Invited Commentary

High-Risk Coronary Atherosclerotic Plaque Assessment by Coronary Computed Tomography Angiography—Should We Use It?

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Coronary computed tomography angiography (CTA) has an increasing role in the diagnostic and prognostic assessment of patients with stable ischemic heart disease (SIHD). The PROMISE trial has tested the hypothesis that coronary CTA anatomic assessment of patients with SIHD would reduce cardiac events compared with conventional stress testing, but it has not found an advantage for a coronary CTA strategy.[1]

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The PROMISE (Prospective Multicenter Imaging Study for Evaluation of Chest Pain) trial[1] has used a standardized protocol, well-defined data definitions, core laboratory oversight, and adjudicated events and has enrolled a large number of patients, which means it provides an excellent opportunity to examine the prognostic role of various features of coronary CTA in the assessment of patients with SIHD. Prior publications have already assessed the prognostic value of calcium scores[2] and the association between coronary CTA findings and risk stratification scores obtained via conventional stress testing.[3] In this issue of *JAMA Cardiology*, Ferencik et al[4] report the results of a PROMISE substudy examining the potential value of coronary CTA assessments of high-risk plaque in 4415 patients. This latest substudy assesses whether high-risk plaque was associated with a higher rate of major adverse cardiovascular events (MACE; defined as death, myocardial infarction, or unstable angina), after adjustment for atherosclerotic cardiovascular disease risk scores and the presence of significant stenosis found by coronary CTA. I will place the results of this study in context and indicate whether coronary CTA assessment of high-risk plaque should be used in the evidence-based clinical care of patients with SIHD.

In 2009, the American Heart Association published a scientific statement[5] that comprehensively outlined criteria for the evaluation of novel risk markers. These criteria include 6 phases of evaluation, which are applicable to the assessment of prognosis by cardiovascular imaging. The first 2 phases, proof of concept and prospective validation, have already been completed for high-risk plaque by coronary CTA. The third stage of evaluation is the question of incremental value: "Does the novel marker add predictive information to established, standard risk factors?"

The inclusion of atherosclerotic cardiovascular disease risk score in the study by Ferencik et al[4] is an attempt to address this question by considering established risk markers. However, this risk score is not ideal for this purpose. It was developed for widespread application in asymptomatic populations and correctly includes stroke as an end point. The PROMISE trial[1] included symptomatic patients with SIHD; stroke was not an end point. A more inclusive analysis would have relied on historical variables of symptomatic patients, which would have included eliciting histories of peripheral vascular disease, cerebrovascular disease, and more details regarding symptoms (eg, the presence of chest pain, dyspnea, and typical angina, or not). These important variables are included in the Supplement of the study by Ferencik et al,[4] but it is not clear whether they were ever considered in the analysis. In addition, a classic study from the Duke databank[6] reported that cardiomegaly found by regular chest radiography and 4 resting electrocardiographic parameters were all statistically significant predictors of survival in patients with SIHD. If available, these parameters should ideally have been included in this analysis as well.

Other than high-risk plaque, the only coronary CTA variable considered in this analysis was significant stenosis (defined as ≥70% stenosis in any vessel or ≥50% in the left main coronary artery). Long-term follow-up of patients undergoing coronary CTA by electron beam tomography[7] reported that such stenoses in 1, 2, or 3 vessels were each independently associated with mortality after adjustment for risk factors and calcium scores. Experienced clinicians recognize that significant stenoses in more arteries are of greater concern. A previous PROMISE study demonstrated the importance of the coronary calcium score.[2] The number of arteries with significant stenoses and the calcium scores should ideally have been considered by Ferencik et al[4] as well.

Given the absence of important historical variables, electrocardiographic variables and other coronary CTA variables, I do not believe that the current study demonstrates that assessing high-risk plaques by coronary CTA is truly incremental to established risk assessment.

After adjusting for only atherosclerotic cardiovascular disease risk and significant stenosis, the added value of assessing high-risk plaques by coronary CTA appears to be modest. The concordance index was 0.71, which was not significantly different from the concordance index without it (0.69; $P = .12$). Although the net reclassification improvement with the addition of high-risk plaque assessment was significant (0.34; 95% CI, 0.02-0.51), the lower bound of the 95% CI was barely above 0.

Net classification improvement can be defined statistically, but its clinical significance generally requires reclassification tables. These tables are critical to the fourth phase of the American Heart Association criteria for evaluation of novel risk markers,[5] which is clinical utility: "Does the novel risk marker change predicted risk sufficiently to change recommended therapy?" Reclassification tables define

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thresholds of risk for clinical decisions. They assess the ability of a new test to move patients across these thresholds, prompting clinical actions that will hopefully improve outcomes. In the case of high-risk plaques, the potential outcomes might include more aggressive risk factor modification or invasive coronary angiography. However, given the low incidence of MACE in this substudy (3.0% overall and 1.2% for hard cardiac events),[4] it is very difficult to project that either one of these steps will improve outcomes.

Because the positive predictive value of the presence of high-risk plaques for MACE was only 6.4%[4] (and could probably be estimated at approximately 3.0% for hard cardiac events), only 1 in 33 patients with high-risk plaque will have a hard cardiac event and therefore potentially benefit. Since high-risk plaque did not predict more MACE in those with significant stenosis (as noted in eFigure 3 and eTable 2 of the Supplement attached to Ferencik et al[4]), percutaneous coronary intervention would seem to be of limited value. Although the predictive value of detection of high-risk plaque appeared to be stronger in younger patients and women (without consideration of other necessary historical, electrocardiographic, and coronary CTA variables), the incidence of MACE in the members of these subgroups who had high-risk plaque remained modest; two-thirds of the MACEs in this study occurred in patients without this condition. More aggressive risk factor modification in patients with high-risk plaque will therefore likely be of limited value. More aggressive risk factor modification on the basis of coronary CTA did not benefit asymptomatic patients with diabetes in a randomized clinical trial,[8] probably because the control group received optimal medical therapy. The societal benefit of improvements in the delivery of secondary prevention to patients with established coronary artery disease, which is currently far from optimal, would likely be far greater.

There is a recognized need to increase value and reduce waste in biomedical research, as initially promising findings do not always improve clinical care. Novel risk markers should be rigorously evaluated before they are used routinely in clinical practice. The detection of high-risk plaques by coronary CTA is an appropriate subject for future research exploring the pathophysiology of plaque biology and its intersection with acute coronary syndromes. However, in my opinion, the evidence is not yet strong enough for us to use it in the clinical care of patients with SIHD.

ARTICLE INFORMATION

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Published Online: January 10, 2018. doi:10.1001/jamacardio.2017.5016

Conflict of Interest Disclosures: The author has completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Gibbons reports personal fees from Peer View Institute and personal fees from Astellas Pharmaceuticals outside the submitted work. No other disclosures were reported.

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