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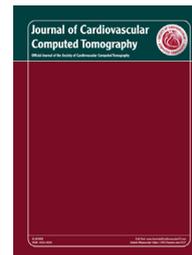
Editorial

What does the PROMISE trial mean for cardiac CT? Outcome of coronary CT angiography vs functional testing in suspected coronary artery disease

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Although current guidelines start to include coronary CT angiography (CTA) for specific patient groups and indications, typically as "class IIa" recommendations, functional testing for ischemia is still recommended as the preferred test (class I indication) to risk stratify and identify patients with increased likelihood of coronary artery disease (CAD) before invasive coronary angiography. Unfortunately, most patients who undergo invasive angiography after ischemia testing have non-obstructive or normal arteries, so obviously diagnostic accuracy is low in current clinical practice.[1] In an analysis of the National Cardiovascular Data Registry (NCDR), of 661,063 patients undergoing elective angiography, 386,003 (58.4%) did not have obstructive CAD. In that subset, the largest cohort had undergone myocardial perfusion imaging, and of 302,651 patients in whom myocardial perfusion imaging studies led to cardiac catheterization, only 134,670 (44.4%) had obstructive disease in invasive angiography. Exercise treadmill testing, stress echocardiography, and magnetic resonance imaging yielded similarly low rates of obstructive disease. In comparison, in the aforementioned NCDR, coronary CTA had been performed in 8323 patients and 5791 (70%) of these were found to have obstructive disease in invasive angiography, representing more than a 50% improvement in identifying patients with obstructive disease compared to any functional test (P < .001).

Thus, the Prospective Multicenter Imaging Study for Evaluation (PROMISE)[2] of chest pain was undertaken to evaluate if this superior test performance would lead to improved outcomes, through lower rates of unnecessary catheterizations, less false-negative test results (untreated CAD), and improved preventive treatment and adherence. Furthermore, the authors assumed higher confidence in coronary CTA results over functional test results, leading to a longer "warranty period" with fewer repeat tests and fewer hospitalizations during follow-up. In the PROMISE trial, 10,003 patients with suspected CAD were randomized to the strategy of initial anatomic testing with the use of coronary CTA or to functional testing (exercise electrocardiography [ECG], nuclear stress testing, or stress echocardiography). The composite primary end point was death, myocardial infarction (MI), hospitalization for unstable angina, or major procedural complication.[2]

Unfortunately, the original study design called for a minimum 2-year follow-up of the cohort, but because of budget restraints, minimum follow-up was decreased to 1 year. This markedly limited the ability of either modality to show superiority. With shorter follow-up and less events, the increased use of preventive therapies used in the coronary CTA arm had little time to improve outcomes, and the "warranty period" hypothesis could not be tested. In the end, the study demonstrated both forms of testing to have comparable outcomes regarding the primary end point. For secondary end points, coronary CTA demonstrated several advantages, including a 34% reduction of death and nonfatal MI at 12 months (hazard ratio = 0.66; P = .039) and fewer invasive catheterizations without obstructive disease (P = .022). Overall, myocardial infarctions were reduced by 25% in the coronary CTA group, very comparable to a meta-analysis demonstrating fewer myocardial infarctions with coronary CTA testing when compared to functional tests.[3] This reduction in myocardial infarction was also seen in the Study of Myocardial Perfusion and Coronary Anatomy Imaging Roles in Coronary Artery Disease,[4] in which coronary CTA led to a >50% reduction in myocardial infarction and death compared to nuclear imaging.

However, the most remarkable finding in PROMISE was the improved diagnostic performance of coronary CTA over functional testing to identify obstructive disease, in a current, pragmatic study design.[2] In the PROMISE cohort, 72.1% of patients undergoing invasive coronary angiography after coronary CTA had obstructive disease compared to only 47.5% of functional test group patients. These numbers are remarkably similar to the NCDR data outlined previously. Furthermore, the number of symptomatic patients found to have obstructive disease with coronary CTA was 439, whereas only 193 patients were identified with functional testing, suggesting a much higher sensitivity for obstructive disease for coronary CTA. This is crucial as we attempt to properly stratify chest pain patients based on symptoms, with revascularization and proper diagnosis of angina hanging in the balance.

