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Coronary CT Angiography as a Diagnostic and Prognostic Tool: Perspective from a Multicenter Randomized Controlled Trial: PROMISE

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Abstract The PROMISE (Prospective multicenter imaging study for evaluation of chest pain) trial compared the effectiveness of coronary CT angiography and functional testing as initial diagnostic test for patients with suspicion for stable coronary artery disease (CAD). With 10,003 patients randomized at 193 sites, the PROMISE trial provides a snapshot of real-world care for this very common presentation. Over a median follow-up of 25 months, PROMISE did not find significant differences in major clinical events (composite endpoint 164 vs. 151, HR 1.04 (0.83–1.29); $p=0.75$) between the two strategies. Other major findings were the large discrepancy between estimates of pre-test likelihood and observed prevalence for obstructive CAD (≥50 %) and the proportion of noninvasive tests positive for ischemia or obstructive CAD (53 vs. 11 %; respectively) and the better efficiency of coronary computed tomography angiography (CTA) to select patients for invasive coronary angiography (ICA) who had obstructive CAD (72 vs. 48 % for coronary CTA and functional testing, respectively). Radiation exposure was higher in the CT arm compared to all functional testing but lower than for nuclear perfusion stress testing. Improvement of patient selection for diagnostic testing and risk stratification will be keys to increase efficacy and efficiency of management of patients with suspicion for stable CAD.

Keywords PROMISE · Computed tomography angiography · Review

Abbreviations

95%CI	95 % confidence interval
CAD	Coronary artery disease
CTA	CT angiography
CVD	Cardiovascular disease
FFR	Fractional flow reserve
HR	Hazard ratio
ICA	Invasive coronary angiography
MACE	Major adverse cardiac event
OMT	Optimal medical therapy
PCI	Percutaneous coronary intervention

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Introduction: Background and Rationale for the PROMISE Trial

Symptoms suggestive of stable coronary artery disease (CAD) are one of the most common presentations in the USA [1]. Many of the 4 million who present with de novo angina pectoris [2] undergo functional diagnostic testing including exercise ECG, echocardiography, or stress nuclear imaging during exercise or pharmacological stress for the evaluation of inducible myocardial ischemia. Functional testing has a class Ia recommendation from the American Heart Association and American College of Cardiology guidelines

for this indication [3]. Large registries suggest a limited diagnostic yield of functional testing to identify patients with obstructive CAD on subsequent invasive coronary angiography (ICA) (40–50 %) [4].

Coronary computed tomography angiography (CTA) is a newer technique that permits noninvasive visualization of the coronary arteries including the evaluation of coronary artery plaque and luminal narrowing. Studies have demonstrated the excellent diagnostic accuracy of coronary CTA to detect the presence and extent of obstructive CAD (defined as either 50 or 70 % stenosis) as compared to ICA with a sensitivity of 95 % (range 91–99 %) and a specificity of 83 % (range 76 to 91 %) [2, 5–7]. In addition, coronary CTA due its ability to provide a more granular assessment of presence and extent of CAD, including non-calcified plaque, provides important prognostic information to risk stratify patients according to their risk of future major adverse cardiac events (MACE) [8–10]. A metaanalysis of 32 studies including 41,960 patients with suspected CAD and a mean follow-up of 2 years demonstrated that the risk for cardiac death or myocardial infarction (MI) was increased six to fifteen times in patients with non-obstructive and obstructive CAD (OR 6.41; 95%CI (2.44–16.84) and OR 14.92; 95%CI (6.78–32.85)), respectively [11]. At the same, the absence of CAD is associated with a very low event rate over the next 5 years (<0.3 % annually) [12, 13].

However, according to the 2008 Medicare Part B database, clinical adoption of CCTA has been slow, for example the utilization rate of myocardial perfusion imaging (MPI) was 15–44 times that of CCTA [14, 15].

Together, these data provided the motivation for the PROMISE (prospective multicenter imaging study for evaluation of chest pain) [16•] trial with the goal to determine whether one of the two available strategies would render benefits on health and economical outcomes in patients with suspicion of stable obstructive CAD in a generalizable real-world care setting.

