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EDITORIAL COMMENT

On the Pathophysiology of Coronary Artery Disease

We Were Told Where to Go But Not How to Get There*

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If you tell people where to go, but not how to get there, you'll be amazed at the results
—George S. Patton (1)

Coronary artery calcium (CAC), as assessed in nonenhanced computed tomography (CT), reflects total coronary atherosclerotic burden and is a powerful predictor of cardiovascular events, providing superior discrimination compared with other subclinical markers of atherosclerosis (2–5). Coronary CT angiography (CTA) was initially used for the exclusion of coronary artery disease in symptomatic patients, whereas CAC established itself in risk reclassification of the subset of asymptomatic patients. From the earlier days, the medical community was amazed by the ability of coronary CTA to provide a detailed evaluation of the total (calcified and noncalcified) atherosclerotic burden, as well as depict several vulnerable plaque features, which was a new feature for a noninvasive examination, leading several groups to invest research efforts in this area. The clinical relevance is also undeniable in coronary artery disease, where first manifestation is frequently myocardial infarction and sudden cardiac death in previously asymptomatic individuals. Therefore, it is of utmost importance that we develop and validate tools for risk stratification. CAC and coronary CTA are becoming ideal candidates, due to their noninvasive nature and the technological advances that we have recently witnessed, leading to impressive reductions in radiation dose (6). One important issue is whether the additional information for lesion location, plaque composition, detailed plaque features, noncalcified plaque burden, and their respective temporal changes provided by coronary CTA can improve the already powerful risk reclassification of the CAC score alone.

The definition of progression and regression of coronary artery disease (CAD) should be revisited in the context of coronary CTA for the following reasons:

1. The first studies addressing this aspect used conventional coronary angiography and had as the main outcome measures changes in the minimum lumen diameter or in percentage of diameter stenosis. That approach was abandoned because of the countless limitations of angiography.
2. In the past decade and until now, the classic progression and regression studies used intravascular ultrasonography and had as the main variables either change in total atheroma volume and/or percentage of atheroma volume. Those studies are also limited because they only imaged a random "representative" coronary segment.
3. Coronary CTA offers both quantitative coronary angiography-like and intravascular ultrasonography (IVUS)-like approaches (7), and allows for evaluation of the total coronary atherosclerotic burden, either by semiquantitative scores such as segment involvement score, segment stenosis score, or CT Leaman scores (8–10) or by dedicated plaque volume quantification software; and, finally, also provides detailed individual high-risk plaque characteristics (like the presence of a napkin-ring sign). We still need to learn which coronary CTA variables would better characterize significant changes in coronary atheroma, which

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are prognostically significant for predicting clinical outcomes and variables that may be sensitive enough to respond to pharmacological interventions, which eventually may translate into changes in clinical events.

The study by Ceponiene et al. (11), published in this issue of *iJACC*, brings some more data to help clarify these issues. The authors included 211 patients undergoing serial coronary CTA scans over a median of 3.3 years and aimed to determine whether CAC progression was correlated with total and specific (fibrous, fibrous-fatty, calcified, and low-attenuated) plaque volumes in coronary CTA scans.

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They found out that the progression of CAC was in line with their coronary CTA atherosclerotic counterparts, both for the expected calcified plaque volume and for the subtler, noncalcified plaque progression. In addition, the authors found that patients with a CAC of zero experienced only minimal progression in total plaque volume over a mean follow-up of 3.3 years. This is in line with the so-called warranty period for patients with a CAC of zero, which has been described by other studies (12). If these results are confirmed in larger trials, they strongly reinforce the role of serial CAC testing for risk stratification. As stated before, coronary CTA can also depict noncalcified plaque and evaluate the degree of stenosis and total and specific plaque burden and more advanced plaque features like the presence of positive remodeling and low-attenuation plaque, and these features have been associated with worse outcomes. Nevertheless, it must be acknowledged that, presently, there are still several limitations preventing routine detailed assessment of plaque volume and characteristics by coronary CTA, as follows:

