Comparison of a Precision Care Strategy With Usual Testing To Guide Management Of Stable Patients With Suspected Coronary Artery Disease

Pamela S. Douglas, Michael Nanna, Michelle Kelsey, Eric Yow, Daniel Mark, Campbell Rogers, and Sreekanth Vemulapalli, on behalf of the PRECISE Investigators

Duke Clinical Research Institute

Funded by HeartFlow, Inc
Background

• New onset stable chest pain is a common problem and requires performance of approximately 4 million tests annually in the US alone

• All clinical practice guidelines (AHA/ACC, ESC, NICE) agree on evaluation goals for such patients, and propose similar strategies to accomplish them. These goals are to:
  • Reduce unnecessary testing by risk stratification and deferred testing
  • Improve diagnostic yield of testing and catheterization
  • Reduce complications and costs by serving as an efficient gatekeeper to invasive testing
  • Optimize preventive medical treatment
Need for Evidence and Hypothesis

• Randomized trial-level evidence is needed to determine the best care pathway to accomplish these consensus goals
  • Prospective validation of a pre-test probability assessment to guide decision making regarding deferral vs immediate testing
  • Prospective evaluation of the safety of deferred testing in symptomatic patients
  • Once a patient is determined to need testing, randomized trial evidence comparing cCTA with selective $\text{FFR}_{\text{CT}}$ versus other modalities as first test

• PRECISE Hypothesis
  • In stable, symptomatic patients with suspected CAD, a Precision Strategy care pathway incorporating a set of actions based on Guideline recommendations will improve outcomes compared to Usual Testing
Non-acute chest pain or equivalent patients requiring testing for suspected CAD
No history of obstructive CAD or CAD testing <1 year: N=2103

Randomization stratified by PROMISE Minimal Risk Score
and preferred first test if usual care

Precision strategy
Testing assigned by PROMISE Minimal Risk Score (PMRS)

- Low Risk
  - Deferred testing

- Elevated Risk
  - cCTA +/- FFR_{CT}

Usual testing
Modality selected by site clinician

- All Risk levels
  - Functional testing
  - OR Direct to cath

All subsequent care and testing decisions made by site clinician
Guideline-directed medical management recommended for all

Primary Endpoint (1 year): Death, Nonfatal MI, Cath w/o obs CAD
Secondary Endpoints: Hierarchical analysis of primary endpoint; Death; Nonfatal MI; Unplanned CV hospitalizations; Preventive med use; Radiation; Cath yield; Resource use; Quality of Life
Using 4,631 PROMISE cCTA pts, we modeled Minimal Risk: 27% w/o CAC, plaque or events

Result: 10 clinical variables predicted Minimal Risk

Validated in SCOT-Heart, Dan-NICAD (n=3,439)

Combined in all 3 cohorts: C stat 0.76
TrialEndpointsandStatisticalAnalysis

• **Composite primary endpoint: All-cause death, nonfatal MI, or cath w/o obstructive CAD**
  - Composite defines *net clinical effectiveness* (efficacy and safety) for this low-risk population
  - Catheterization without obstructive CAD was defined as the absence of any positive invasive FFR/iFR or any QCA-measured stenosis ≥50% in epicardial vessel ≥2mm diameter
  - Lower rates of cath w/o obs CAD associated w better QOL, fewer complications, lower costs

• All primary endpoint events were adjudicated by blinded Clinical Events Committee

• **Statistical analysis**
  - Sample size of 2100 provided ≥90% power to detect a 35% reduction in primary endpoint
  - All comparisons performed as Intention To Treat with time-to-event analysis, using log rank testing. Cox proportional hazards adjusted for age, sex, CAD risk equivalent, and intended test type at randomization

• The statistical team had full access to the complete data base and performed all analyses independently of the trial sponsor
Overall, 92% tested per protocol

Randomized (N= 2103)
(65 NA and European sites; Dec 2018-May 2021)

1:1

Allocation

Precision Strategy (N = 1057)
- Low Risk (21%)
  - No testing (89%)
  - CTA +/- FFRCT (93%)
- Elevated Risk (79%)

Usual Testing (N = 1046)
- Low Risk (21%)
  - Usual test (86%)
  - Usual test (94%)
- Elevated Risk (79%)

