Research paper

Safety of coronary CT angiography and functional testing for stable chest pain in the PROMISE trial: A randomized comparison of test complications, incidental findings, and radiation dose

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ABSTRACT

Background: Coronary computed tomography angiography (CTA) and functional testing strategies for stable chest pain yield similar outcomes; one aspect that may guide test choice is safety.

Methods: We compared test safety (test complications, incidental findings, and effective radiation dose) between CTA and functional testing as-tested in PROMISE (PROspective Multicenter Imaging Study for Evaluation of Chest Pain). In the subgroup whose physicians intended nuclear stress over other functional tests if randomized to the functional arm, we compared radiation dose of CTA versus nuclear stress and identified characteristics associated with dose.

Results: Of 9470 patients, none had major and <1% had minor complications (CTA: 0.8% [37/4633] vs. functional: 0.6% [27/4837]). CTA identified more incidental findings (11.6% [539/4633] vs. 0.7% [34/4837], p < 0.001), most commonly pulmonary nodules (9.4%, 437/4633). CTA had similar 90-day cumulative radiation dose to functional testing. However, in the subgroup whose physicians intended nuclear stress (CTA 3147; nuclear 3203), CTA had lower median index test (8.8 vs. 12.6 mSv, p < 0.001) and 90-day cumulative (11.6 vs. 13.1 mSv, p < 0.001) dose, independent of patient characteristics. The lowest nuclear doses employed 1-day Tc-99m protocols (12.2 mSv). The lowest CTA doses were at sites performing >500 CTAs/year (6.9 mSv) and with advanced (latest available) CT scanners (5.5 mSv).

Conclusion: Complications were negligibly rare for both CTA and functional testing. CTA detects more incidental findings. Compared to nuclear stress testing, CTA’s lower radiation dose, independent of patient characteristics, makes it an attractive test choice. Radiation dose varies with imaging protocol, indicating opportunities to further reduce dose.

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1. Introduction

Stable chest pain is one of the most common indications for noninvasive diagnostic testing in the United States, with over 4 million Americans undergoing outpatient testing for suspected coronary artery disease (CAD) annually. Most have a functional test (exercise tolerance testing [ETT], stress echocardiography, or nuclear stress testing). Recent randomized controlled trials have demonstrated that anatomic coronary computed tomography angiography (CTA) is a maturing diagnostic alternative with similar cardiovascular outcomes.4–6

One aspect that may contribute to test choice is test safety. Early reports of high radiation dose and frequent incidental findings have been barriers to the adoption of CTA.6–8 A randomized as-tested comparison of test safety between CTA and functional testing, with safety defined by test complications, incidental findings, and radiation dose, has not been performed. PROMISE (PROspective Multicenter Imaging Study for Evaluation of Chest Pain), a pragmatic multicenter randomized controlled trial of an initial anatomic (CTA) versus functional testing strategy for stable chest pain, presents an opportunity to compare the safety of CTA and functional testing.4 In PROMISE, anatomic CTA and functional testing strategies had similar rates of adverse cardiovascular events, test complications, and 90-day cumulative radiation dose; however, this as-randomized comparison included patients who were not tested or had the other test.

We therefore carried out an as-tested assessment of the safety of CTA versus functional testing in PROMISE based on test complications, incidental findings, and index test and 90-day cumulative radiation dose. Furthermore, in the subgroup of patients whose physicians prespecified nuclear stress testing as the intended functional test if the patient were randomly assigned to the functional testing group, we compared the radiation dose of CTA versus nuclear stress testing and identified patient and technical characteristics associated with dose.

2. Methods

2.1. Population and study design

This prespecified analysis was planned within the PROMISE trial; the design and results of the trial are detailed elsewhere.5,7 Briefly, after providing written informed consent, outpatients with stable chest pain and without known CAD were enrolled at 193 North American sites between July 2010 and September 2013. Subjects were randomly assigned to an initial anatomic (CTA) or functional (exercise or pharmacologic nuclear stress, stress echocardiography, or ETT per physician choice) testing strategy. Baseline characteristics including cardiovascular risk factors were collected at enrollment. Prior to randomization, treating physicians specified whether a functional test the patient should receive if he or she were randomized to the functional arm,5 with randomization stratified by this preference (i.e., those patients whose physicians preferred nuclear testing were randomized in a 1:1 ratio to CTA vs. functional testing). Subjects were followed for a median of 25 months for a composite of major adverse cardiovascular events including death, myocardial infarction, hospitalization for unstable angina, and major procedural complications as adjudicated by an independent clinical events committee.

