The Denser the Merrier? The Developing Story of Vascular Calcification

Márcio Sommer Bittencourt, MD, MPH, PhD

The coronary artery calcium (CAC) score, the Agatston score, is a robust noninvasive surrogate marker of coronary atherosclerosis, which is strongly associated with increased risk of incident cardiovascular events and mortality.1 Its ability to predict adverse cardiovascular outcome is incremental to traditional risk factors used in clinical risk prediction,2,3 and it has been validated by studies on a wide spectrum of sex, age, ethnic, and racial backgrounds.1,4 The association between vascular calcification and worse prognosis has also been documented in other extracoronary vascular territories.5,6 In particular, the presence and extent of abdominal aortic calcification (AAC), measured using the Agatston method, is associated with a higher risk of incident cardiovascular events and mortality in several studies.7

The Agatston score has been developed to quantify the total amount of vessel calcification, and it is calculated by multiplying the calcification area by a density factor.8 This calculation assumes that any increase in the amount of calcification would indicate a higher atherosclerosis burden and worse prognosis. Yet, recent studies have questioned whether both components of the score, calcification area and density, have similar implications for prognosis. In a previous analysis of MESA (Multi-Ethnic Study of Atherosclerosis),9 the investigators estimated the averaged CAC density by dividing the Agatston CAC score by the CAC volume. In this study, the coronary calcium volume was strongly associated with adverse prognosis, whereas higher calcium density was inversely associated with incident events. Although these data have questioned the previous understanding that the more vascular calcification the worse the prognosis, previous studies on the plaque stabilization effects of statins had already suggested that vascular calcifications may also be involved in plaque stabilization. For example, some studies have demonstrated that statins may increase the overall CAC score irrespective of the low-density lipoprotein cholesterol and adverse event reduction.10,11 Moreover, intravascular ultrasound studies have demonstrated that this increase in plaque calcification is mainly a change in plaque composition toward a more stable plaque, and not an increase in atherosclerotic burden, at least in coronary vessels.12

In this issue of Circulation: Cardiovascular Imaging, Forbang et al13 have further expanded this knowledge by demonstrating a somewhat similar pattern of association between the Agatston score components and incident events, now for the AACs. This new subanalysis of MESA demonstrated that although AAC volumes were associated with incident coronary heart disease, cardiovascular disease, and all-cause mortality, AAC density was not. Despite the limited power of the smaller sample size included in this analysis, high AAC density was protective for all-cause mortality, whereas a nonsignificant trend was noted for incident cardiovascular disease.

Interestingly, the association of AAC and CAC volumes and events persisted even after mutual adjustment for coronary and abdominal volumes and densities. These findings suggest that the higher the extent (ie, volume) of the vascular calcification, the higher the risk of events, irrespective of the vascular bed involved in the atherosclerotic process. These results further support the idea that atherosclerosis is a systemic disease of the entire vascular system, despite a variable distribution of disease involvement across different vascular territories.

On the other hand, once AAC and CAC densities and volumes are combined, the prognostic implication of vascular density is less impressive. Nevertheless, AAC density remained a significant predictor of all-cause mortality, whereas CAC density remained associated with coronary heart disease. Although both were numerically associated with a lower risk of incident cardiovascular disease, neither reached statistical significance. Still, hazard ratios for all outcomes tend to the protective side for both AAC and CAC densities for all outcomes.

Several factors may explain the lack of protective effect of higher calcium densities in this multivariable analysis. First, the sample size in the present MESA subanalysis is much smaller than the initial MESA study that evaluated only the CAC score.9 Second, because calcification density and volume are strongly correlated, as demonstrated in this study, there is potential collinearity between those predictors in each of the 2 vascular territories. Third, a collinearity between both density measures, AAC and CAC, may also have occurred. Fourth, the information on vascular density is limited by the imperfect data collection because densities were indirectly estimated from the relationship between CAC scores and volumes. Thus, was the full spectrum of calcium densities...
available, they would more likely be associated with a lower rate of events.

Despite these methodological limitations, the current results corroborate previous findings by suggesting that the extent of vascular calcification, irrespective of the vascular territory, is the true marker of risk in the Agatston score. Those results are in line with compelling literature that plaque extent (ie, global atherosclerotic burden) is a key marker of increased risk of events.\textsuperscript{14,15}

The findings also suggest that the higher calcium density may be an indicator of more stable atherosclerotic plaques, which are less likely to lead to acute complication. Remarkably, those findings may also be true for other non-coronary vascular territories, such as the abdominal aorta. This is of particular interest because the mechanism leading to complications of aortic atherosclerosis may not be similar to the mechanism leading to acute coronary syndromes. In the aorta, the atherosclerotic process is mostly associated with the development of aneurysms, embolization, and a higher risk of dissection and rupture. Notwithstanding those differences, although the extent of plaque (and calcification) predicts events, calcification density seems to confer some degree of protection, irrespective of the vascular bed involved.

Overall, the present data by Forfang et al\textsuperscript{12} pose 2 questions for changes in clinical practice. First, should the widely validated Agatston score be replaced by a new measure for vascular calcification in the routine risk stratification? Although the pathophysiology and epidemiological data suggest no, an alternative measure of vascular calcification has yet been validated to the extent needed to replace this score. However, because more data on vascular calcification volumes become available, this may become the standard risk tool to be incorporated into practice. Second, can the calcium volumes be used as markers of atherosclerotic disease progression for patients currently on statins? Current evidence suggests that the increase in the Agatston score with the use of statins is most likely related to plaque stabilization and changes in plaque composition, but not in overall plaque volume. However, no study to date has evaluated if this effect of statins in plaque composition can be discriminated with the separate analysis of calcification density and volume instead of the Agatston score itself. Third, is there a clinical role for the isolated value of calcium density, and can it be used as a marker of plaque stability? Despite the evidence to support the concept that higher plaque density is associated with more stable plaques, the practical use of such measures is still a developing story that needs to be resolved before incorporation into clinical routine.

Disclosures

None.

References


Key Words: Editorials • atherosclerosis • prognosis • risk factors • sample size • vascular calcification
The Denser the Merrier?: The Developing Story of Vascular Calcification
Márcio Sommer Bittencourt

Circ Cardiovasc Imaging. 2016;9:
doi: 10.1161/CIRCIMAGING.116.005685
Circulation: Cardiovascular Imaging is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2016 American Heart Association, Inc. All rights reserved.
Print ISSN: 1941-9651. Online ISSN: 1942-0080

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circimaging.ahajournals.org/content/9/11/e005685

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation: Cardiovascular Imaging can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation: Cardiovascular Imaging is online at:
http://circimaging.ahajournals.org/subscriptions/