Follow Up

Analytic cohort (N=1057)
- Median f-u duration 11.8 months
  - Complete in 96%

Analysis

Analytic cohort (N=1046)
## Baseline Characteristics

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Precision Strategy (N=1057)</th>
<th>Usual Testing (N=1046)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age — yr</td>
<td>58.0 ± 11.5</td>
<td>58.9 ± 11.6</td>
</tr>
<tr>
<td>Women</td>
<td>508 (48%)</td>
<td>539 (52%)</td>
</tr>
<tr>
<td>Racial or ethnic minority group</td>
<td>165 (16%)</td>
<td>171 (16%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Precision Strategy (N=1057)</th>
<th>Usual Testing (N=1046)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥1 major CV risk factor</td>
<td>990 (94%)</td>
<td>985 (94%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>642 (61%)</td>
<td>606 (58%)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>176 (17%)</td>
<td>197 (19%)</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>668 (63%)</td>
<td>681 (65%)</td>
</tr>
<tr>
<td>Family history of premature CAD</td>
<td>404 (38%)</td>
<td>395 (38%)</td>
</tr>
<tr>
<td>Current or past tobacco use</td>
<td>544 (52%)</td>
<td>554 (53%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Risk scores</th>
<th>Precision Strategy (N=1057)</th>
<th>Usual Testing (N=1046)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Updated D-F pretest probability</td>
<td>16.0 (10.0, 26.0)</td>
<td>16.0 (10.0, 26.0)</td>
</tr>
<tr>
<td>ASCVD 10-year</td>
<td>7.92 (3.4, 15.7)</td>
<td>8.22 (3.3, 17.2)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Primary symptom</th>
<th>Precision Strategy (N=1057)</th>
<th>Usual Testing (N=1046)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chest pain</td>
<td>870 (82%)</td>
<td>876 (84%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Anginal type</th>
<th>Precision Strategy (N=1057)</th>
<th>Usual Testing (N=1046)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Typical angina (cardiac)</td>
<td>249 (24%)</td>
<td>257 (25%)</td>
</tr>
</tbody>
</table>
Initial Diagnostic Test Performed

**Precision Strategy**
N=1057

- No Test: 174, 16%
- Coronary CTA: 512, 48%
- CTA + FFR<sub>CT</sub>: 323, 31%
- Direct to ICA: 4, 0%
- Stress cMR: 10, 1%
- Treadmill ECG: 16, 2%
- SPECT/PET: 17, 2%

**Usual Testing**
N=1046

- No Test: 68, 7%
- SPECT / PET: 333, 32%
- Stress Echo: 313, 30%
- Direct to ICA: 101, 10%
- Treadmill ECG: 116, 11%
- Stress cMR: 101, 10%
- Coronary CTA + FFR<sub>CT</sub>: 4, 0%
- Coronary CTA: 10, 1%
Primary Endpoint: Death, MI, or Cath w/o Obstructive CAD

**Unadjusted Hazard Ratio 0.35**
95%CI 0.25-0.50

**Adjusted Hazard Ratio 0.29**
95%CI 0.20-0.41

Win ratio = 2.81 (1.36-6.41)

Median f/u 11.8 mo  
Complete in 96%
## Primary Endpoint Events

<table>
<thead>
<tr>
<th>Event</th>
<th>Precision Strategy (N=1057)</th>
<th>Usual Testing (N=1046)</th>
<th>Adjusted Hazard Ratio (95% CI)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary endpoint composite</td>
<td>44 (4.2%)</td>
<td>118 (11.3%)</td>
<td>0.29 (0.20-0.41)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Death or MI</td>
<td>18 (1.7%)</td>
<td>12 (1.1%)</td>
<td>1.57 (0.76-3.27)</td>
<td></td>
</tr>
<tr>
<td>All cause death</td>
<td>5 (0.5%)</td>
<td>7 (0.7%)</td>
<td>0.74 (0.24-2.35)</td>
<td></td>
</tr>
<tr>
<td>Nonfatal MI</td>
<td>13 (1.2%)</td>
<td>5 (0.5%)</td>
<td>2.67 (0.94-7.52)</td>
<td></td>
</tr>
<tr>
<td>ICA w/o obstructive CAD</td>
<td>27 (2.6%)</td>
<td>107 (10.2%)</td>
<td>0.18 (0.12-0.30)</td>
<td></td>
</tr>
</tbody>
</table>

Notes: Deaths include one participant with a fatal MI. One MI on the day of randomization was determined by CEC to have preceded study entry and was excluded.