Design and Population of the PROMISE Trial

The PROMISE trial was a randomized comparative effectiveness trial in stable outpatient chest pain patients who required noninvasive cardiac testing to determine the presence or absence of obstructive CAD or myocardial ischemia. Eligible patients were randomly assigned to either coronary CTA or functional testing (exercise electrocardiography, stress echocardiography, or nuclear stress testing). Major inclusion criteria for the PROMISE trial were men ≥45 and women ≥50 years of age with symptoms suspicious for obstructive CAD but without known CAD. Major exclusion criteria were acute or unstable presentation or any class I indication for urgent invasive catheterization, LVEF <40 %, and contraindications for CTA. The study was performed at 193 community and academic medical centers in the USA and Canada. Participating sites had established expertise in cardiology, radiology, primary care, urgent care, and anesthesiology. The sites were certified and had experienced readers interpreting cardiac test results. The trial provided recommendations for patient management but in keeping with the principles of an effectiveness trial, care was decided by local physicians.

The population of the PROMISE trial included 53 % women and 17 % ethnic minorities. Patients were middle-aged (mean age 60.8 ± 8.3 years), had a high burden of cardiovascular risk factors (mean 2.4 ± 1.1 of the following 5 risk factors; 21.4 % had diabetes, 65.0 % had hypertension, 51.1 % were past or current tobacco users, 67.7 % had dyslipidemia, and 32.1 % had family history of premature CAD); the majority had atypical chest pain (77.7 %) resulting in a mean pretest likelihood for obstructive CAD of 53 % based on the combined Diamond and Forrester (DF) and Coronary Artery Surgery Study risk score. In 67.6 % of all patients, the 10-year risk for ASCVD events was ≥7.5 %. Overall, patients enrolled in the PROMISE trial had demographics, cardiovascular risk profile, and pre-test likelihood consistent with low to intermediate risk of CAD and in whom a noninvasive test was reasonable and indicated per guidelines [3].

Results of the PROMISE Trial

The primary endpoint of the PROMISE trial was a composite of death, myocardial infarction, hospitalization for unstable angina, or major procedural complication. After a median follow-up of 25 months (interquartile range 18 to 34 months), there was no significant difference in time to the primary composite endpoint in the CTA-based strategy as compared to functional testing (164 vs. 151; HR 1.04; 95%CI (0.83–1.29); $p = 0.75$) or any of its components (death or nonfatal myocardial infarction 104 vs. 112; HR 0.88; 95%CI (0.67–1.15); $p = 0.35$; death or nonfatal myocardial infarction or hospitalization for unstable angina 162 vs. 148; HR 1.04; 95%CI (0.84–1.31); $p = 0.70$), and in the combination of the primary endpoint plus catheterization showing no obstructive CAD (332 vs. 353; HR 0.91; 95%CI (0.78–1.06); $p = 0.22$) between two study groups. There was a significantly lower number of ICAs showing no obstructive CAD in the CTA arm as compared to the functional arm (170/4996 (3.4 %) vs. 213/5007 (4.3 %); $p = 0.02$) (see Table 1).

Across the trial, we observed a low rate of both ICA and revascularization (1015/10,003 (10.1 %) and 469/10,003 (4.7 %), respectively). However, compared to functional testing, more patients in the CT arm underwent ICA and revascularization (609/4996 (12.2 %) vs. 406/5007 (8.1 %) and 311/4996 (6.2 %) vs. 158/5007 (3.2 %), respectively; both $p < 0.001$).

Table 1 Selected baseline characteristics and endpoints of PROMISE trial participants in respect to the diagnostic approach

Baseline characteristics	CTA strategy ($N=4996$)	Functional testing strategy ($N=5007$)	Adjusted hazard Ratio (95 % CI)	P value
Mean age—yr	60.7 ± 8.3	60.9 ± 8.3		ns
Female sex—no. (%)	2595 (51.9)	2675 (53.4)		ns
Risk burden				
Mean no. of risk factors per patient	2.4 ± 1.1	2.4 ± 1.1		ns
Mean combined Diamond and Forrester and Coronary Artery Surgery Study risk score	53.4 ± 21.4	53.2 ± 21.4		ns
Relevant medication—no./total no. (%)				
Statin	2215/4783 (46.3)	2174/4786 (45.4)		ns
Aspirin	2164/4783 (45.2)	2116/4786 (44.2)		ns
Endpoints				
Clinical end point—no. of patients				
Primary composite end point	164	151	1.04 (0.83–1.29)	0.75
Death from any cause	74	75		
Nonfatal myocardial infarction	30	40		
Hospitalization for unstable angina	61	41		
Major procedural complication	4	5		
Death or nonfatal myocardial infarction	104	112	0.88 (0.67–1.15)	0.35
Death, nonfatal myocardial infarction, or hospitalization for unstable angina	162	148	1.04 (0.84–1.31)	0.70
Test-related end point				
Invasive catheterization showing no obstructive CAD—no. (%)	170 (3.4)	213 (4.3)	–	0.02
Cumulative radiation exposure in all procedures ≤90 days after randomization—mSv				
All patients	12.0 ± 8.5	10.1 ± 9.0	–	<0.001
Median	10.0	11.3		
Interquartile range	5.6–17.2	0.0–13.5		
Intended functional test before randomization				
Nuclear stress testing	12.0 ± 8.4	14.1 ± 7.6	–	<0.001
Median	10.1	12.6		
Interquartile range	5.7–17.1	11.1–16.0		