1. The still low spatial resolution of current generation scanners, which, as in the case of the present study, performed on a regular 64-slice scanner with a spatial resolution of 500 to 600 μm at best. This limits a reliable assessment of plaque composition as the authors claimed in this report.
2. Large intraobserver and interobserver variability (which was not described in the study by Ceponiene et al. [11]). Examples of this limitation are the cases with lower CACS in the follow-up examinations, which probably reflect more interscan variability rather than a true biological event (regression of calcified plaque), explaining why the authors assumed negative delta CACS as zero progression, as other researchers did in recent similar studies (13).
3. These measurements can be very time consuming. These last 2 limitations can be at least partially minimized by semiautomated software for plaque volume, like that used by the authors in the present study (11). Note, the offline QAngioCT software (Medis Medical Imaging Systems, BV, Leiden, the Netherlands) has never been validated against histology for the assessment of plaque composition and therefore the results in this report are open to question.

The report by Ceponiene et al. (11) focused more on total coronary plaque burden as opposed to specific detailed vulnerable plaque features, which has been recently reinforced by the mid-term results of the landmark study by Motoyama et al. (14). In that study, although high-risk plaque features (both positive remodeling and low-attenuation plaque) depicted by coronary CTA were independent predictors of acute coronary syndromes. Over a long follow-up, the absolute number of events was the same as that for the larger subset of patients without these high-risk features, suggesting that we cannot rely only on these detailed plaque features to prevent CV events but must also consider the total atherosclerotic burden and take into account the dynamic pathophysiology of CAD. Interestingly, in the study by Ceponiene et al. (11), plaque progression was also independently associated with events, which reinforces the need for more natural history studies.

Besides these challenges that every imaging modality is facing in the evaluation of the natural history of CAD, some important limitations of the study from Ceponiene et al. (11) should also be pointed out, because they might prevent generalization of their conclusions to CAD as a whole, as follows:

1. The authors excluded patients who had undergone revascularization between the 2 scans and therefore might have excluded patients experiencing a higher progression of CAD. One alternative could have been to include patients undergoing revascularization (just excluding the treated segment from analysis, due to the limitation of plaque evaluation in the presence of stents), but in a segment-based rather than a patient-based analysis, as if it was the case of the present study. Likewise, and as an obvious limitation to all of this imaging-based natural history studies, patients experiencing the worst event, cardiac death, did not make it to the study's imaging follow-up.

Therefore, the population evaluated in the study by Ceponiene et al. (11) might have been shifted to a lower risk subset of CAD patients and not reflect the ones with the more malign phenotype of coronary atherosclerosis.

2. Another important limitation is related to the impact of statins on CAC progression, which changes natural history of coronary atherosclerosis. At a post hoc patient level analysis of 8 prospective randomized trials with serial IVUS, it was documented that, independent of their plaque regressive effects, statins promoted atheroma calcification (15). Although Ceponiene et al. (11) report that at the baseline only 34% of the patients were taking statins, some of them might have started in the 3.3-year period between the first and follow-up scans, especially after the clinicians were aware of the results of the first scan and probably more so in patients with higher coronary atherosclerotic burden. The percentage of patients taking statins at follow-up is not reported, nor is the statin dose, but probably far from the ones used in the studies that proved the concept of stopping and even reversing the progression of coronary atherosclerotic lesions with aggressive lipid-lowering treatments (16).
3. The option of an evaluation of plaque progression per patient and not per lesion imposed further limitations on the study, making it difficult to conclude the pathophysiology of atheroma composition and calcification. One could assume that the same degree of per-patient plaque progression might have come from the build-up of new plaque or the progression and growth of existing plaque, and if this last scenario were the case, it might also have been the result of previous noncalcified plaque turning into a more benign calcified phenotype.
4. Finally, the authors found that plaque progression did not differ between men and women. This point was further emphasized in the discussion as a finding in line with a previous IVUS study. We have reported a summary of landmark progression and regression studies in which an inconsistent response to statins has been observed in women but not in men (17).

Even considering the limitations listed above, the study by Ceponiene et al. (11) brings some new data to the discussion of the value of serial CAC measurements in risk stratification, as CAC progression seems to parallel not only calcified but also noncalcified plaque volume progression. This is an area still in need of further research, the natural history of coronary atherosclerosis, the "*where to go*" for researcher in this field. We were not told "*how to get there*," but we believe that CACS and coronary CTA will prove to be valuable tools and that at the end of the journey we will certainly be "*amazed by the results*"! (1).

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