In the first part of this as-tested analysis, test complications, potentially significant incidental findings, and 90-day cumulative radiation dose were compared between CTA and functional testing. The second part of the analysis focused on radiation dose in the subgroup of patients whose physician specified that they intended nuclear stress testing should the patient be randomized to the functional arm. In this subgroup, index test radiation dose and 90-day cumulative radiation dose were compared between CTA and nuclear stress testing, again as tested. Patient, site experience, and technological factors associated with radiation dose were described.

All PROMISE subjects who had functional testing or CTA as their first test were included. Patients who had no test or who had invasive coronary angiography (ICA) as their first test were excluded. Computed tomography (CT) protocols commonly include a non-contrast CT for assessment of coronary artery calcium score before contrast-enhanced CTA to assess coronary artery stenosis. Some sites chose not to proceed with CTA in patients with a high calcium score8; these participants were excluded as the radiation dose from calcium score CT alone is substantially lower than for CTA.

2.2. Diagnostic testing

CTA, ETT, stress echocardiography, and exercise or pharmacologic nuclear stress testing were performed by local physicians in accordance with professional society guidelines. Electrocardiography (ECG)-gated CTA was performed on single or dual source CT scanners with at least 64 slices.8,9 For nuclear stress testing, the imaging protocol and administered agent were recorded; for CTA, the CT scanner model and whether a prospective or retrospective ECG-triggered or gated protocol was used were recorded. “Advanced” CT scanners were defined as 64 + slice CT scanners that were each of the 4 largest vendors’ newest model during the study period (GE Discovery CT750 HD, Philips Brilliance iCT, Siemens Definition Flash, Toshiba Aquilion ONE), with all other CT scanners considered “standard.” At the beginning of the trial, sites completed surveys in which they reported their annual volume of nuclear stress and CTA testing as a measure of their experience.

2.3. Test complications

Prespecified test complications were collected by site personnel and considered up to 24 h after the randomized test. For both CTA and functional testing, major complications were defined as death, renal failure requiring dialysis, or anaphylaxis requiring emergency respiratory and/or circulatory support. For CTA, minor complications included mild intravenous contrast reactions, contrast extravasation, and adverse reactions to nitroglycerin or beta blockers administered during the examination. For functional testing, minor complications included hemodynamic instability or hypotension, arrhythmia, and adverse drug reactions. Hospitalizations related to test complications were also collected. A full list of test complications and their definitions is provided in the Supplementary Material.

2.4. Incidental findings

Site physicians reported prespecified potentially clinically significant incidental findings found on CTA, stress echocardiography,
and nuclear stress testing. Potentially significant incidental findings on CTA included coronary anomalies, lung nodules, pulmonary embolism, pneumonia, aortic aneurysm, aortic dissection, and hiatal hernia, which could be a source for chest pain. For stress echocardiography these included moderate or large pericardial effusion or tamponade, moderate or severe aortic or mitral stenosis, moderate or severe aortic insufficiency, moderate or severe mitral regurgitation, moderate or severe pulmonary hypertension, hypertrophic obstructive cardiomyopathy, endocarditis, mitral prolapse, and aortic root aneurysm. For nuclear stress testing, these included radiotracer uptake within the lung, breast, or axilla.

2.5. Estimated effective radiation dose

Effective radiation dose was estimated in units of millisieverts (mSv) using standard methods. For CTA, the estimated effective dose was calculated as the product of the dose length product (DLP) and a standard chest k-factor of 0.014 mSv mGy$^{-1}$ cm$^{-1}$. For nuclear stress imaging, the estimated simple effective dose was calculated as the product of the administered activity by the effective dose coefficient for that tracer and protocol. Cumulative 90-day effective radiation dose was defined as radiation dose due to the index test plus any additional cardiovascular testing or procedures performed within 90 days after randomization, including CTA, nuclear stress testing, ICA, and coronary interventions. The protocol for imputation of ICA, CTA, and nuclear stress testing radiation doses is described in the Supplementary Material.

