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EDITORIAL COMMENT

The Intima-Media Thickness Age Is Over

The Time of Multiterritorial Subclinical Plaque Quantification Has Come*

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Risk equations based on cardiovascular risk factors (CVRFs) have constituted the cornerstone of cardiovascular disease (CVD) risk stratification for decades. However, although these traditional tools provide a good estimate of CVD risk at the population level, they often fail to predict an individual's lifetime risk for CVD events.[1] Besides, CVRFs may predict CVD events only at the statistical level. However, at the mechanistic level, CVRFs are linked to events mainly through atherosclerotic plaque formation. Thus, it is very plausible that direct visualization and measurement of atherosclerotic plaque burden and extension will improve risk stratification. Noncontrast cardiac computed tomography can identify coronary calcification, which is a surrogate for atherosclerotic disease. Conversely, vascular ultrasound (VUS) directly identifies atherosclerotic plaques at the large, easily accessible, arteries (eg, carotids, femorals), and is very convenient because it is noninvasive, does not require contrast, and is not associated with radiation. Based on recent evidence, the latest clinical practice guidelines do recommend atherosclerosis screening, by coronary artery calcium scoring (CACS) quantification and/or by peripheral artery plaque visualization using VUS as risk modifiers for CVD risk stratification in low-risk to moderate-risk subjects.[2,3] Another potential strength of subclinical atherosclerosis visualization is that it may by itself provide a useful tool to induce lifestyle modifications and improve CVD risk.[4]

Although most efforts for atherosclerosis screening with VUS have been focused on the carotid territory, the femoral region is gaining more focus because it has recently been recognized that atherosclerotic plaques grow earlier in this vascular territory, as shown, among others, by the PESA (Progression of Early Subclinical Atherosclerosis) study.[5] Besides, the AWHS (Aragon Workers' Health Study) has shown that femoral atherosclerotic plaque presence is more strongly associated with CVRFs than carotid plaque presence or CACS.[6]

For many years, the carotid territory has been explored by measuring intima-media thickness (IMT), but recent data have shown that this is not a good surrogate for atherosclerosis. Cumulative evidence shows that IMT does not reflect true atherosclerosis, but it is rather a marker of vascular aging. The use of carotid IMT, a poor surrogate for atherosclerosis, has introduced a significant noise when testing the role of subclinical atherosclerosis visualization to improve CVD risk prediction. Current clinical practice guidelines[7] discourage the systematic measurement of carotid IMT because it has shown little or no improvement for CVD events prediction when added to conventional CVRF scales.[8] Conversely, actual atherosclerotic plaque identification and quantification (area or volume) by 2-dimensional (2D) and 3-dimensional (3D) VUS has clearly shown to improve risk stratification.

CAFES-CAVE (Carotid and femoral ultrasound morphology screening and cardiovascular events in

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low risk subjects: a 10-year follow-up study) was one of the first initiatives that combined both carotid and femoral atherosclerotic plaque presence and severity (though qualitatively assessed with a traditional 4-grade scale) and concluded that the combination of both parameters had the highest value for subsequent CVD events prediction.[9] A few years afterward, the BioImage (A Clinical Study of Burden of Atherosclerotic Disease in an At-Risk Population) study demonstrated that subclinical atherosclerosis burden and, more importantly, the combination of imaging modalities to assess atherosclerosis extension on multiple vascular territories (CACS and carotid VUS) are independent predictors for the development of CVD events.[10] Despite the fact that these data were solid, one limitation of the BioImage study was that the population enrolled was relatively old (mean age 69 years). In addition, the femoral territory was not screened.

