diabetes mellitus, and hyperfibrinogenaemia). Evidence for treatment benefit in primary prevention has been less than overwhelming, and the application of such strategies is questionable on cost-effectiveness grounds, particularly in light of the constraints on public health resources.

## Subclinical atherosclerosis: documentation and relevance in prevention

Atherogenesis is a diffuse process spanning 3 to 4 decades or more, from early-stage endothelial dysfunction and arterial intima-media thickening to clinical manifestation.[1] Early intervention to stop or slow the atherogenic process before any clinical manifestation is a logical course of action. In the past, documentation of subclinical atherosclerosis was difficult if not impossible. Recently, however, several non-invasive diagnostic technologies have emerged as reliable, highly reproducible, and fairly affordable methods for the early detection of subclinical atherosclerosis, including high-resolution ultrasonic imaging of carotid plaque and intima-media thickening,[2,3] flow-mediated dilatation as a marker of endothelial function in peripheral arteries,[4] electron beam computed tomographic coronary calcification score and multi-slice computed tomographic coronary angiography, magnetic resonance brain and total body angiography, and transesophageal aortic imaging. The relevance of such surrogate atherosclerosis markers have been confirmed by their high rates of success predicting cardiovascular outcomes in both median- and long-term follow-up and interventional studies.[5] This is not surprising, as the development of these prognostic surrogate markers may categorically represent the end results of interaction between risk factors and genetic predisposition in the subjects concerned. However, while the development of atherosclerosis may be related to multiple rather than single genes, the documentation of these surrogate markers may provide a relatively inexpensive and readily available evaluation of the genetic predisposition in the individual, and urge the consideration of earlier intervention in high-risk patients.

Data from large-scale clinical trials demonstrating a benefit with more upstream preventive strategies (by documentation of surrogate atherosclerotic markers) are awaited with much interest. Meanwhile, the advances in vascular imaging technologies will promote a more logical categorisation of atherosclerosis preventive philosophy as prevention on community levels (primary prevention), in preclinical but high-surrogate-risk subjects (secondary prevention), and in patients with prior atherosclerotic events (tertiary prevention). More data on the benefit and cost effectiveness of such preventive strategies are expected in the near future.

## Ankle brachial index and global atherosclerosis risk evaluation

To be better prepared for this proactive prevention policy, all practitioners are entrusted with the responsibility of competency in assessing the presence and extent of subclinical or clinical atherosclerosis, particularly among patients with atherosclerotic risk factors. A good history of atherosclerotic symptoms and a targeted physical examination (eg peripheral pulses and bruit, fundal blood vessels by ophthalmoscope) are good clinical practice. Similarly, measurement of ankle brachial index (ABI)—the ratio of systolic blood pressure in ankle to that of brachial artery as illustrated and reported in the current issue[6]—correlates with the extent of diseased arterial beds and the prevalence of risk factors in both symptomatic and asymptomatic groups. Among the 210 symptomatic and high-risk asymptomatic Hong Kong Chinese cohort, 134 had normal

(>0.9) ABI (33.6% symptomatic), 34 had mildly reduced (0.7-0.9) ABI (55.9% symptomatic), and 42 had more severely reduced (<0.7) ABI (88.1% symptomatic), giving odds ratios for symptomatic atherosclerotic diseases of 0.5, 1.3, and 7.4, respectively. In fact, ABI has been well established and widely utilised in Europe and Australia, in both clinical practice and research, for the evaluation of obstructive lower limb arterial disease (both symptomatic and subclinical) and overall cardiovascular risk assessment.[7] Measuring ABI (using either simple Doppler detection or manual palpation) emerges as a simple bedside value-added procedure and a reliable surrogate marker, highly predictive of total cardiovascular mortality and morbidity.

The timely report by Tsang et al[6] in this issue should help to popularise this simple bedside assessment, in conjunction with other non-invasive imaging methods, for documenting atherosclerosis occurrence, assessing global atherosclerotic risk, and selecting preventive strategies in Hong Kong.

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