2.6. Statistical analysis

Demographics, risk factors, and the composite outcome of major adverse cardiovascular events are presented as medians (inter-quartile range [IQR]) and means (standard deviations [SD]) for continuous variables; the frequency (percentage) of patients in each category are presented for nominal variables.

In the first part of the analysis, comparisons between the CT and functional testing groups were performed using the Wilcoxon rank sum test for continuous variables and Pearson’s chi-square or Fisher exact tests for categorical variables. Diagnostic test complications and incidental findings were tabulated and compared between the patients having CT versus functional testing. Likewise, the 90-day cumulative effective radiation dose was tabulated and compared between the CT and functional testing groups.

The second part of the analysis focused on comparisons of radiation dose between CT and nuclear stress testing in the randomization strata of patients whose physicians intended to refer for nuclear stress testing if the patient were randomly assigned to the functional testing strategy. First the index test radiation dose in mSv of patients having nuclear stress versus CTA was compared using the Wilcoxon rank sum test. The percent of index test doses $\leq 9$ mSv was compared against the American Society of Nuclear Cardiology goal that 50% of nuclear stress tests have a radiation dose $\leq 9$ mSv. As a secondary outcome, 90-day cumulative radiation dose was also compared. Radiation dose was then summarized within specific prospectively chosen subgroups to assess whether patient-specific factors known to affect dose— including sex, age $\geq 65$ years, obesity (body mass index [BMI] $\geq 30$ kg/m$^2$), and baseline resting heart rate at the enrollment physical examination $\geq 75$ beats per minute—changed the relationship between nuclear stress and CTA index test and 90-day cumulative radiation dose using the Wilcoxon rank sum test. For each of the above categories, a multivariable model was developed to compare CTA and nuclear stress testing radiation dose while controlling for the other patient-specific factors. Second, $R^2$ values for each patient factor were then compared to assess the relative effect on the dose of CTA versus nuclear stress testing. Finally, radiation dose was then summarized based on site- and protocol-specific factors, including use of an advanced CT scanner, retrospective versus prospectively ECG-gated CTA protocols, nuclear stress test protocol and tracer, and site self-reported annual volume of nuclear stress and CTA testing.

Statistical analysis was performed using SAS (version 9.4) and JMP Pro (version 12) from the SAS Institute (Cary, North Carolina). All statistical testing was 2-sided using a level of significance of 0.05.

3. Results

3.1. Patient population, characteristics, and adverse cardiovascular events

Of the 10,003 patients enrolled in PROMISE, 404 had no testing and 29 had ICA as a first test (Fig. 1A). Of the remaining 9570 patients, 4733 had CT and 4837 had functional testing. Of the 4733 who had CT, 4633 completed CTA while 100 had only a noncontrast calcium score CT. Of the 4837 having functional testing, 3263 had nuclear stress testing, 1083 had stress echocardiography, and 491 had ETT. Baseline characteristics and adverse cardiovascular events were similar between the groups having CTA and functional testing (Table 1).

3.2. Test complications — CTA versus functional testing

There were no major test complications (cardiac arrest, severe bronchospasm, anaphylaxis, renal failure requiring dialysis, or death) in either arm. Minor test complications were similarly rare for CTA (0.8%, 37/4633) and functional testing (0.6%, 27/4837, $p = 0.15$, Table 2), with individual complications detailed in Table 3. For CTA, the most common minor complications were mild contrast reactions (0.5%, 22/4633) and contrast extravasation at the site of the IV (0.3%, 12/4633). For stress echocardiography, the most common complication was hypotension (0.2%, 2/1083). For nuclear stress testing, the most common minor complications were hypotension (0.2%, 6/3263), ventricular tachycardia (0.2%, 5/3263), and dipyridamole/adenosine-related events (0.2%, 5/3263). Overall, 5 patients in the functional arm (ETT n = 1, stress echocardiography n = 1, nuclear stress testing n = 3) and none having CTA were hospitalized due to complications attributed to the index test.

