A Randomized Comparison of Anatomic versus Functional Diagnostic Testing Strategies in Symptomatic Patients with Suspected Coronary Artery Disease

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On behalf of the PROMISE Investigators

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New onset stable chest pain accounts for approximately 4 million stress tests annually in the United States.

Limited randomized data in stable CP pts to guide care:
- Little consensus about which test is preferable
- Impact of testing on health-related outcomes is unexplored

Current testing practices raise concerns regarding frequent testing of very low risk populations and high rates of finding no obstructive coronary artery disease in patients undergoing elective catheterization.
Coronary CT angiography (CTA) could reduce unneeded invasive testing and improve outcomes

- Higher positive and negative predictive accuracy for CAD
- Ability to detect a broader spectrum of CAD, including prognostically important, non-obstructive disease
- CTA is superior to usual care in 3 RCTs of acute CP patients

The impact of the information derived from an initial strategy of noninvasive anatomic versus functional test data on subsequent management and clinical outcomes in stable chest pain patients is unknown.
PROMISE Study Hypothesis and Design

**Hypothesis:** As compared to functional testing, an initial strategy of anatomic testing with CTA would improve the health outcomes of patients with symptoms suspicious for CAD who require further testing.

**Design:** Multicenter, randomized, pragmatic comparative effectiveness trial comparing these two contemporary diagnostic strategies.
PROMISE Trial Design

Symptoms suspicious for significant CAD
Requiring non-emergent noninvasive testing

1:1 Randomization — 10,000 patients
Stratified by site and intended functional test

Anatomic strategy
- 64+ slice CTA

Functional strategy
- Exercise ECG or exercise imaging
- Pharmacologic stress imaging

Tests read locally; Results immediately available
Subsequent testing/management by site care team, per guidelines

Minimum follow-up 12 months
Study Population

Inclusion criteria

- Non-urgent, noninvasive CV testing clinically necessary
- No history of CAD or recent CAD evaluation
- Age ≥55 years (men) or ≥65 years (women) OR
- Age 45–54 years (men) or 50–64 years (women) with ≥1 major cardiac risk factor

Exclusion criteria

- Unstable hemodynamics or arrhythmias
- Urgent evaluation for R/O ACS
- Known significant congenital, valvular or cardiomyopathic heart disease
- Any reason the patient could not be safely randomized
Study Procedures

- Diagnostic testing quality control for all modalities
  - Certification of sites and test readers prior to beginning enrollment
  - Ongoing quality control throughout the trial

- Tests performed and interpreted locally
  - Test information sheets outlining diagnostic and prognostic implications of findings in each modality

- Site clinical team made all subsequent care decisions; Optimal medical therapy encouraged
  - Patient and caregiver educational materials
Effectiveness and Safety Endpoints

- **Primary endpoint**
  - All-cause mortality, myocardial infarction, unstable angina hospitalization, and major complications from CV procedures (stroke, bleeding, renal failure, anaphylaxis)

- **Secondary endpoints**
  - Primary endpoint + invasive catheterization without obstructive CAD
  - Other components of the primary endpoint
  - Invasive catheterization without obstructive CAD
  - Cumulative radiation exposure ≤90 days
  - (Resource utilization)

- All events adjudicated by blinded Clinical Events Committee
Statistical Analysis

- Sample size was chosen to provide 90% power for detecting a 20% relative reduction in the primary endpoint with CTA.
- All treatment comparisons performed as randomized (ITT).
- For clinical endpoints, time-to-event analysis was performed using the Cox model.
- To account for subject heterogeneity, comparisons were adjusted for age, sex, CAD risk equivalent, and intended functional test at randomization.
- All testing was two-sided and included 95% confidence intervals.
Randomization and Follow-up

**Randomized**
(n=10,003; 193 NA sites; July 2010 – Sept 2013)

- **Anatomic testing strategy (CTA)** (n=4996)
  - Received CTA/CAC as 1st test (n=4686, 94%)
    - Received other test as 1st test (n=154, 3%)
    - No test (n=156, 3%)
  - 12-month follow-up
    - Completed 4750 (95%)

- **Functional testing strategy** (n=5007)
  - Received functional test as 1st test (n=4692, 94%)
    - Stress nuclear (67%)
    - Stress echo (23%)
    - Ex ECG (10%)
  - 12-month follow-up
    - Completed 4600 (92%)

**Allocation**

**Follow-up**

Median follow-up: 25 months (IQR 18, 34)
Maximum follow-up: 50 months
## Baseline Characteristics