There were no death or MI events in the Precision Strategy participants assigned to deferred testing.
## Primary Endpoint: Subgroup Analysis

### Favors Precision Strategy vs. Favors Usual testing

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>PS</th>
<th>UT</th>
<th>Interaction P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td>0.417</td>
</tr>
<tr>
<td>Male</td>
<td>27/549 (5.6%)</td>
<td>60/507 (12.7%)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>17/508 (3.4%)</td>
<td>58/539 (11.8%)</td>
<td></td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td>0.318</td>
</tr>
<tr>
<td>&lt;65</td>
<td>20/737 (2.8%)</td>
<td>60/693 (9.4%)</td>
<td></td>
</tr>
<tr>
<td>≥65</td>
<td>24/320 (8.8%)</td>
<td>58/353 (18.0%)</td>
<td></td>
</tr>
<tr>
<td><strong>Race/Ethnicity</strong></td>
<td></td>
<td></td>
<td>0.954</td>
</tr>
<tr>
<td>White/Non-Hispanic</td>
<td>39/892 (4.8%)</td>
<td>103/875 (12.6%)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>5/165 (3.2%)</td>
<td>15/171 (10.3%)</td>
<td></td>
</tr>
<tr>
<td><strong>Geographic region</strong></td>
<td></td>
<td></td>
<td>0.143</td>
</tr>
<tr>
<td>North America</td>
<td>19/609 (3.2%)</td>
<td>38/596 (7.7%)</td>
<td></td>
</tr>
<tr>
<td>Europe</td>
<td>25/448 (5.6%)</td>
<td>80/450 (18.0%)</td>
<td></td>
</tr>
<tr>
<td><strong>CAD equivalent (diabetes or peripheral arterial disease)</strong></td>
<td></td>
<td></td>
<td>0.690</td>
</tr>
<tr>
<td>Yes</td>
<td>12/226 (5.5%)</td>
<td>37/237 (15.8%)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>32/831 (3.8%)</td>
<td>81/809 (11.2%)</td>
<td></td>
</tr>
<tr>
<td><strong>Primary symptom presentation</strong></td>
<td></td>
<td></td>
<td>0.451</td>
</tr>
<tr>
<td>Typical angina (cardiac)</td>
<td>17/249 (6.9%)</td>
<td>41/257 (16.3%)</td>
<td></td>
</tr>
<tr>
<td>Atypical pain (possible cardiac)</td>
<td>16/600 (2.2%)</td>
<td>66/597 (11.8%)</td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td>4/86 (4.8%)</td>
<td>7/77 (15.5%)</td>
<td></td>
</tr>
<tr>
<td>Non anginal (non cardiac)/other</td>
<td>1/14 (0.6%)</td>
<td>0/7 (0.0%)</td>
<td></td>
</tr>
<tr>
<td><strong>Intended first test is</strong></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Invasive</td>
<td>8/105 (7.7%)</td>
<td>68/105 (66.1%)</td>
<td></td>
</tr>
<tr>
<td>Noninvasive</td>
<td>36/952 (4.2%)</td>
<td>50/941 (6.3%)</td>
<td></td>
</tr>
<tr>
<td><strong>PROMISE Minimal Risk Score</strong></td>
<td></td>
<td></td>
<td>0.648</td>
</tr>
<tr>
<td>Low</td>
<td>4/224 (1.8%)</td>
<td>14/219 (8.0%)</td>
<td></td>
</tr>
<tr>
<td>Elevated + atherosclerosis</td>
<td>40/833 (5.3%)</td>
<td>104/827 (13.2%)</td>
<td></td>
</tr>
<tr>
<td><strong>Diamond and Forrester pre test probability</strong></td>
<td></td>
<td></td>
<td>0.882</td>
</tr>
<tr>
<td>&lt;5% pretest probability</td>
<td>0/63 (0.0%)</td>
<td>1/44 (2.3%)</td>
<td></td>
</tr>
<tr>
<td>5-15%</td>
<td>11/414 (2.8%)</td>
<td>39/411 (10.5%)</td>
<td></td>
</tr>
<tr>
<td>&gt;15%</td>
<td>26/475 (6.1%)</td>
<td>74/483 (16.4%)</td>
<td></td>
</tr>
<tr>
<td><strong>ASCVD 10-year event risk score</strong></td>
<td></td>
<td></td>
<td>0.109</td>
</tr>
<tr>
<td>5-15%</td>
<td>3/356 (0.9%)</td>
<td>25/345 (8.4%)</td>
<td></td>
</tr>
<tr>
<td>&gt;15%</td>
<td>17/374 (4.6%)</td>
<td>32/327 (9.9%)</td>
<td></td>
</tr>
<tr>
<td>&gt;20%</td>
<td>24/327 (8.5%)</td>
<td>61/374 (17.7%)</td>
<td></td>
</tr>
</tbody>
</table>
Secondary Effectiveness Endpoints

