EDITORIAL COMMENT

The Never-Ending Story on Coronary Calcium

Is it Predictive, Punitive, or Protective?*

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High-risk atherosclerotic plaques are pathologically characterized by a thin fibrous cap and substantial plaque burden with a large necrotic core, intense macrophage infiltration, and spotty calcification (1–5). Multiple invasive imaging modalities can reliably identify these markers but their ability to predict long-term outcomes has been rather modest (2,6). Noninvasive imaging modalities, such as computed tomography (CT), have been used to identify many of these high-risk plaque features (7) and reveal that coronary artery calcification (CAC) is one of the strongest predictors of future cardiac events (8). However, few studies have related CAC on CT to coronary plaque volume. Importantly, progression of CAC and overall plaque volume has potent adverse consequences (9). Furthermore, a reduction in plaque and necrotic core volume during therapy is often associated with plaque stabilization and improved outcomes, but less data are available regarding CAC in this regard. It is unknown if changes in CAC track alterations in plaque volume over time, especially following intercurrent aggressive risk factor control as a part of guideline-directed preventive therapy. It has long been speculated that although microcalcification and spotty calcification are definable components of plaque vulnerability,

increasing CAC extent represents a more advanced stage of atherosclerosis and the process of calcification occurs as a stabilizing force in the setting of high-risk atherosclerotic plaque characterized as echolucent or low attenuation (7). CAC may thus have implications that are different from the prognostic import of plaque volume itself.

CAC AND STATINS AND EVENTS

Multiple observations suggest that statin therapy, which markedly reduces overall cardiovascular events, seems to increase atherosclerotic plaque density and CAC scores on CT (1). In 1 trial substudy, CAC progression was greater in frequent versus less frequent statin users (8.2 ± 0.5 mm^3 vs. 4.2 ± 1.1 mm^3; p < 0.01) (2). It is, however, unclear if statins actively aid in plaque mineralization or if it is the inflammatory cell death within the lipid core that adds to the overall volume of calcified plaque and an increase in the overall CAC score (1). Beyond observations, several randomized clinical trials revealed that statin therapy did not attenuate CAC plaque progression (3). These small, intermediate outcome trials have numerous limitations but also have a consistent message. Regression or attenuation of calcified plaque has not been reported within the rigors of a clinical trial.

In this issue of the *Journal*, Puri et al. (10) report on serial changes in coronary atheroma using intravascular ultrasound (IVUS) from 8 pooled clinical trials following high-dose, low-dose, or no-statin therapy. Importantly, these pooled results allow for an examination of a decidedly larger sample of 3,495 patients, including 1,545 patients receiving high-intensity statin therapy (HIST) and 1,726 patients receiving low-intensity statin therapy (LIST), and a limited

sample of patients (n = 224) receiving no lipid-lowering treatment. One may argue against the legitimacy of combining these disparate trials with varying aims, statin doses, and patient populations; despite the use of weighted propensity scoring techniques. It is also obvious that IVUS, although used for this purpose in other studies, may not be the optimal technique for quantifying CAC. Yet, the presented findings are intriguing, possibly important in portraying CAC in a new light and certainly worthy of further discussion or even debate. These authors reported that HIST elicited a marked reduction in percent atheroma volume (p < 0.0001), as has been consistently reported, whereas lesser doses of statin or no-statin therapy allowed progression of atheroma volume. Interestingly, the calculation of an IVUS calcium index revealed provocative findings: a significant increase in the calcium index following statin therapy (both HIST [+0.044] and LIST [+0.038]) far greater than that reported for the 224 patients not on statins (+0.02). HIST had greater progression in calcification as compared with LIST (when both were compared with the small, no treatment group) that did not reach significance between the statin groups. There was, thus, a clear interplay between changes in plaque volumes (and potentially events) and the change in CAC. CAC seemed to progress independent of change in plaque regression or progression and was greater with statin use. These findings partly support what many have posited but without definitive evidence.

