Perspective

Noninvasive testing strategies in symptomatic, intermediate-risk CAD patients: a perspective on the "PROMISE" trial and its potential implementation in clinical practice

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Abstract: While the results of the Prospective Multicenter Imaging Study for Evaluation of Chest Pain trial (PROMISE trial) are negative for the primary outcome, the results from this large, contemporary trial of >10,000 patients provide important insights into clinical management of patients presenting with chest pain. The results reinforce that while diagnostic testing is an important component of modern management, its choice should be directed by a clinician in a clinical context and with subsequent management in mind. Based on presentation and pre-test probability, the clinician will decide if any additional testing necessary is necessary and if that is the case chose the most appropriate test according to current guidelines, applied to the individual patient and clinical scenario.

Keywords: Chest pain; coronary computed tomography; computed tomography angiography (CTA); stress testing; Prospective Multicenter Imaging Study for Evaluation of Chest Pain trial (PROMISE trial)

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The 'Prospective Multicenter Imaging Study for Evaluation of Chest Pain' (PROMISE) is a large, randomized control study, assessing the role of coronary computed tomography angiography (CTA) *vs*. stress testing in the management of new-onset chest pain in patients without diagnosed coronary artery disease (CAD). The results were recently presented at the ACC (American College of Cardiology) meeting and simultaneously published online in the *New England Journal of Medicine* (1). Choice of the most appropriate diagnostic approach in this large patient population is an important, routine clinical problem. Over the last few decades, along with better therapeutic options, the number and quality of diagnostic test has significantly increased, and consensus regarding appropriate diagnostic strategies is incomplete. In current 2014 ACC appropriate use criteria (AUC) guidelines, CTA is consider appropriate for patients with intermediate pre-test probability of CAD, if the ECG is uninterpretable or the patient is unable to exercise (2). For patients with interpretable ECG and ability to exercise CTA is rated as 'may be appropriate'.

In the context of this limited recommendation, the hypothesis of the Promise trial (designed around 2010) was that initial anatomic testing would provide information that would result in superior long-term health outcome as compared to an initial functional testing strategy. The authors randomly assigned 10,003 patients to anatomic assessment with CTA (n=4,996) or functional testing (n=5,007) with nuclear stress testing (67.3 percent), stress echocardiography (22.5 percent) or EKG stress (10.3 percent). A total of 310 patients (6.2%) in the CTA group and 315 patients (6.3%) in the functional test groups did not undergo CTA or functional testing as the initial test, respectively. The composite endpoint was death, myocardial infarction, hospitalization for unstable angina or other major procedural complication. Notably, "need for revascularization" was not included as an endpoint. Secondary endpoints included the percentage of cardiac catheterization that did not show obstructive CAD

('unnecessary catheterization'), and radiation exposure. Regarding the primary endpoint, the trial was negative and showed no significant difference in primary events between the coronary CTA arm and the stress-testing arm (3.3 percent *vs*. 3 percent) at 2 years. The coronary CTA strategy lead to more downstream cardiac catheterizations, but significantly fewer patients with no obstructive CAD, meaning fewer 'unnecessary' catheterization, confirming the high-negative predictive value of coronary CTA.

The trial hypothesis reflects the excitement that has been associated with the establishment of coronary CTA as a diagnostic alternative. However, demonstrating superiority of one diagnostic test is complicated, as clinical outcome is influence by subsequent management rather than the test itself. The reported results are more realistic and in fact reflect current clinical practice, as described in the ACC AUC criteria (2). Notable, these criteria do not rate diagnostic modalities relative to each other, but rather described appropriateness of each modality relative to clinical scenarios.

How should the results of the PROMISE trial be interpreted in the context of clinical practice? First of all, study design was designed to be highly relevant to clinical practice in the USA. The trial was supported solely by the National Institute of Health (NIH) and was performed entirely in the United States. This ensured that conflict of interest and differences in variations of selection criteria and optimal medical therapies were kept to a minimum.

Interestingly, results of this large contemporary trial of patient with new-onset chest pain demonstrate important changes in clinical practice compared to prior data. Pre-test likelihood of obstructive CAD was calculated using from the 'Diamond and Forrester' as well as 'Coronary Artery Surgery Study' criteria, both of which were developed in the 1970s. These formulas classify the majority of patient with the above described enrollment criteria in the intermediate risk category, where non-invasive testing provides the biggest impact. Surprisingly, the actual event rate was much lower than predicted by the above criteria. This finding likely reflects that significant changes in clinical practice have occurred in the last few decades, including life style changes and potent drugs for hyperlipidemia, hypertension, and diabetes, which have been successful in reducing cardiovascular events. The above criteria for risk assessment may therefore be outdated, and more relevant updated criteria are needed for determining the pre-test likelihood of CAD.