3.3. Incidental findings — CTA versus functional testing

More patients had potentially significant incidental findings with CTA than with functional testing (11.6%, 539/4633 vs. 0.7%, 34/4837, $p < 0.001$ (Table 3)). The most common CTA incidental finding was lung nodules (9.4%, 437/4633). Other CTA findings with the potential to cause chest pain included coronary anomalies (1.5%, 71/4633), pulmonary embolism (0.1%, 4/4633), pneumonia (0.2%, 9/4633), and aortic dissection (0.2%, 8/4633). In all, 2.0% (93/4633) had one of the above findings potentially causing chest pain. In addition, 7.7% (358/4633) had hiatal hernia and 1.9% (89/4633) had aortic aneurysm, both of which in some instances can also be a source of chest pain. In the functional arm, abnormal breast uptake of radiotracer (0.3%, 11/3263) on nuclear stress testing, and mitral regurgitation (1.0%, 11/1083) on stress echocardiography were the most common incidental findings.
3.4. 90-day cumulative effective radiation dose — CTA versus functional testing

As tested, CTA had a lower median (10.3 vs. 11.5 mSv) but higher mean (12.5 vs. 10.6 mSv) 90-day cumulative effective radiation dose than functional testing (both p < 0.001, Table 2).

3.5. Subgroup intended for nuclear stress testing — CTA versus nuclear stress testing

Of the 10,003 patients enrolled in PROMISE, physicians prespecified nuclear stress testing as the intended test should the patient be randomized to the functional arm in 68% (6781/10,003; Fig. 1B). This subgroup was characterized by a significantly higher burden of cardiovascular risk factors and more major adverse cardiovascular events (3.4% vs. 2.6%, p = 0.044) than those prespecified for ETT or stress echocardiography (Supplemental Table 1). Of the 6781 intended for nuclear stress testing, 6.4% (432) did not complete CTA or nuclear stress testing. The remaining 6349 patients comprised the analytic subgroup intended for nuclear stress testing who were randomized to and completed CTA (3146) or nuclear stress testing (3203). There were similar cardiovascular risk factors and adverse cardiovascular events between those having CTA and nuclear stress testing (Table 1).

3.6. Index test and 90-day cumulative radiation dose — CTA versus nuclear stress testing

In the subgroup prespecified for nuclear stress testing, median (IQR) index test effective radiation dose was lower for CTA than for nuclear stress testing, 8.8 mSv (5.3, 14.6) versus 12.6 mSv (11.3, 14.6), p < 0.001 (Fig. 2). Likewise, mean (±SD) index test effective dose was also lower for CTA, 10.4 ± 6.6 mSv versus 14.1 ± 5.6 mSv, p < 0.001. A significantly higher percentage of CTA index test doses were ≤9 mSv compared to nuclear stress testing (51.2% vs. 7.0%, p < 0.001). Similar results were observed for 90-day cumulative

Fig. 1. (A) Main analysis comparing test complications, incidental findings, and radiation dose between computed tomography angiography (CTA) and functional testing, as tested. (B) Sub-analysis with randomization stratified to the subgroup of patients whose physician intended to refer for nuclear stress testing if randomized to the functional arm. Radiation dose and patient, technology, and site factors associated with dose were compared for CTA versus nuclear stress testing. CAD indicates coronary artery disease; CT, computed tomography; ETT, exercise tolerance test; ICA, invasive coronary angiography; PROMISE, PROspective Multicenter Imaging Study for Evaluation of Chest Pain.
3.8. Patient factors and nuclear stress testing radiation dose

Index test and 90-day cumulative radiation doses remained lower for CTA than nuclear stress testing across all tested subgroups including women, those aged ≥65 years, the obese (BMI ≥30 kg/m²), and those with a resting heart rate ≥75 beats per minute after adjustment for risk factors (all p < 0.001, Supplemental Fig. 1).

3.7. Patient factors and CTA radiation dose

Among the patients who had CTA, men received a higher median index test radiation dose than women (9.3 vs. 8.5 mSv, p < 0.001), the obese had a higher dose than the non-obese (10.5 vs. 7.8 mSv, p < 0.001), and those with a baseline resting heart rate >75 beats per minute had a higher dose than those with a lower heart rate (9.4 vs. 8.4 mSv, p < 0.001) (Table 4). Similar significant relationships between 90-day cumulative CTA radiation dose and sex, BMI, and heart rate are enumerated in Supplemental Table 2.

