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EDITORIAL COMMENT

Nonobstructive Coronary Plaque Matters*

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Accumulation of atherosclerotic plaque in the wall of our coronary arteries is often described as ubiquitous, unavoidable, and innocent, except for instances where it might cause either obstructive or eruptive disease. Obstructive atherosclerotic disease occurs when excess plaque accumulates beyond maladaptive positive remodeling. Then luminal encroachment might cause stress-induced ischemia. Eruptive atherosclerotic disease relates to plaque composition and activity more than to stenosis severity and causes unstable angina, myocardial infarction, or sudden cardiac death due to atherothrombosis and abrupt coronary artery occlusion. It is said that the former hurts, whereas the latter kills.

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The evidence supporting these paradigms is restricted to clinical pathological observations that were obtained in patients having reached the tail end of the spectrum of coronary artery disease (CAD). Because coronary atherosclerosis could only be detected during catheter-based procedures—be it by angiography, intravascular ultrasound, optical coherence tomography, and few other invasive imaging techniques—limited information was available on the significance of earlier stages of coronary atherosclerotic disease in healthy carriers of the disease or subjects with atypical or mild symptoms.

With the advent of coronary computed tomographic angiography (CCTA), coronary anatomy and the progress of atherosclerosis can be directly imaged non-invasively, with the potential of revealing preclinical stages of the disease. From this perspective, the current publication by Lin et al. (1) represents an essential milestone contribution. Lin et al. (1) have indeed studied and analyzed in detail by CCTA the coronary anatomy of over 2,500 subjects; follow-up was obtained for 3 years on average, and 58 mortality events were counted. Subjects were not known to have CAD and had variable risk profiles and an 11% estimated 10-year risk of CAD (by modified Framingham risk score). Symptoms were variable but typical for angina in <1 of 3 subjects. The CCTA was able to rule out any CAD involvement in nearly 60% of the subjects, who experienced a very low rate of yearly mortality during follow-up (0.34%). The presence of any plaque was associated, after adjusting for risk factors, with 1.98 hazard ratio for all-cause mortality. With more extensive plaque burden, mortality risk increased sharply up to 5.12 hazard ratio with 5 or more coronary segments showing non-obstructive plaque. The authors conclude that "the presence and extent of non-obstructive plaque augments prediction of incident mortality above and beyond conventional clinical risk assessment."

Importance of plaque composition. It is striking that Lin et al. (1) could not identify any relationship between intermediate-term mortality and plaque composition, defined as noncalcified, calcified, or mixed. Kristensen et al. (2) have revisited this issue in 312 patients presenting with non–ST-segment elevation myocardial infarction (NSTEMI) undergoing both CCTA and invasive angiography. Of 1.454 lesions detected by CCTA, 313 obstructive lesions were revascularized and 1.141 deemed non-obstructive. Per-patient revascularization rate was 75%. After a mean follow-up of 16 months, 23 events occurred, of which only 4 were revascularization procedures. Predictive value of CCTA-derived variables was assessed by univariate and multivariate regression analysis. The no-obstructive, no-calcified plaque volume provided incremental prognostic value (hazard ratio: 1.18, 95% CI: 1.06 to 1.31, $p = 0.002$) over clinical variables, including multivessel disease, prior myocardial infarction, and left ventricular ejection fraction. High residual risk after NSTEMI was again identified by increased nonobstructive plaque burden. Of note, from the reported number of diseased vessels, invasive coronary angiography had detected nearly 450 significant stenoses, of which over 130 were left untreated. Because follow-up data were obtained from electronic discharge letters, the new culprit lesions in the event group could not be identified as "non-obstructive" or "obstructive left untreated" at index evaluation.

Nevertheless, both studies (1,2) suggest that the load of nonobstructive plaque contributes to survival outcome, across the spectrum of CAD, from mildly symptomatic subjects to acutely sick patients.

Study limitations. Both groups of authors (1,2) provide a lucid description of the limitations of their respective studies, including the finite spatial resolution of 64-detector row CCTA; the variability and limited accuracy of plaque characterization; the lack of quantitative analysis of stenosis severity; the absence of detailed evaluation of plaque make-up with, for instance, intravascular ultrasound imaging; and the absence of complementary evaluation with calcium scoring. Lin et al. (1) caution against extrapolating

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their findings to healthy, asymptomatic, worried well subjects who would undergo CCTA for screening purposes. Kristensen et al. (2) acknowledge the relatively small sample size of their study, the limited number of events, and the lack of demonstration of a causal relationship between acute events and nonobstructive plaque burden.

However, the main limitation of both studies was not mentioned, namely that lone anatomic evaluation of stenosis severity does not qualify the physiological significance of obstruction from the hemodynamic viewpoint. Both Meijboom et al. (3) and Sarno et al. (4) have shown that 7% to 12% of seemingly nonobstructive plaques are actually responsible for significantly decreased pressure-derived fractional flow reserve. In addition, diffuse atherosclerosis without focal luminal encroachment can also prevent matching flow increases in response to demand, thereby causing myocardial ischemia (5). The popular dichotomous paradigm that opposes chronic, intermittent ischemia caused by severe obstruction—on the one hand—with acute, unpredictable ischemia caused by sudden disruption of nonobstructive but active plaque—on the other—therefore remains plausible but unproven. It can indeed be hypothesized that coronary events will occur mostly in the subset of patients carrying plaque that seems mild by anatomy but is significant by hemodynamic status. Only prospective studies combining noninvasive evaluation of coronary anatomy and function will unravel whether chronic and acute presentations of CAD indeed stem from distinct mechanisms or share a common substrate

Clinical implications. Notwithstanding putative mechanisms, it remains that increasing non-obstructive plaque burden identifies subjects at risk of dying in the intermediate term, beyond conventional risk factors and profiles. Patients recovering from NSTEMI require extensive secondary prevention anyhow. Additional therapies (6) beyond current standard of care, aiming at reducing the excess residual risk, are currently being tested in the SOLID–TIMI 52 (Stabilization Of pLaques usIng Darapladib–Thrombolysis In Myocardial Infarction 52) and STABILITY (Stabilization of Atherosclerotic Plaque by Initiation of Darapladib Therapy) trials.

Lin et al. (1) are suggesting that mildly symptomatic subjects who would not qualify for primary prevention otherwise might benefit from lifestyle modification and drug therapy, given the risk associated with nonobstructive plaque burden on CCTA, with the potential of risk reduction and survival benefit. In their study, subjects without plaque had 1.2% mortality over 3 years, as opposed to 3.4% in the presence of any nonobstructive plaque. Assuming a realistic 10% relative risk reduction with treatment, at least 30,000 subjects/study arm should be included. To demonstrate that such personalized intervention might be more efficacious and/or cost-effective in the mid-term than preventative measures targeting the entire population as a blanket strategy, subsets at even higher risk with a substantial number of nonobstructive plaques (so-called triple-vessel nonobstructive disease) should be included. Indeed, a 10% relative risk reduction from a control 10% mortality rate could be detected in a 28,000-patient, large, randomized clinical trial (14,000/arm).

For the first time, the study by Lin et al. (1) raises the question and might support the opportunity for testing "interventional" primary prevention in healthy carriers of extensive non-obstructive CAD, detected by CCTA at an early clinical stage.

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