Title

Coronary Artery Calcium Progression: Increasing CAC Is Associated With Increased Events.

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unfavorable outcomes in stroke patients. Indeed, it is not surprising that initial studies reporting the prognostic usefulness of LVH in various populations frequently used ECG-based methods for LVH assessment. However, it is also not surprising that the sensitivity of ECG criteria for LVH is quite low compared with imaging methods, including echocardiography or cardiac magnetic resonance. Hence, a recent study has proposed a novel ECG criterion for LVH diagnosis to improve diagnostic performance over traditional criteria (2). Although this new criterion outperformed the classic Cornell criteria, its sensitivity was still 62% compared with echocardiography, the reference standard used in this study. Thus when discussing the predictive ability of ECG-derived LVH, it should be considered that a substantial portion of cases of true anatomic LVH may be misclassified as normal according to ECG criteria. Despite this limitation, we agree with Dr. Inamo and colleagues that ECG-defined LVH has prognostic relevance in stroke patients, as supported by data demonstrating that ECG-diagnosed LVH independently predicted outcomes even after adjusting for imaging-based left ventricular (LV) mass. It can be speculated that the development of ECG changes associated with increased LV mass per se may offer prognostic information by reflecting the complex alterations in electrical properties of myocardium.

With regard to the interaction between LV geometry and blood pressure (BP), we think that the findings by Inamo and colleagues, the U-shaped relationship of mortality with BP regardless of the presence of ECG-based LVH, should be cautiously interpreted, given the aforementioned limitation. In other words, the U-shaped association between mortality and BP in patients without LVH could stem from the misclassification of true LVH as normal. Furthermore, although their exclusion criteria included patients with significant aortic stenosis, there is a possibility that potential confounding diseases were not excluded, such as valvular heart disease (other than aortic stenosis), cardiomyopathy, or pericardial diseases. However, because our hypothesis also remains just an intriguing possibility, we definitely agree with Dr. Inamo and colleagues and the excellent accompanying editorial by Drs. Gillebert and Chirinos (3) that further studies are warranted to verify the interaction between LV remodeling and BP as prognosticators in stroke patients and to elucidate its underlying mechanisms.

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Coronary Artery Calcium Progression: Increasing CAC Is Associated With Increased Events

We read with interest the well written paper by Mori et al. (1) related to coronary artery calcium (CAC) progression. Despite the apparent emphasis on clinical utility implied from the title, “What Does It Really Mean” (1), the clinical importance of CAC progression is never addressed in the paper. The clinical perspectives section of this paper infers that better acquisition parameters using computed tomography are required to assess CAC progression, but Mori et al. (1) fail to cite or refer to even 1 study published related to CAC progression and subsequent cardiovascular (CV) events. The ultimate proof of a surrogate marker is that it can discern or predict CV endpoints, which Mori et al. (1) did not address. There are dozens of studies published demonstrating that CAC progression is associated with increased CV events (2), including such large prospective studies as MESA (Multi-Ethnic Study of Atherosclerosis) (3), as well as large observational studies in thousands of patients (4). The studies, encompassing more than 20,000 participants in total, consistently demonstrate that an increase in CAC is associated with a 4- to 7-fold increase in CV events, independent of the baseline CAC score, CV risk factors, and demographic variables.

Furthermore, studies have demonstrated that progression of CAC is significantly associated with an increase in both calcified and noncalcified plaque volume, paralleling an increase in atherosclerosis

burden and CV risk (5). There is no doubt that an increasing Agatston score (the most common measure of CAC) is associated with increasing overall atherosclerosis and more CV events. What we need to identify is the best method to abate or slow the atherosclerosis process, which is still under active investigation, and whether acting on CAC progression can potentially alter future CV events.

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THE AUTHORS REPLY:

We read with interest the comment by Drs. Budoff and Tayek on our paper, "Coronary Artery Calcification and Its Progression: What Does It Really Mean?" (1). Drs. Budoff and Tayek are concerned about our lack of citation of studies pertaining to coronary artery calcium (CAC) progression and subsequent cardiovascular events. References 2 and 3 in our paper highlight the role of CAC detection and risk of future events on a population basis. We certainly acknowledge that there are copious data showing an important association between CAC progression and subsequent cardiac events, as referenced by Dr. Budoff and colleagues. Although CAC and its progression can predict generic risk of cardiovascular events, it cannot yet be used prospectively to identify a culprit lesion. Moreover, our review is meant to highlight the complexities of this subject while demonstrating the discrepancy between what is known pathologically and how CAC is currently used in the clinic. Reference 3 in our paper highlights this by showing that whereas CAC volume is positively associated with cardiovascular disease events, at any levels of CAC volume CAC density is inversely and significantly associated with cardiovascular disease events (2). We demonstrate through pathology that patterns of calcification such as sheet calcification correlate more with plaque stability, whereas microcalcification and fragmented calcification correlate with thin cap fibroatheroma and plaque rupture. From a pathological point of view, just looking at CAC score (Agatston score) is not enough to understand fully the complex relationship between vascular calcification and plaque stability or instability. Although it is very practical clinically, it fails to tell when the event will take place or which lesion will cause an event. Based on our current pathological understanding of the subject, we believe the presence of calcium (small, fragmented, spotty) is a better predictor of unstable plaque; however, heavy calcium (diffuse, fibrocalcific plaques, sheet of calcium) is a better predictor of stable plaque. If this type of analysis were to be added to current CAC scoring, perhaps on the basis of higher-resolution computed tomography imaging than is currently available, it could allow us to distinguish better which specific patients are at risk of future events. Identification of patients harboring high-risk plaques may allow for more intensive medical therapy, lowering their risk of future events.

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