<table>
<thead>
<tr>
<th>Demographics</th>
<th>CTA (n=4996)</th>
<th>Functional (n=5007)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age — mean ± SD, yrs</td>
<td>60.7 ± 8.3</td>
<td>60.9 ± 8.3</td>
</tr>
<tr>
<td>Female sex — %</td>
<td>52</td>
<td>53</td>
</tr>
<tr>
<td>Non-white race — %</td>
<td>16</td>
<td>15</td>
</tr>
<tr>
<td>Hypertension — %</td>
<td>65</td>
<td>65</td>
</tr>
<tr>
<td>Diabetes — %</td>
<td>21</td>
<td>22</td>
</tr>
<tr>
<td>Dyslipidemia — %</td>
<td>67</td>
<td>68</td>
</tr>
<tr>
<td>Family hx premature CAD — %</td>
<td>33</td>
<td>32</td>
</tr>
<tr>
<td>Current or past smoking — %</td>
<td>51</td>
<td>51</td>
</tr>
<tr>
<td>1° Symptom Chest pain or DOE — %</td>
<td>88</td>
<td>88</td>
</tr>
<tr>
<td>Anginal type Typical or atypical — %</td>
<td>89</td>
<td>89</td>
</tr>
<tr>
<td>Pretest probability CAD</td>
<td>Diamond–Forrester/CASS — mean %</td>
<td>53.4</td>
</tr>
</tbody>
</table>
Primary Endpoint:
Death, MI, Unstable Angina, Major Complications

CTA: Functional
Hazard Ratio: 1.04
(95% CI: 0.83, 1.29)
P = 0.750

12 Months
HR 0.94; p=0.682
Secondary Endpoint:
Primary Endpoint + Catheterization w/o Obstructive CAD

HR 0.85; p=0.055

CTA: Functional
Hazard Ratio: 0.91
(95% CI: 0.78, 1.06)
P-value: 0.217
Secondary Endpoint:
Death or Non-fatal MI

CTA: Functional
Hazard Ratio: 0.88
(95% CI: 0.67, 1.15)
P-value: 0.348

HR 0.66; p=0.049
<table>
<thead>
<tr>
<th>Event</th>
<th>CTA (n=4996)</th>
<th>Functional (n=5007)</th>
<th>Adj HR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary endpoint composite</td>
<td>164</td>
<td>151</td>
<td>1.04 (0.83–1.29)</td>
<td>0.750</td>
</tr>
<tr>
<td>All-cause death</td>
<td>74</td>
<td>75</td>
<td></td>
<td>0.750</td>
</tr>
<tr>
<td>Nonfatal MI</td>
<td>30</td>
<td>40</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unstable angina hosp</td>
<td>61</td>
<td>41</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major procedural complications</td>
<td>4</td>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary endpoint plus cath without obstructive CAD</td>
<td>332</td>
<td>353</td>
<td>0.91 (0.78–1.06)</td>
<td>0.217</td>
</tr>
<tr>
<td>Death or nonfatal MI</td>
<td>104</td>
<td>112</td>
<td>0.88 (0.67–1.15)</td>
<td>0.348</td>
</tr>
<tr>
<td>Death, nonfatal MI, or unstable angina hospitalization</td>
<td>162</td>
<td>148</td>
<td>1.04 (0.84–1.31)</td>
<td>0.703</td>
</tr>
</tbody>
</table>
## Primary Endpoint: Subgroup Analyses