**Test performed**
- Precision Strategy: 18.3%
- Usual Testing: 13.3%

**All p < 0.01**

**Diagnostic Catheterization**
- Positive test: 18.3%  13.3%

**Dx Cath and Obstructive CAD**
- Cath without Obs CAD:
  - PS: 20%
  - UT: 60%

**Dx Cath and Yield for Revasc**
- Cath without Revasc:
  - PS: 28%
  - UT: 70%

**Revascularization**
- CABG:
  - PS: 21%
  - UT: 32%

**Bars**
- Precision Strategy
- Usual Testing

**Legend**
- PS: Precision Strategy
- UT: Usual Testing
Secondary Effectiveness Endpoints, continued

- **Lipid-lowering Medication Use (%):**
  - Precision Strategy: 45
  - Usual Testing: 40
  - **P** < 0.001

- **Antiplatelet Medication Use (%):**
  - Precision Strategy: 35
  - Usual Testing: 25
  - **P** < 0.001

- **Anti-hypertensive Medication Use (%):**
  - Precision Strategy: 60
  - Usual Testing: 55
  - **P** = 0.10

- **Frequent Angina (SAQ AF ≤80) (%):**
  - Precision Strategy: 70
  - Usual Testing: 65
  - **P** = 0.24

Baseline, 45 days, 6 months, 12 months
Limitations

- The Precision Strategy care pathway includes several actions reflective of real-world decision-making: risk stratification, deferred testing, and use of cCTA with selective FFR_{CT} as the initial test. The separate effects of each action cannot be determined.

- PRECISE’s pragmatic trial design precludes evaluation of different Usual Testing choices or close monitoring of the trial’s recommendations to use Optimal Medical Treatment.

- PRECISE does not address outcomes beyond the trial duration of 12 months.

- Detailed results of outcomes in low risk participants and costs/resource use will be reported separately.
PRECISE Summary and Conclusion

• PRECISE demonstrates the net clinical effectiveness of the Precision Strategy with a 70% reduction of the composite of death, non-fatal MI or catheterization without obstructive CAD, compared to Usual Testing at 1 year.

• PRECISE addresses critical knowledge gaps in the evaluation of symptomatic, low-intermediate risk patients with suspected CAD, by defining and testing a specific care pathway concordant with Guideline recommendations:
  • Outcomes were improved using deferred testing for quantitively-determined minimal-risk patients and cCTA with selective FFR<sub>CT</sub> in all others.

• The Precision Strategy is a preferred approach in evaluating patients with stable symptoms and suspected coronary artery disease.
THANK YOU to PRECISE Participants, Investigators, Sites
THANK YOU to the PRECISE Team!!

Steering Committee
- Pamela S. Douglas, Chair
- Ori Ben-Yehuda
- Colin Berry
- Robert A. Byrne
- Nick Curzen
- Bernard De Bruyne
- Christopher B. Fordyce
- Michelle Kelsey
- Christopher Kramer
- Jonathon Leipsic
- Daniel Mark
- Sarah Mullen
- Michael Nanna
- Manesh R. Patel
- Campbell Rogers
- Gregg W. Stone
- James E. Udelson
- Robert W. Yeh

Statistical Team
- Hussein Al-Khalidi
- Eric Yow

Operational Leadership
- Aija Caune
- Whitney Huey
- Beth Martinez
- Sarah Mullen

Clinical Events Committee
- Shea E. Hogan, Co-chair
- Bjorn Redfors, Co-chair
- Marc Bonaca
- David J. Engel
- W. Schuyler Jones

QCA Core Lab, CRF
- Ziad A. Ali

Data and Safety Monitoring Board, CRF
- Anthony N. DeMaria, Chair
- Andrew Kahn
- Robert A. Pelberg
- Stuart J. Pocock
- Binita Shah
- Ozgu Melek Issever (non-voting)

Participant Research Operations, DCRI
- Khaula Baloch
- Jennifer Martin
- Betsy O’Neal
- Tina Harding
- Linda Davidson-Ray
- Thomas Redick
- PRO Interviewers
THANK YOU