Invited Commentary

The Importance of Coronary Artery Calcium Density

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In this issue of *JAMA Cardiology*,[1] an international research group reports results from the Incident Coronary Events Identified by Computed Tomography (ICONIC) Study, a prospective nested case-control study. Patients underwent coronary computed tomography angiography (CCTA) for suspected coronary artery disease (CAD). After a mean follow-up of 3.9 years, 189 patients were identified with acute coronary syndrome (ACS) and propensity-matched to 189 controls who remained ACS free. Importantly, the propensity matching included the qualitative coronary atherosclerotic extent based on CCTA. Overall, cases had less calcified coronary plaque and more fatty, fibrous, and necrotic core plaques. The most striking result was the greater number of high-attenuation plaques in controls, plaques with more than 1000 Hounsfield units that the authors termed *1K plaque*.

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Higher coronary artery calcium (CAC) density has previously been shown to be associated with a reduced risk of coronary events in a large multiethnic cohort free of CAD at baseline.[2] This protective association became evident only after adjustment for CAC volume, underscoring the elevated risk of the presence and extent of calcified atherosclerosis in the coronary arteries and the partial mitigation of risk marked by highly dense calcium. With additional follow-up, this association was shown to be consistent across subgroups defined by age, sex, race/ethnicity, diabetes, estimated glomerular filtration rate, and atherosclerotic cardiovascular disease (ASCVD) risk score.[3] This study[1] extends this observation of the protective association of densely calcified plaque to persons with image-documented CAD at baseline.

Considering all CAD risk factors and all subclinical CAD measures, extensive population-based research has shown CAC to be the strongest single marker of CAD risk[4] The combined measures of CAC volume and CAC density have shown to account for more risk area under the receiver operator characteristic curve than the combination of the risk factors in the standard ASCVD risk equation (ie, total cholesterol levels, high-density lipoprotein cholesterol levels, systolic blood pressure, hypertension medication use, diabetes, and current smoking[3]). Thus, prevention guidelines routinely suggest considering CAC as a "tie-breaker" in persons with borderline ASCVD risk for whom the decision to initiate certain preventive treatment strategies is ambiguous.[5] The Agatston score is widely used to quantify CAC in risk prediction, but the score is upwardly weighted for a higher density, which is "backward" because CAC density appears to be protective. Nonetheless, the Agatston score works well because of its high association with CAC volume, which works even better. The best prediction comes from considering the independent associations of CAC volume (positive) and CAC density (inverse) separately.[2,3]

With optimal CAC density imaging, the predictive strength in terms of the hazard ratio (HR) per standard deviation increment of CAC density (inverse) is only modestly less than that of CAC volume (positive).[2,3] In the scanners used in the Multi-Ethnic Study of Atherosclerosis (MESA) at baseline 2 decades ago, CAC density and CAC volume were associated with better prediction when electron beam computed tomography (EBCT) scanners were used compared with multidetector computed tomography (MDCT) scanners. However, production of EBCT scanners was halted in 2006 and EBCT scanners are rarely used today. The older MDCT scanners have been mostly replaced with newer updated MDCT scanners that use more slices. To our knowledge, no population data are currently available for the predictive value of either CAC volume or CAC density on these newer scanners. In this article focusing on CAD patients at baseline,[1] the authors note that the Hounsfield unit thresholds for CAC with CCTA are higher than for cardiac computed tomography without contrast because CCTA increases the attenuation of all vascular structures. With this increased attenuation, the CAC density results are consistent with earlier noncontrast studies showing an inverse association for CAC density.

The authors note that in the subgroup of patients older than 75 years, 1K plaque was not less common in the patients with ACS. With the aging of the population and thus coronary patients, such a finding could be important. However, this subgroup was small and not well matched for total plaque volume. In MESA, the HRs per SD of CAC density were actually somewhat more protective in those 65 years or older (HR per SD, 0.675) than those younger than 65 years (HR per SD, 0.765).[3]

Considering atherosclerotic plaque in other vascular beds, the plaque density in the ascending thoracic aorta showed a strong inverse association with CAD incidence (HR per SD, 0.48; $P < .01$) and an increase in ATC with a mean follow-up of 2.4 years was associated with a markedly reduced CAD risk (HR per SD, 0.29; $P = .001$).[6] Analyses of plaque density in the abdominal aorta showed no significant association with CAD.[7]

The ICONIC authors concluded that measurement of 1K plaque may improve risk stratification beyond plaque burden.[1] We agree but wonder whether it will have any therapeutic implication. Patients with known CAD should receive maximal preventive therapy in any case. However, new attention to the associations of plaque density may be useful. The authors note one such association, that good evidence suggests that statins increase calcification and reduce necrotic core volume, presumably stabilizing plaque. Other associations of CAC density have been published and the associations for CAC volume and density are a mirror image, whereby standard risk factors are associated with increased

CAC volume and reduced CAC density.[8] Notably, with multivariable adjustment there are markedly lower levels of CAC volume and higher levels of CAC density in ethnic minorities compared with non-Hispanic white individuals. Emerging definitions of CAC measures and their implications have been highlighted in recent reviews.[9,10]

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Published Online: January 22, 2020. doi:10.1001/jamacardio.2019.5745

Conflict of Interest Disclosures: None reported.

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