<table>
<thead>
<tr>
<th>Subject group</th>
<th>Interaction P-value</th>
<th>N</th>
<th>Hazard ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>All subjects</td>
<td></td>
<td>10,003</td>
<td>1.04</td>
<td>0.83, 1.29</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65</td>
<td>0.591</td>
<td>7111</td>
<td>1.10</td>
<td>0.82, 1.47</td>
</tr>
<tr>
<td>≥65</td>
<td>0.591</td>
<td>2892</td>
<td>0.97</td>
<td>0.69, 1.36</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>0.698</td>
<td>4733</td>
<td>0.99</td>
<td>0.74, 1.32</td>
</tr>
<tr>
<td>Female</td>
<td>0.698</td>
<td>5270</td>
<td>1.08</td>
<td>0.76, 1.51</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>0.100</td>
<td>8371</td>
<td>0.95</td>
<td>0.74, 1.20</td>
</tr>
<tr>
<td>Non-white</td>
<td>0.100</td>
<td>1545</td>
<td>1.62</td>
<td>0.89, 2.92</td>
</tr>
<tr>
<td>Pre-test risk assessment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low risk (≤30%)</td>
<td>0.341</td>
<td>3755</td>
<td>1.33</td>
<td>0.88, 2.00</td>
</tr>
<tr>
<td>Intermediate risk (31-70%)</td>
<td>0.341</td>
<td>5750</td>
<td>0.92</td>
<td>0.69, 1.23</td>
</tr>
<tr>
<td>High risk (&gt;70%)</td>
<td>0.341</td>
<td>481</td>
<td>0.94</td>
<td>0.51, 1.74</td>
</tr>
<tr>
<td>CAD equivalent</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>0.142</td>
<td>2531</td>
<td>0.83</td>
<td>0.57, 1.20</td>
</tr>
<tr>
<td>No</td>
<td>0.142</td>
<td>7472</td>
<td>1.17</td>
<td>0.89, 1.54</td>
</tr>
<tr>
<td>Pretest probability of CAD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low risk (&lt;10%)</td>
<td>0.603</td>
<td>250</td>
<td>2.30</td>
<td>0.45, 11.68</td>
</tr>
<tr>
<td>Intermediate risk (10–90%)</td>
<td>0.603</td>
<td>9258</td>
<td>1.00</td>
<td>0.79, 1.26</td>
</tr>
<tr>
<td>High risk (&gt;90%)</td>
<td>0.603</td>
<td>495</td>
<td>1.08</td>
<td>0.53, 2.23</td>
</tr>
<tr>
<td>Functional test randomization stratum</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stress nuclear</td>
<td>0.293</td>
<td>6781</td>
<td>0.93</td>
<td>0.72, 1.21</td>
</tr>
<tr>
<td>Stress echo</td>
<td>0.293</td>
<td>2236</td>
<td>1.27</td>
<td>0.78, 2.05</td>
</tr>
<tr>
<td>Exercise ECG</td>
<td>0.293</td>
<td>986</td>
<td>1.80</td>
<td>0.66, 4.86</td>
</tr>
</tbody>
</table>

**Anatomic testing better**

**Functional testing better**
### Secondary Endpoint: Catheterization Without Obstructive CAD ≤90 days

<table>
<thead>
<tr>
<th></th>
<th>CTA (n=4996)</th>
<th>Functional (n=5007)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Invasive catheterization without obstructive CAD — N (%)</td>
<td>170 (3.4)</td>
<td>213 (4.3)</td>
<td>0.022</td>
</tr>
<tr>
<td>Invasive catheterization</td>
<td>609 (12.2%)</td>
<td>406 (8.1%)</td>
<td></td>
</tr>
<tr>
<td>With obstructive CAD (% of caths)</td>
<td>439 (72.1%)</td>
<td>193 (47.5%)</td>
<td></td>
</tr>
<tr>
<td>Revascularization</td>
<td>311 (6.2%)</td>
<td>158 (3.2%)</td>
<td></td>
</tr>
<tr>
<td>CABG</td>
<td>72</td>
<td>38</td>
<td></td>
</tr>
</tbody>
</table>
## Secondary Endpoint: Cumulative Radiation Exposure ≤90 days

<table>
<thead>
<tr>
<th>Mean ± SD; mSv</th>
<th>CTA (n=4996)</th>
<th>Functional (n=5007)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All patients</strong></td>
<td>12.0 ± 8.5</td>
<td>10.1 ± 9.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>No radiation exposure</td>
<td>4%</td>
<td>33%</td>
<td></td>
</tr>
<tr>
<td>Intended nuclear stress test randomization stratum</td>
<td>12.0 ± 8.4</td>
<td>14.1 ± 7.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Intended stress echo randomization stratum</td>
<td>12.6 ± 9.0</td>
<td>1.3 ± 4.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Intended exercise ECG randomization stratum</td>
<td>10.4 ± 7.8</td>
<td>2.3 ± 5.4</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Summary

- PROMISE enrolled a symptomatic, intermediate risk population for whom testing is currently recommended.
- There is a low event rate in this contemporary population.
- There were no significant differences in outcomes between an initial anatomic (CTA) or functional testing strategy with respect to the primary endpoint overall or in any subgroup.
- An initial CTA strategy was associated with a lower rate of invasive catheterization without obstructive CAD.
- Radiation exposure was higher in CTA arm overall, but lower in those patients for whom a nuclear test was specified at randomization as the intended functional test, and who were then randomized to CTA.
Conclusions

- Compared to usual care using a functional testing strategy, use of an initial anatomic testing strategy employing CTA did not improve clinical outcomes in patients with suspected CAD.
- Our results suggest that CTA is a viable alternative to functional testing.
- These real-world results should inform noninvasive testing choices in clinical care as well as provide guidance to future studies of diagnostic strategies in suspected heart disease.
Outcomes of Anatomical versus Functional Testing for Coronary Artery Disease

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ABSTRACT

BACKGROUND

Many patients have symptoms suggestive of coronary artery disease (CAD) and are often evaluated with the use of diagnostic testing, although there are limited data from randomized trials to guide care.
THANK YOU to PROMISE Patients and Sites...
...and to the PROMISE Team

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