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In this issue of the *Journal of the American College of Cardiology*, a study by Nicolaides et al[11] aimed to demonstrate the ability of 2D-VUS carotid and femoral plaque measurements over classical CVRFs to improve the prediction of actual CVD events. A total of 985 asymptomatic subjects aged 40-84 years (mean age 58; 55% women) from the Cyprus Atherosclerosis Study were included. Participants underwent a 2D-VUS scan of the carotid and femoral territories with subsequent measurement of plaque burden (plaque maximum thickness and areas) and a proxy for atherosclerosis extension (assessed by the number of bifurcations affected by atherosclerotic plaques). The primary outcome was the incidence of CVD events that was prospectively collected based on hospital records and included fatal or nonfatal myocardial infarction, onset of angina, coronary artery revascularization, ischemic stroke or transient ischemic attack, and onset of claudication or critical limb ischemia. During a mean follow-up of nearly 13 years, a total of 154 first CVD events occurred. The main findings of this study are as follows: 1) 2D-VUS measurements of subclinical plaque size significantly improved the prediction of CVD events over classical CVRFs; 2) extension of subclinical atherosclerotic disease (ie, number of bifurcations involved) was also associated with an increased risk of CVD events; 3) the predictive value of femoral subclinical atherosclerosis is superior to carotid territory evaluation; and 4) the predictive capacity of femoral atherosclerosis quantification (plaque area and plaque maximum thickness) is superior to carotid IMT measurement. These results support the value of multiterritorial screening for atherosclerosis extension that has already been documented in other cohorts[5,10] and validate a critical concept: atherosclerosis is a systemic disease.

Some limitations should be acknowledged. First, this study was performed in a relatively old population, whereas prevention strategies are desperately needed for middle-aged subjects. Despite the relatively low incidence of acute CVD events in younger subjects (at low or intermediate CVD risk) compared with those at higher risk, the absolute number of preventable events coming from this group is very large because the denominator (population at risk) and the cumulative life-time risk are higher. Second, this was a cross-sectional study, but atherosclerosis is a dynamic condition with a rapidly progressing course.[12] Therefore, it is intuitive to argue that not only plaque presence but also plaque development or progression over the years will have prognostic value. Third, this study only included 2D-VUS acquisitions, but 3D-VUS offers some advantages over 2D scanning. The authors mention the size and weight of the transducer, time needed for 3D acquisition, and the cost among the disadvantages of 3D vs 2D-VUS. However, it has been recently demonstrated that the use of new transducers and improved 3D plaque quantification software provides accurate volume plaque measurements, and it reduces time of analysis by 46%.[13] In the upcoming years, artificial intelligence for automatic vessel and plaque segmentation can vastly increase generalizability of 3D-VUS in the real life. Besides, 3D plaque quantification can be undertaken by trained technicians, not necessarily physicians, thus allowing for additional cost reductions apart from time saving. Furthermore, trying to assess disease progression using 2D-VUS measurements is very challenging. For instance, the variables used in the present study (maximum plaque thickness and area of the thickest plaque) would in our view be extremely difficult to interpret on serial evaluations. The easiest and most reproducible way to evaluate atherosclerosis progression is global plaque burden on 3D-VUS. Therefore, studies having serial longitudinal global plaque volume evaluation on multiple territories using 3D-VUS (eg, PESA or BioImage, among others) are placed in a very strong position to explore the impact of atherosclerosis progression (and its pace) on CVD events across the spectrum of cardiovascular health to disease transition.[14]

One remarkable point about the present results is that femoral plaque thickness and plaque area have a similar performance to predict CVD events. In theory,

this may simplify the 2D-VUS analyses because plaque thickness is an easier (and more reproducible) measurement than area calculation. This is in line with prior evidence from BioImage comparing carotid plaque thickness with plaque burden (although measured on serial cross-sectional 2D images, not with true 3D technology).[15] Conversely, plaques may grow longitudinally to the vessel wall (without increasing their maximum thickness), and this might also have an impact on events. Because plaque volume is a superior measurement than plaque area, one may argue that volume changes will be a better predictor of CVD events than area. Another point is that, besides plaque size, plaque composition on magnetic resonance imaging has been found to be predictive of coronary and cerebrovascular disease events.[16] Other plaque characteristics, such as increased metabolic activity, might have additional predictive value, and this remains to be further explored. Finally, the authors have focused on plaques located in bifurcations, but extension of atherosclerosis beyond this landmark occurs[5] and may also have an impact on CVD events.

Overall, Nicolaides et al[11] should be congratulated for providing one important piece of the puzzle of atherosclerosis visualization for prediction of CVD events, especially validating the concept that atherosclerosis is a systemic disease and the superiority of scanning the femoral territory for CVD risk stratification. Overall, the identification of subclinical atherosclerotic disease will revolutionize the way we conceive CVD risk estimation in asymptomatic individuals in the next years. These scientific advances must go hand in hand with the development of user-friendly automatic quantification algorithms in order to make screening feasible at the population level.

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