

# Variability in the intima-media thickness measurement as marker for cardiovascular risk? Not quite settled yet

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For over two decades the measurement of carotid intima-media thickness (CIMT) has been applied in cardiovascular research. There is a wealth of evidence supporting its value. A thickened CIMT measurement does not lead directly to the occurrence of a myocardial infarction or stroke, but merely reflects what is going on in the vasculature of an individual. Similarly, the rate of change in CIMT over time is a reflection of how the development of atherosclerosis is altered over time. Both these CIMT measurements are reflections of cardiovascular risk (1,2). Over the years, researchers have looked for other aspects that may arise from the B-mode image from which CIMT is measured and that may be of additional value in cardiovascular research and potentially in a clinical setting. Amongst others, these have included the assessment of vascular age using CIMT (3), the determination of the composition of the CIMT by measurement of grey scale median (4,5), measurement of carotid wall volume (6) and assessment of irregularity of the carotid segment from which CIMT is measured (7,8). The relevance for measurement of segment irregularity stems from observations that measurements of surface features may be powerful determinants of cardiovascular risk (9). Irregularity of an arterial segment has been suggested to reflect increased risk of rupture and/or presence of hemorrhage in the wall, or a reflection of inflammation of the arterial wall, all conditions that increases cardiovascular risk (10).

In this issue of the journal, Saba and co-workers present the results of a small study in 20 patients in whom they have assessed the far wall common carotid intima-media thickness variability (11). They propose this new technique as a powerful method to study carotid atherosclerotic

disease, and as a method to identify patients with a risk of cerebrovascular disease. The common CIMT variability was assessed with dedicated software using longitudinal B-mode images stored on videotape as part of the measurement of the CIMT. In their study they showed a reasonable reproducibility and suggested a relation between increased common CIMT variability and previous stroke. They concluded that future studies are needed to confirm these findings and relate the measurement to established risk factors. Their study was small and therefore raises many unaddressed questions.

One is whether the measurement of CIMT variability at the level of the far wall of the common carotid segment is the best location to measure. It is well known from clinical observations that atherosclerosis in the carotid artery develops in an asymmetric manner and even asymmetrical in every carotid segment (the common, the bifurcation and the internal). We recently confirmed this by studying the distribution of maximum CIMT in various populations with different cardiovascular risk using the baseline data from four recent international multicenter randomized controlled trials in which the carotid artery was systematically examined using the same ultrasound protocol and method to quantify CIMT (12). We showed that the pattern of asymmetry in carotid segments is similar in men and women, across age groups, among races and between European and US populations, underscoring the hypothesis that local hemodynamic factors play a major role in atherosclerosis development (12). In addition, several studies showed that irregularities in the arterial wall tend to form on the flow divider side in the common carotid artery and opposite the flow divider in the bifurcation region

(13-15). So, it seems that standardized approach, based on pathophysiologic concepts, making use of a fixed angles of interrogation approach of the ultrasound probe, seems a sensible way to proceed. Following this line of thinking, should we have only one measurement of irregularity in one carotid segment, or should we have several, in one or more carotid segments? Evidence on this issue is not available but certainly of great interest when this measurement is either clinically used as measurement of risk or used in intervention studies as primary outcome.

Another important point to realize is that the measurement of irregularity, as a marker of risk, combines two aspects of atherosclerosis, notably the level of atherosclerosis (value of the thickness, extent of abnormalities) and its surface pattern. It would seem likely that an increased CIMT goes hand in hand with more irregularities of the arterial wall. However, Saba and co-workers showed that only CIMT variability, and not CIMT alone, related to previous stroke. This suggests that more vulnerable patients have a different surface pattern and do not necessarily have a thickened CIMT. Ideally, one should compare individuals that have the same burden of atherosclerosis (e.g., maximum CIMT), but differ in the magnitude of irregularity of the atherosclerosis. If individuals that differ in irregularity are not equal in burden of atherosclerosis, the relation with increased cardiovascular risk is merely a reflection of the difference in atherosclerosis burden than in irregularity per sé.

The paper by Saba is not entirely clear on how the measurements are done. It seems that the measurements are performed by observers using manual tracings. Subtle variation in positioning of the tracer by observers may considerably affect the values. Automated edge detection programme may be beneficial in that regards, especially when one restricts to far wall common carotid images.

Finally, similar to the evidence that has become available for carotid intima-media thickness (CIMT) measurements, a comprehensive research program with a focus on CIMT variability should provide data on reproducibility on a larger scale, its relation with unfavourable levels of risk factors and atherosclerosis elsewhere in the arterial system and its relation with risk of vascular events. In addition, one should study whether change in carotid intima-media thickness variability over time can be readily assessed and modified by treatment. Finally, one should study whether CIMT variability provide incremental prognostic information over and above that provided by a normal CIMT measurements. The aspect that makes such a programme feasible is the

world wide availability of extensive imaging material stored that, using dedicated and appropriate study designs can be used to quickly address these outstanding issues.

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