Similarly surprising is the relatively low rate of patients referred for cardiac catheterization based on the initial positive test result, but with no obstructive CAD (false positive initial test = 'unnecessary' catheterization). This rate was 3.4 percent after CTA *vs*. 4.3 percent after stress testing. In other words, in the PROMISE trial, an abnormal CTA or stress test was associated with an approximately 96 percent likelihood of finding a significant lesion on angiography. This suggests that in contemporary practice, if there is appropriate patient selection, unnecessary downstream testing is not a major issue. This finding shows significant progress, considering that previously data from some of the same authors demonstrated that after some forms of noninvasive testing, only 38 percent of subsequent catheterizations showed significant CAD (3).

It is also important to comment on the results regarding radiation exposure. The mean radiation dose for CTA was higher than for stress testing (12 *vs*. 10.1 mSv), but the median radiation dose for CTA was lower (10 *vs*. 11.3 mSv). However, a comparison of the two techniques that are associated with radiation exposure—CTA and nuclear stress testing—the median radiation dose in the CTA group was significantly lower (10.1 *vs*. 12.6 mSv). These results are complex, and only partially reflect current practice, as experienced centers have been able to lower the radiation dosage associated with a coronary CTA to less than 5 mSv (and less than 1 mSv in many cases) and also have reduced the radiation exposure associated with nuclear stress testing (4).

Lastly, recent trials demonstrate that coronary CTA provides important information beyond luminal stenosis, including plaque burden and plaque characteristics, which appear to have impact on hemodynamic significance of coronary lesions (5). Furthermore the emergence of newer techniques, including noninvasive CT fractional flow reserve (CT-FFR) measurement and stress perfusion by CT, that can be added to the anatomic analysis, may impact on the diagnostic value of coronary CTA in the future, but conclusive data is forthcoming (6).

Choice of a specific test for individual patients is left to the discretion of the treating physician, and the above described results influence the decision for the most appropriate testing strategy. For example in a young (particularly female) patient, where susceptibility to radiation is highest and plain EKG stress has a high rate of abnormal baseline EKG abnormalities, a stress echocardiogram could be the most appropriate initial test, if performed in a high-volume center with technical experience and proficiency. In contrast, in patients where

the radiation dose is less of a concern, coronary CTA could be the most appropriate option, because, based on the PROMISE trial results, it is less likely to result in 'unnecessary' downstream catheterizations.

In summary, while the results of the PROMISE trial are negative for the primary outcome, the results from this large, contemporary trial of >10,000 patients provide important insights into clinical management of patients presenting with chest pain. The results reinforce that while diagnostic testing is an important component of modern management, its choice should be directed by a clinician in a clinical context and with subsequent management in mind.

Based on presentation and pre-test probability, the clinician will decide if any additional testing necessary is necessary and if that is the case chose the most appropriate test according to current guidelines, applied to the individual patient and clinical scenario (2).

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References

1. Douglas PS, Hoffmann U, Patel MR, et al. Outcomes of Anatomical versus Functional Testing for Coronary Artery Disease. N Engl J Med 2015;372:1291-300.
2. Wolk MJ, Bailey SR, Doherty JU, et al. ACCF/AHA/ASE/ASNC/HFSA/HRS/SCAI/SCCT/SCMR/STS 2013 multimodality appropriate use criteria for the detection and risk assessment of stable ischemic heart disease: a report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, American Heart Association, American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Failure Society of America, Heart Rhythm Society, Society for Cardiovascular Angiography and Interventions, Society of Cardiovascular Computed Tomography, Society for Cardiovascular Magnetic Resonance, and Society of Thoracic Surgeons. J Am Coll Cardiol 2014;63:380-406.
3. Patel MR, Peterson ED, Dai D, et al. Low diagnostic yield of elective coronary angiography. N Engl J Med 2010;362:886-95.
4. Schoenhagen P, Baker ME. Our preoccupation with ultra-low dose radiation exposure. Low contrast resolution and cardiovascular CT imaging. J Cardiovasc Comput Tomogr 2014;8:426-8.
5. Park HB, Heo R, ó Hartaigh B, et al. Atherosclerotic plaque characteristics by CT angiography identify coronary lesions that cause ischemia: a direct comparison to fractional flow reserve. JACC Cardiovasc Imaging 2015;8:1-10.
6. Schoenhagen P, Desai MY. Computed Tomography-Based Fractional Flow Reserve (FFR-CT). Circ J 2015;79:300-2.

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