3.8. Patient factors and nuclear stress testing radiation dose

Among the patients who had nuclear stress testing, men (12.7 mSv vs. 12.4 mSv for women, p = 0.001) and the obese (12.7 vs. 12.3 mSv for non-obese, p < 0.001) also had higher median index test radiation dose (Table 4). There was no association between baseline heart rate >75 beats per minute and nuclear stress testing dose (p = 0.40). For 90-day cumulative radiation dose, there was not a significant association between age ≥65 years and dose; otherwise, the associations were similar as for index test dose (Supplemental Table 2).

Baseline resting heart rate >75 beats per minute had a significantly greater impact on the effective radiation dose of CTA than nuclear stress testing (p = 0.042), with a nonsignificant trend toward a greater impact for obesity and age (Table 4 for index test dose and Supplemental Table 2 for 90-day cumulative dose).

3.9. Imaging protocol and site experience – CTA versus nuclear stress testing

Radiation dose varied with site-related factors including the type of CT scanner, annual volume of CTA, and CTA or nuclear stress test protocol (Table 5). The 12.2% of patients who had CTA using an advanced CT scanner had a lower median index test radiation dose.
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The PROMISE trial found that, in stable outpatients with suspected CAD, anatomic CTA and functional testing strategies resulted in a similar rate of cardiovascular events. Given this state of equipoise, test safety should help guide test choice. In the current prespecified as-tested randomized comparison of test safety in the PROMISE trial, CTA and functional testing had a similar very low 1% rate of minor test complications and no major complications. CTA detected substantially more potentially significant incidental findings. CTA had similar 90-day cumulative radiation dose to functional testing overall. However, in the subgroup of patients whom physicians intended to refer for nuclear stress testing if randomly assigned to the functional testing arm, CTA had significantly lower index test dose (p < 0.001) than those who had CTA on a standard CT scanner (5.5 vs. 9.3 mSv, p < 0.001). Most CTA (74.3%) was performed using a prospectively ECG-triggered scan, which had a lower index radiation dose than retrospectively ECG-gated scans (6.6 vs. 9.8 mSv, p < 0.001). Most nuclear stress testing was performed with a 1-day Tc 99m Sestamibi or Tetrofosmin rest/stress (77%, 2462/3203; index test, 12.2 mSv) or stress/rest (3.2%, 103/3203; index test, 12.7 mSv) protocol, with a lower index test radiation dose (p < 0.001) than 2-day protocols and 1-day protocols including a Thallium 201 tracer (Table 5). Median CTA index test dose was inversely associated with the site’s self-reported annual CTA volume (12.3 mSv for sites performing 1–100 CTAs/year, 10.4 mSv for 101–500 CTAs/year, and 6.9 mSv for >500 CTAs/year, p for trend <0.001). Similar relationships were seen for 90-day cumulative radiation dose. There was no linear association between site annual volume of nuclear stress testing and radiation dose.

4. Discussion

Our findings confirm previous reports that incidental findings are substantially more frequent on CTA as compared to functional testing.32–24 Findings with the potential to cause chest pain such as coronary anomalies, pneumonia, pulmonary embolism, and

### Table 3

#### Table 3 (continued)

<table>
<thead>
<tr>
<th>Incidental findings</th>
<th>N</th>
<th>%</th>
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<tbody>
<tr>
<td>CTA (n = 4633)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coronary anomaly</td>
<td>539</td>
<td>11.6</td>
</tr>
<tr>
<td>Lung nodule</td>
<td>437</td>
<td>9.4</td>
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<tr>
<td>Size of largest</td>
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<td></td>
</tr>
<tr>
<td>≤4 mm</td>
<td>201</td>
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<tr>
<td>5–7 mm</td>
<td>161</td>
<td>3.5</td>
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<tr>
<td>≥8 mm</td>
<td>74</td>
<td>1.6</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>4</td>
<td>0.1</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>9</td>
<td>0.2</td>
</tr>
<tr>
<td>Aortic aneurysm</td>
<td>89</td>
<td>1.9</td>
</tr>
<tr>
<td>Aortic dissection</td>
<td>8</td>
<td>0.2</td>
</tr>
<tr>
<td>Hiatal hernia</td>
<td>358</td>
<td>7.7</td>
</tr>
</tbody>
</table>