These somewhat controversial findings may find support from other recent work that reported dissociation between the CAC score and events under certain conditions. The Multi-Ethnic Study of Atherosclerosis found that more dense plaque in the setting of more extensive CAC scores were observationally associated with a reduced hazard for cardiovascular events (5). It gets even more fascinating! If CAC progression is associated with higher event risk over time, its dissociation from changes in plaque volume and events post-therapy raise important questions. CAC may not be a monolithic unit, as is commonly conceived, and patterns of CAC (e.g., spotty calcification vs. more coalesced calcification) or its density may have different meanings than 1 lone number (the Agatston CAC score). It is well-substantiated that risk factors account for only a small proportion of CAC risk, and control of risk factors do not seem to significantly impact differences in CAC. The more recent Heinz Nixdorf Recall registry suggests that CAC progression is inevitable and predictable based on age and baseline CAC alone and is unaffected by the burden of risk factors (11). It might thus appear that the merit of CAC

in predicting events is largely contained in its presence and progression (12). More importantly, as a corollary, the CAC score or its progression might not be as predictive once plaque-altering treatment is initiated (e.g., statins). In this latter setting, treatment that changes plaque volume and impacts on event occurrence seems to oppose the directionality of changes in the CAC score or extent. These findings should prompt another look into whether the strong relationship between CAC progression and events stands intact during adequate statin therapy. Similarly, how much of the predicted risk associated with CAC scores (a score that is rather insensitive to modulation) is contained in the risk of the extent of coronary plaque (which is a modifiable parameter) is moot. At least among symptomatic patients in the Coronary CTA Evaluation For Clinical Outcomes: An International Multicenter Registry, plaque distribution and extent robustly predicted all-cause mortality and myocardial infarction, even after adjusting for CAC (13). One message from the study by Puri et al.(10) is that if CAC is reflecting the risk solely of plaque volume, the risk relationship may not remain as robust once plaque is modified. It is possible that once risk is detected with CAC, an attenuation of CAC progression may not be a useful goal of therapy, but a reduction in events should certainly be the primary focus. This explains the negative clinical trials that failed to achieve their primary endpoint of attenuating CAC progression following intercurrent statin use (3). A failure to measure coexisting noncalcified plaque burden and other high-risk atherosclerotic plaque features within prior CAC trials may have led to the fatal flaw and negative trial findings.

Importantly, we should only consider the current results as hypothesis-generating, even though they are intriguing. They cannot infer causality and the degree to which baseline clinical factors promote calcification is unknown. The IVUS calcification index has multiple limitations including the fact that severely calcified plaques were excluded. The index is very likely a poor quantitative or comparative measure when compared with CT methods; it might, however, have some validity in predicting directional change (vs. magnitudinal alterations), because the same index was applied serially in this pooled analysis. Certainly, this report is worthy of additional investigation.

What are possible future avenues of inquiry? Further investigation is warranted as to whether calcification within the coronary arteries can be seen as protective and a sign of blocking further progression of high-risk, low-density plaque. Preclinical research is revealing complex biochemical pathways

(e.g., those switching on osteoblast transcription factors, such as Runx2, in vascular smooth muscle cells) that can be modulated to attenuate or even promote vascular mineralization as needed (14). Knowing what CAC means within the context of plaque alterations will be important. These results (4) would also suggest, as others have postulated, that the effectiveness of risk stratification is based on the concept that CAC is a bystander of coexisting high-risk atherosclerotic plaque and that variable components (i.e., density and volume) (5) of the CAC score may be more or less critical components of cardiac event risk. This remains a never-ending story that is incompletely defined but vital to addressing the detection gap for atherosclerotic disease. Identification of the vulnerable patient remains elusive and without established treatment targeted to known atherosclerotic disease pathways that would lead to effective risk reduction. We are still left with the most important question: Although CAC predicts risk, is it via an intrinsic property of CAC or by being a marker of high-risk plaque that coronary artery mineralization is trying to stabilize? For CAC, paraphrasing Hamlet's speech, *"To be or not to be"* and *"Whether tis nobler … to suffer CAC or to take arms against its sea of troubles,"* still remains a crucial but as yet unanswered question.

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