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## SCIENTIFIC EDITORIAL

# The prognostic value of carotid intima-media thickness revisited

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Preventive treatment of high-risk asymptomatic individuals requires preliminary accurate prediction of their probability of developing a future cardiovascular event. Non-invasive detection of subclinical atherosclerosis by peripheral artery echo-Doppler or computed tomography (CT)-assessed coronary artery calcifications (CAC) aims at improving the predictive value of traditional risk assessment as provided by the Framingham risk score (FRS) or its derived risk charts [1–4]. B-mode ultrasonographically assessed carotid intima-media thickness (CIMT) is an inexpensive, non-invasive, precise and reproducible artery wall marker. It is predictive of subsequent coronary heart disease and stroke [5,6], the two leading causes of cardiovascular death. For these reasons, in both North American [2] and European [3,4] guidelines for cardiovascular disease (CVD) prevention, CIMT measurement is encouraged for the detection of subjects at high risk of coronary heart disease among asymptomatic individuals at apparently intermediate risk. The strength of the added value of CIMT in cardiovascular prediction remains questionable, however, and solid evidence on its usefulness is still lacking for applying these recommendations in clinical practice.

It is well recognized that CIMT is associated with most of the traditional cardiovascular risk factors, emerging biomarkers and other subclinical cardiovascular alterations or organ damage (for further information, see Simon et al. [5]). CIMT is thus considered an early integrator of the effects of multiple risk factors on the arterial wall [5]. Also, a large number of prospective studies have demonstrated that carotid artery intima-medial wall thickening is predictive of major cardiovascular events, independently of traditional risk factors, with risk ratios ranging from 1.4 to 5.1 for coronary heart disease, and from 2.0 to 3.5 for stroke [5–8]. Because of its established predictive value and its quantitative measurement with high precision and reproducibility rates, CIMT is also being employed as a surrogate endpoint in numerous clinical trials involving lipid-lowering or antihypertensive drugs [5].

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Nevertheless, conflicting results have been published among studies on the added value of CIMT measurements in cardiovascular risk prediction. These differences may account for methodological heterogeneities across cohorts in terms of study design, segments chosen for CIMT measurement (common, bifurcation, internal carotid artery), inclusion or exclusion of plaques, cut-off values for risk categories, and definition and incidence of cardiovascular endpoints [6,8]. Recent epidemiological advances indicate that it is not sufficient that a biomarker provides independent significant hazards ratio associated with CVD incidence: the strengths of its predictive value also requires that it carries powerful discrimination and reclassification [9]. Discrimination refers to the ability of a biomarker to separate adequately those subjects who will, from those who will not, develop an overt CVD. It can be assessed by the area under the curve (AUC) of the receiving operating characteristic (ROC) curve, or *c*-statistic, which incorporates the sensitivity and specificity of the biomarker's predictive power against the observed events [9]. Reclassification assesses the proportion of individuals adequately moved between risk categories by the application of the biomarker [9]. It can be expressed as the net reclassification improvement (NRI) index, summing the proportion of patients with an event reclassified as at high risk and that of event-free subjects reclassified as at low risk [9].

In 2012, the weakness of CIMT for predicting cardiovascular risk was illustrated by two major publications [8,10]. The USE-IMT meta-analysis was based on data from 45,828 individuals from 14 cohort studies worldwide with a median follow-up of 11 years [8]. The lack of discrimination power was illustrated by the negligible increase in *c*-statistic AUC, by only 0.002 for total CVD-event prediction with FRS + CIMT vs FRS alone (0.759 vs 0.757, respectively). Similarly, only a small proportion of subjects were correctly upgraded or downgraded from the intermediate-risk category (NRI = 3.2% in men and 3.9% in women) [8]. The Multi-Ethnic Study of Atherosclerosis (MESA) investigators compared the improvement in 6.7-year CVD prediction of six risk markers (CT-assessed CAC, CIMT, ankle-brachial index, brachial flow-mediated vasodilation, high-sensitivity C-reactive protein and family history of coronary heart disease) within intermediate-risk participants (FRS = 5–20% at 10 years) [10]. Again in this study, CIMT increased modestly the *c*-statistic AUC from 0.623 (FRS alone) to 0.652 (FRS + CIMT), similar to the other markers, with the exception of CAC, which showed the highest increment in AUC up to 0.784. Consistently, few intermediate-risk subjects were appropriately reclassified by CIMT (NRI = 6%), similar to other markers, with the exception of CAC, which reclassified adequately 46.6% of intermediate-risk subjects.

Carotid artery plaque may be a better predictive marker than CIMT. Indeed, when measured in the common carotid artery usually free from atherosclerotic plaque, CIMT is not a specific marker of the atherosclerotic process, but it reflects medial hypertrophy, particularly as a consequence of hypertension or ageing [5]. Accordingly, pooled data from several longitudinal studies showed that the absolute risk of coronary heart disease at 10 years associated with the presence of carotid plaque was 25% (high risk), compared with 8% (low

risk) in the absence of plaque, contrasting with an absolute risk of 11 to 15% (still intermediate risk) in subjects with CIMT > 95th percentile [11]. Additionally, the Framingham investigators recently showed that the maximal CIMT of the internal carotid artery (potentially integrating plaque) added predictive value to FRS alone, whereas the mean CIMT of the common carotid artery did not [12]. Similarly, the Atherosclerosis Risk In Communities (ARIC) investigators found that plaque information, in addition to CIMT, resulted in a NRI of 9.9% in a general multiethnic population [13].

Technological progress, the availability of ultrasound equipment and the reliability and simplicity of the method, have allowed the widespread use of CIMT measurement for stratifying cardiovascular risk. Obviously, CIMT remains of major interest for physiopathological studies and clinical trials. However, the current recommendation to measure CIMT in order to reclassify intermediate-risk subjects [2–4] is not supported by its actual predictive value, which suffers established weakness beyond traditional risk factors compared with that of carotid plaque and coronary artery calcinosis.

## Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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