

Limited accuracy of carotid progression of intima-media thickness in predicting clinical cardiovascular outcome

Michael Y. Henein^{1,2,3}, Pompilio Faggiano⁴, Federico Vancheri⁵

1 Institute of Public Health and Clinical Medicine, Umea University, Umea, Sweden

2 Brunel University London, Uxbridge, Middlesex, United Kingdom

3 St George's, University of London, London, United Kingdom

4 Cardiology Division, Spedali Civili and University of Brescia, Brescia, Italy

5 Internal Medicine, Ospedale S Elia, Caltanissetta, Italy

Atherosclerosis-related coronary and cerebrovascular diseases account for most deaths worldwide. Although many risk factors contribute to the pathophysiology of atherosclerosis, inflammation is the common route towards its progression. The systemic vascular inflammatory process that results in atherosclerosis starts in early life and increases with age. Obviously, there is a long subclinical asymptomatic period before the development of an overt clinical disease. Lots of efforts have been made by clinicians and scientists to modify the course of the disease and to slow its progression during its subclinical phase. This disease prevention strategy is mainly based on conventional risk factors control and life style optimization. With such a big number of variables involved, an individualistic approach has become an important determinant of a favored clinical outcome. For an accurate follow-up of individuals, particularly those with significant risks for atherosclerosis, it is important to use a simple, accurate, and reproducible method for assessing phenotypic expression of the disease, even in the absence of clinical manifestations of a "subclinical disease." Such a method would allow an early detection of a disease, and hence guide towards optimum risk control. Two non-invasive measures, namely, coronary artery calcium (CAC) detected by computed tomography scanning and carotid artery intima-media thickness (CIMT) as well as plaque characterization measured by B-mode ultrasound, are currently used in clinical practice for assessing subclinical atherosclerosis in the coronary circulation and the carotid tree, respectively.^{1,2}

In recent years, CIMT has emerged as the most simple and reproducible imaging technique for

assessing atherosclerotic burden and the risk of future cardiovascular (CV) events.³ A positive association between progression of CIMT over time and stroke and myocardial infarction has been reported.⁴ On the other hand, statin treatment has been shown to slow CIMT progression.⁵ CIMT, however, does not have a consistent accuracy in predicting CV events.⁶ While the presence and extent of CIMT seem to be linked to the CV risk, its changes over time do not correlate with future clinical outcome.⁷ Overall, the results indicate that CIMT has a limited additional value over existing CV risk prediction models.⁸ Hence, its use in clinical practice for prediction of CV events is not recommended by current guidelines.⁹

In the present issue of the *Polish Archives of Internal Medicine (Pol Arch Intern Med)*, Gacon et al¹⁰ report a study investigating the value of the progression or regression of CIMT over time in predicting subsequent major cerebral and coronary events (MACCEs). Two large groups of patients, one with symptomatic significant coronary artery disease (CAD) and a high rate of classic CV risk factors, and the other without CAD but peripheral atherosclerotic lesions with >50% lumen reduction, were studied. CIMT was measured at baseline and subsequently twice, after 1 to 2 and 3 to 4 years.

The results of this study demonstrate some inconsistencies in the relationship between CIMT and CV risk prediction. Compared with patients with peripheral artery disease, the mean CIMT at baseline was significantly higher in patients with CAD who had worse CV risk factors, which was modestly associated with a higher rate of subsequent MACCEs. These patients, however, did not show any difference in the CIMT progression

Correspondence to:

Michael Y. Henein, MSc, PhD,
Umea University, Umea, Sweden,
phone: +46-0907850000,
email: michael.henein@umu.se

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rate compared with those with peripheral artery disease, despite standard treatment. Furthermore, one-third of patients in each group showed regression of the CIMT values, which was maintained at follow-up in only a fourth. Such regression in CIMT was associated with a reduced risk of MACCEs. Although approximately 80% of patients showed some degree of progression, the changes in CIMT over the years were not related and could not be predicted by conventional CV risk factors. Moreover, the significant prognostic value of a repeated assessment of CIMT changes was limited only to the small group of patients who demonstrated stable CIMT regression, while in those with CIMT progression, it had limited prognostic value for subsequent CV events.

There are some possible methodological and biological explanations for the discordance between CIMT change and CV risk observed in the study by Gacon et al¹⁰ as well as in several other studies.

First, the mean annual change in CIMT is consistently very small, accounting for only a fraction of a millimeter, which is within the range of human error, using the currently available ultrasound software. Therefore, measurements done by different sonographers and even small differences in the measurement site several months after the first measurement may reduce the accuracy of the CIMT value. Accordingly, the assessment of reproducibility of these measures should be taken into account when evaluating changes in carotid atherosclerosis over time.

Second, the phase of the cardiac cycle when CIMT is measured differs among studies and is often ignored to be reported. During systole, the arterial lumen diameter increases, leading to CIMT thinning.¹¹ Repeated measurements in different phases of the cardiac cycle may affect the progression or regression pattern.

Third, the inclusion of the carotid plaque in the CIMT analysis may differ between studies, due to different diagnostic methodologies. CIMT and plaques are both expression of atherosclerosis, but different pathophysiology underlie their development. CIMT represents intimal thickening and smooth muscle hypertrophy, induced by age, hypertension, and genetic determinants.¹² Carotid plaques are formed by intimal thickening with lipid content and fibrous cap, strictly associated with classic CV risk factors and aortic stiffness.¹³ In addition to different patterns of association with CV risk factors, CIMT and plaques show different association with future CV disease. In a population study, CIMT was strongly associated with stroke, whereas plaques were more directly associated with future coronary artery disease.¹⁴ Whether CIMT and plaques are parts of a continuous process or separate phenotypes remains debated. Furthermore, both conditions may superimpose with variable predominance, which may account for the difference in the prediction of future CV events in different studies.

Thus, despite the unique feasibility of CIMT assessment in daily practice, the above limitations urge the need for either fully automated ultrasound systems that avoid human intervention with such fine measurements or more advanced technologies that can provide better diagnostic accuracy of the relationship between CIMT and plaques and CV risk in the general population. Ideally, a technology that is accurate in providing information on plaque characterization and vulnerability using computerized algorithms based on a gray-scale pixel analysis should be the best clinical option.¹⁵ Else, a 3-dimensional carotid ultrasound measurement of plaque burden or magnetic resonance imaging¹⁶ could be a substitute, although the 2 techniques are known for their temporal and spatial resolution limitations.

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