Of interest, PROMISE used the Diamond-Forrester rule to evaluate the prevalence of disease, which estimated pretest probability to be 53.4%, whereas only 8.8% of patients undergoing coronary CTA indeed had obstructive disease. This demonstrates the issues of using algorithms developed 35 years ago, when functional testing and invasive angiography was only used in very high-risk cohorts. A new algorithm to estimate the likelihood of coronary stenoses has been developed using coronary CTA, which may perform better in our current testing environment.[5]

Although the results of PROMISE demonstrated better diagnostic accuracy of coronary CTA, it also demonstrated an obvious advantage of an anatomic approach, allowing more preventive therapies to be applied. Although there was increased utilization of preventive therapies in the CT arm in PROMISE (Pamela Douglas, MD, personal communication, 2015), events were not significantly reduced. This is almost certainly due to the shortened follow-up. One-year minimum follow-up is just not enough to show differences in outcomes due to increased use of preventive therapies. In stable CAD, there is no improvement of outcomes in the first year of statin or aspirin use, but as time progresses, the event curves in multiple studies diverge. Longer follow-up would have almost definitely demonstrated additional outcome advantages of coronary CTA. This was impressively demonstrated in a second large-scale study published simultaneously to PROMISE, called CT coronary angiography in patients with suspected angina due to coronary heart disease (SCOT-HEART).[6] In SCOT-HEART, 4142 patients with suspected CAD were randomized to receive either only standard workup (in most cases, functional testing) or standard workup plus coronary CTA. In this prospective trial, coronary CTA reclassified the diagnosis of CAD in 27% of patients, and the diagnosis of angina due to coronary heart disease in 23% of patients (standard of care 1% and 1%; $P < .0001$). This changed planned investigations (15% vs 1%; $P < .0001$) and treatments (23% vs 5%; $P < .0001$). After 1.7 years, coronary CTA was associated with a 38% reduction in fatal and nonfatal myocardial infarction, which missed significance by just a thread (hazard ratio, 0.62; 95% confidence interval, 0.38–1.01; $P = .0527$). Coronary CTA also led to clearer diagnoses and better targeted interventions. Three-year follow-up in SCOT-HEART demonstrated that the cardiovascular event rate was reduced by 50% in the coronary CTA group ($\sim 2.5\%$ vs $\sim 1.7\%$; $P = .015$). This supports the concept that the incremental use of preventive therapies will have a long-term beneficial effect.

In the design of the PROMISE trial, there was subtle bias against coronary CTA in patients that were randomized to receive either coronary CTA or the functional test of choice at that institution. Typically, there is not uniform expertise for all diagnostic tests at any given center. Hence, coronary CTA was not being used optimally by all of the 193 PROMISE study sites. The radiation doses of coronary CTA were relatively high, and this led to a higher overall radiation exposure in the CT cohort than in the functional testing cohort. Although coronary CTA patients received lower overall doses than patients who underwent nuclear imaging (12.0 vs 14.1 mSv; $P < .001$), patients in the coronary CTA cohort had a total dose (including follow-up testing) of 12.0 ± 8.5 mSv, significantly higher than in the cohort randomized to functional testing (10.1 ± 9.1 mSv; $P < .001$). Although this was weighted by the 33% of patients in the functional arm who had no radiation exposure at all (stress echocardiography or exercise ECG testing), it still represents an opportunity for improvement with cardiac CT. Contemporary radiation exposure for coronary CTA should be lower than 10 to 12 mSv, with easy modifications such as use of 100 kV and prospectively ECG-triggered acquisition readily available in most scanners. Currently, coronary CTA is used much less frequently than functional stress testing, despite the better performance for both preventive measure initiation and diagnostic yield. An important clinical application is to properly diagnose patients. A recent study demonstrated that absence of CAD on initial coronary CTA was associated with lower costs and decreased downstream use compared to the presence of nonobstructive and obstructive CAD, without an increase in clinical events.[7] Thus, although short-term outcomes were equivalent in PROMISE between coronary CTA and functional testing, clinical utility was not.

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