BP indicates blood pressure; CTA, computed tomography angiography; ETT, exercise tolerance test.
aortic dissection were found in 2% of patients having CTA. Put in context, only 12% of PROMISE patients had obstructive CAD on CTA. Nevertheless most incidental findings were truly incidental and would not be expected to cause chest pain, most commonly lung nodules seen in 9%. In PROMISE the outcomes of incidental findings and noncardiac downstream testing was not collected, which precludes an analysis of their impact. However, other studies have suggested that follow-up of lung nodules incidentally detected on coronary CTA by the 2005 Fleischner Society guidelines resulted in a 4.6% relative reduction in lung cancer mortality, but at an estimated cost per quality adjusted life year (QALY) of $154,700. On the other hand, for high risk heavy smokers the National Lung Screening Trial found that screening chest CT and follow-up of lung nodules was cost-effective at $81,000 per QALY. Clinical trials are necessary to determine in which nodule and patient risk categories follow-up is necessary. The Watch The Spot

Table 4

<table>
<thead>
<tr>
<th>Patient characteristic</th>
<th>Nuclear</th>
<th>CTA</th>
<th>p for effect on nuclear vs CTA R²</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Median (IQR) in mSv</td>
<td>Mean ± SD in mSv</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65 years</td>
<td>2159</td>
<td>12.7 (11.3, 15.0)</td>
<td>14.3 ± 5.7</td>
</tr>
<tr>
<td>≥65 years</td>
<td>1044</td>
<td>12.3 (11.2, 13.8)</td>
<td>13.5 ± 5.2</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1417</td>
<td>12.7 (11.4, 15.2)</td>
<td>14.4 ± 5.7</td>
</tr>
<tr>
<td>Female</td>
<td>1786</td>
<td>12.4 (11.2, 14.1)</td>
<td>13.8 ± 5.4</td>
</tr>
<tr>
<td>BMI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not Obese (&lt;30 kg/m²)</td>
<td>1537</td>
<td>12.3 (11.2, 13.7)</td>
<td>13.8 ± 5.7</td>
</tr>
<tr>
<td>Obese (≥30 kg/m²)</td>
<td>1638</td>
<td>12.7 (11.4, 15.7)</td>
<td>14.3 ± 5.4</td>
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<tr>
<td>Heart rate&lt;sup&gt;a&lt;/sup&gt;</td>
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<td>&lt;75 bpm</td>
<td>1895</td>
<td>12.6 (11.3, 14.6)</td>
<td>14.1 ± 5.6</td>
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<tr>
<td>≥75 bpm</td>
<td>1300</td>
<td>12.5 (11.3, 14.5)</td>
<td>14.0 ± 5.4</td>
</tr>
</tbody>
</table>

BMI indicates body mass index; CTA, computed tomography angiography.

<sup>a</sup> Resting heart rate was recorded at the enrollment physical examination.

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nuclear stress testing over ETT or stress echocardiography in two-in addition to radiation dose. Despite the fact that nuclear stress tests for a given patient is multifactorial, incorporating cardiovas-note that, if these functional tests with no radiation dose are chosen comparison because one-third of functional tests (i.e., ETT or stress-echocardiography) delivered no radiation dose. It is important to-testing.\(^3\)\(^0\) Patients with well-controlled angina with a lower risk of cardiovascular events were randomized to the functional arm. In this group, CTA's index test effective radiation dose was 30% lower than nuclear stress testing (median 8.8 vs. 12.6 mSv, p < 0.001). CTA's lower radiation dose than nuclear stress testing was durable across all tested subgroups, including patients traditionally difficult to image with CTA, such as the obese and those with a resting heart rate \(\geq 75\) beats per minute.  

### 4.1. Opportunities to lower radiation dose

**PROMISE was designed to reflect actual care of patients with** stable chest pain in a broad cross-section of 193 North American sites during the enrollment period from 2010 through 2013. The radiation dose data should be interpreted in the context of ongoing technological advances for both CTA and nuclear stress testing. The CTA index test radiation dose in PROMISE (median 8.8 mSv) was lower than the median 12 mSv reported in the 2007 PROTECTION I trial: an ongoing 40,000-subject pragmatic comparative effective-ness trial, aims to assess whether a less intensive follow-up strategy is safe and cost-effective.\(^3\)\(^0\) In 2017 the Fleischner Society released updated guidelines which raise the size threshold for lung nodule follow-up and should result in substantially less downstream testing.\(^3\)\(^0\)