Plus–minus values are means ± SD. (From: N Engl J Med, Douglas PS, Hoffmann U, Patel MR, et al., Outcomes of anatomical versus functional testing for coronary artery disease, 372(14):1291–1300, 2015, Massachusetts Medical Society. Reprinted with permission from the Massachusetts Medical Society) [16]. The data shown here are results from the PROMISE trial [16]

CAD coronary artery disease

Prevalence of Obstructive CAD and Myocardial Ischemia

The mean pre-test likelihood of obstructive CAD in the PROMISE trial based on a combined Diamond and Forrester and Coronary Artery Surgery Study risk score was 53.3 ± 21.4 %. This was much higher than the observed prevalence of obstructive CAD after coronary CTA (12.6 %) or myocardial ischemia after functional testing (11.7 %) [17]. Similar findings were published recently by the CONFIRM registry in 14,048 patients reporting a substantially lower prevalence of obstructive CAD in coronary CTA than that predicted by Diamond and Forrester criteria (18 % vs. 51 % and 10 % vs. 42 % for ≥50 and ≥70 % stenosis thresholds, respectively) [18].

The primary reason for this discrepancy is that the patient population assessed for obstructive CAD has significantly changed since George Diamond and James Forrester reported their findings in 1979 [19]. For instance, lifestyle changes have led to a marked decrease in cigarette smoking from 42 % in 1965 to 30 % in 1985, and 18 % in 2014 [20, 21]. In addition, Diamond and Forrester based their observations on ICA. Several studies suggest that modifying the Diamond Forrester model by inclusion of risk factors, the agreement between the projected, and observed prevalence of obstructive CAD can be improved in contemporary populations using coronary CTA as the gold standard for obstructive CAD [22–24].

Health Outcomes

The primary composite endpoint (death, myocardial infarction, hospitalization for unstable angina, or major procedural complication) occurred in 3.1 % of patients during a median of 25 months of follow-up in the PROMISE trial, which is lower than the anticipated 8 % over 2.5 years in the functional arm based on historical and national claims data [10, 17, 25, 26]. Contributing factors include a lower than expected disease burden, changes in lifestyle and increase in preventive medical therapy such as aspirin and statins as compared to historical populations (45 % of patients were on antiplatelet therapy and 46 % on statin therapy), and perhaps in a minor way a small decrease in the minimum follow-up from 2 to 1 years. However, the observed annual event rate in PROMISE (1.5 %) is consistent with other recent trials such as SCOT-HEART [27] (annual event rate 0.9 %), suggesting that contemporary populations of patients with suspicion of stable CAD are at intermediate Framingham Risk, making medical therapy the preferred choice of treatment.

Coronary Revascularization and Health Outcomes

Another observation of the PROMISE trial was that the higher rate of revascularization after coronary CTA as compared to functional testing CT arm (311/4996 (6.2 %) vs. 158/5007 (3.2 %); $p < 0.001$) did not translate into a lower MACE rate. Similar results were previously reported from randomized comparative effectiveness trials in the acute chest pain setting (ROMICAT-II, ACRIN-PA, and CT-STAT) [28–30]. Whether the effectiveness of coronary revascularization in stable chest pain can be improved by limiting this procedure to lesions with proven hemodynamic significance is the motivation and primary hypothesis of an ongoing NHLBI funded trial—International Study of Comparative Health Effectiveness with Medical and Invasive Approaches (ISCHEMIA).