**PROMISE previously reported that patients randomized to CTA had a lower median (10.3 vs. 11.2 mSv) but higher mean (12.0 vs. 10.1 mSv) 90-day cumulative effective radiation dose than patients randomized to functional testing, but this included those who were not tested.\(^3\)\(^0\)** As tested in the current analysis, there was essentially the same relationship with CTA having lower median (10.3 vs. 11.5 mSv) but higher mean (12.5 vs. 10.6 mSv) 90-day cumulative effective radiation dose than functional testing. This is a difficult comparison because one-third of functional tests (i.e., ETT or stress echocardiography) delivered no radiation dose. It is important to note that, if these functional tests with no radiation dose are chosen over nuclear stress testing, the exam requiring radiation will obviously have substantially greater dose.

The choice to pursue nuclear stress testing over other functional tests for a given patient is multifactorial, incorporating cardiovascular risk profile, exercise capacity, ECG, cost, and local availability in addition to radiation dose. Despite the fact that nuclear stress testing necessarily gives more radiation dose, physicians chose nuclear stress testing over ETT or stress echocardiography in two-thirds of PROMISE patients. This reflects contemporary practice in the United States, where nuclear stress testing is the most common functional imaging test.\(^3\)\(^1\)\(^2\) Furthermore, PROMISE patients intended for nuclear stress testing were a high risk group with greater cardiovascular risk factors and major adverse cardiovascular events than patients intended for other functional tests. For these reasons, we focused our second analysis of radiation dose on the randomization strata of patients whom their physicians intended to refer for nuclear stress testing if randomized to the functional arm. In this group, CTA's index test effective radiation dose was 30% lower than nuclear stress testing (median 8.8 vs. 12.6 mSv, p < 0.001). CTA's lower radiation dose than nuclear stress-
doses fail to reach the American Society of Nuclear Cardiology’s goal of at least 50% of nuclear stress tests having a dose <9 mSv.6 In PROMISE, only 7% of nuclear stress studies were <9 mSv, in comparison to 51% of CTA. While nuclear stress testing is substantially more mature than CTA, there is also room for dose reduction. Radiation dose is approximately 20% higher in US laboratories compared to non-US laboratories, and this gap could in part be bridged by following best practices such as avoiding dual-isotope protocols, using weight-adjusted doses, performing stress-only imaging in appropriate patients, and using advanced single-photon emission computed tomography (SPECT) cameras.4,12 Three expert sites not in PROMISE injecting a low dose of 99mTc and using stress-only imaging with advanced SPECT cameras reported doses as low as 1.2 mSv in 101 patients, although obese patients (who made up half of the PROMISE population) were excluded.39 In PROMISE, most nuclear stress testing was performed with a SPECT 99mTc tracer-based protocol, with only 10% having a SPECT study including a 201Th tracer. Positron emission tomography (PET) stress testing, which was not used in PROMISE, may provide lower dose examinations, with expert PET sites reporting low radiation doses on the order of 3 mSv for 82Rb, 13N-ammonia, and 15O-water based protocols.40 Stress perfusion cardiovascular magnetic resonance was not performed in PROMISE, but could have provided an alternative with no radiation dose.41 CTA had a 3.8-mSv lower median effective dose than nuclear stress testing. This dose difference is roughly equivalent to 38 2-view chest radiographs and on the order of the approximately 3-mSv average annual dose from natural background radiation in the United States.4 This difference is low and unlikely to be of clinical significance for individual patients. Nevertheless, the most conservative approach is to treat any radiation dose as increasing the risk of cancer on a population basis.43,44 In the United States, nuclear stress testing accounts for 22% of the total population effective dose from all diagnostic imaging tests including non-cardiac imaging, and so choosing CTA as a lower dose alternative for some patients could have a substantial impact.45 Alternative tests with no radiation dose (i.e., ETT or stress echocardiography) should also be considered in appropriate patients.

4.3. Conclusions

Both CTA and functional stress testing are safe, with minor complications in <1%. CTA detects more potentially significant incidental findings. CTA’s lower radiation dose than nuclear stress testing, independent of patient characteristics, makes it an attractive alternative test for the evaluation of stable chest pain. Radiation dose varies substantially with equipment, site experience, and imaging protocol, indicating opportunities to further reduce dose.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jcct.2017.08.005.

References