In addition, the fact that caregivers were aware of the results of noninvasive diagnostic testing could have lead to differences in the outcome of unstable angina requiring hospitalization (ascertainment bias). For example, a patient in the CT arm, diagnosed with a 50 % stenosis who was subsequently medically managed and who presents with recurring symptoms may have been more likely hospitalized for work-up as compared to a patient who also has 50 % stenosis but, as most of these patients do, had a normal functional test and who is more likely to undergo outpatient work-up given similar presentation. Indeed, 50 % more patients were diagnosed with "hospitalization for unstable angina" after coronary CTA as compared to functional testing (61 vs. 41, respectively), while this trend was reversed for myocardial infarction (30 vs. 40, respectively).

Opportunities to Improve Risk Stratification and Selection for PCI Candidates in Stable Chest Pain Patients CAD

Improved Risk Stratification—High-Risk Coronary Plaque

While coronary artery stenosis has been the hallmark for diagnostic and prognostic assessment, data suggest that up to two thirds of acute myocardial infarctions (MI) occur at locations in the coronary artery tree where there previously was no obstructive CAD [31, 32]. The PROSPECT trial for instance, in patients undergoing coronary revascularization after MI using intravascular ultrasound (IVUS), found that 50 % of recurrent cardiovascular events originated from non-stenotic plaque characterized by a thin fibrous cap, plaque burden >70 % (plaque occupying >70 % of cross-sectional vessel area), and luminal diameter <4 mm [2]. These features were associated with a three- to fivefold increased risk for MACE [33•].

Technical progress in coronary CTA has enabled a more granular noninvasive assessment of coronary plaque morphology and composition. For example, low CT attenuation (<30 HU) and Napkin Ring Sign (NRS) in CT accurately represent plaque with a large lipid-rich/necrotic core and a thin fibrous cap in intravascular imaging and histology [34–45], and remodeling index and increased plaque burden can be accurately detected and measured by coronary CTA as compared to IVUS [46–48]. Several studies in populations similar to the PROMISE trial suggest that presence of high-risk plaque confers a six- and twelvefold excess risk for MACE, independent of traditional CV risk factors and obstructive CAD [49–51, 52•]. Hence, high-risk plaque may improve risk stratification, especially in those with non-obstructive disease.

Improved Selection for Candidates for PCI–FFR-CT

In addition, recent studies suggest that noninvasive estimation of fractional coronary flow reserve (FFR) is possible using modeled computational fluid dynamics based on regular contrast enhanced coronary CTA data sets [53]. Using this methodology, FFR-CT can be calculated in good correlation with invasive FFR measurements ($r = 0.63$–0.82) [54–56] and may have favorably increased the specificity of coronary CTA. For example, the NXT trial in 252 patients reported an increase in specificity compared to invasive FFR per patient from 34 % based on anatomic CTA assessment to 79 % based on FFR-CT [56]. This

may have a favorable effect on resource use as compared to a strategy of referring patients directly to ICA with more than a 50 % reduction of initially planned ICA procedures in the FFR-CT group [57].

Radiation Exposure

In the PROMISE trial, the overall mean radiation exposure of the CTA arm was higher compared to the functional arm (12.0 ± 8.5 vs. 10.1 ± 9.0 mSv; $p < 0.001$). However, functional testing with no radiation exposure (exercise ECG and stress echocardiography, see Table 1) were included in these calculations. These tests were performed in 10.2 % and 22.5 % of the patients undergoing a functional testing strategy, respectively. The majority of patients underwent nuclear myocardial perfusion imaging (67.3 %). Among the group of patients who were intended to undergo nuclear myocardial perfusion imaging before randomization ($n = 6781$), the 90-day cumulative radiation exposure was significantly higher as compared to the CTA group (12.0 ± 8.4 vs. 14.1 ± 7.6; $p < 0.001$).

As both nuclear and CT technology improve over time, a decrease in radiation dose can be achieved using advanced technology. For instance, a rapid decrease in radiation exposure during a 6-year period between 2005 and 2010 has been observed with CTA with median doses decreasing by nearly 75 % from 13.1 to 3.3 mSv [58].

Conclusion

The PROMISE trial compared the effectiveness of coronary CT angiography and functional testing as initial diagnostic test for patients with suspicion for stable CAD and provided a snapshot of real-world care for this very common presentation. PROMISE did not find significant differences in major clinical events between the two strategies. However, lessons from PROMISE include the need to improve patient selection for diagnostic testing and coronary revascularization as well as to focus on improvement of risk stratification and medical therapy.

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Compliance with Ethical Standards

Conflict of Interest Daniel O. Bittner and Maros Ferencik declare that they have no conflict of interest.

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