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ORIGINAL ARTICLE

Economic Outcomes With Precision Diagnostic Testing Versus Usual Testing in Stable Chest Pain: Results From the PRECISE Randomized Trial

Derek S. Chew, MD, MSc; Daniel B. Mark, MD, MPH; Yanhong Li, MD, MS; Michael G. Nanna, MD, MHS; Michelle D. Kelsey, MD; Melanie R. Daniels, BA; Linda Davidson-Ray, MA; Khaula N. Baloch, MPH; Campbell Rogers, MD; Manesh R. Patel, MD; Kevin J. Anstrom, PhD; Nick Curzen, BM, PhD; Sreekanth Vemulapalli, MD; Pamela S. Douglas, MD; on behalf of the PRECISE Investigators

BACKGROUND: The PRECISE (Prospective Randomized Trial of the Optimal Evaluation of Cardiac Symptoms and Revascularization) demonstrated that a precision diagnostic strategy reduced the primary composite of death, nonfatal myocardial infarction, or catheterization without obstructive coronary artery disease by 65% in patients with nonacute chest pain compared with usual testing. Medical cost was a prespecified secondary end point.

METHODS: PRECISE randomized 2103 patients between December 2018 and May 2021 to usual testing or a precision strategy that used deferred testing for the lowest risk patients (20%) and coronary computed tomographic angiography with selective computed tomography–derived fractional flow reserve for the remainder. Resource use consumption data were collected from all study participants and hospital cost data from US participants (n=1125) to estimate total medical costs. The primary and secondary economic outcomes were total costs at 12 months and at 45 days, respectively, from the US health care system perspective. The mean cost differences between the 2 strategies were reported by intention-to-treat.

RESULTS: At 45 days, total costs were similar between the precision strategy and usual testing (mean difference, $182 [95% CI, −$555 to $661]). By 12 months, percutaneous coronary intervention and coronary artery bypass surgery had been performed in 7.2% and 2.0% of precision strategy patients and 3.5% and 1.7% of usual testing patients, respectively. At 1 year, precision strategy costs were $5299 versus $4821 for usual testing (mean difference, $478 [95% CI, −$889 to $1437]; *P*=0.43). Precision care decreased mean per-patient diagnostic cost by 27% and increased mean per-patient revascularization costs by 67%.

CONCLUSIONS: In the PRECISE trial, the precision strategy, a risk-based approach endorsed by current clinical practice guidelines, improved the clinical efficiency of testing and had similar costs to usual testing at 45 days and a nonsignificant $478 cost difference at 1 year.

REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifier: NCT03702244.

Key Words: chest pain ■ coronary artery disease ■ electrocardiography ■ precision medicine ■ prospective studies

See Editorial by Hulten and Di Carli and Article by Mark et al

Correspondence to: Daniel B. Mark, MD, MPH, Duke Clinical Research Institute, P.O. Box 17969, Durham, NC 27715. Email daniel.mark@duke.edu
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WHAT IS KNOWN

- Nonacute chest pain remains one of the most common symptoms causing patients to seek medical care and one of the most challenging for clinicians to assess.
- Two prior randomized trials compared a coronary computed tomographic angiography–based strategy with a usual testing strategy and established the coronary computed tomographic angiography–based approach as a reasonable first test in these patients.
- The PRECISE trial (Prospective Randomized Trial of the Optimal Evaluation of Cardiac Symptoms and Revascularization) adapted the routine coronary computed tomographic angiography strategy by deferring testing for lowest risk subjects and adding selective coronary computed tomographic angiography FFR analysis and found that the new precision strategy reduced the composite of death, nonfatal myocardial infarction, or catheterization without obstructive coronary artery disease by 65%.

WHAT THE STUDY ADDS

- The precision strategy decreased mean per-patient diagnostic cost by 27% and increased mean per-patient revascularization costs by 67%.
- The precision strategy had similar costs to usual testing at 45 days and a nonsignificant $478 cost difference at 1 year.

Nonstandard Abbreviations and Acronyms

CAD	coronary artery disease
cCTA	coronary computed tomographic angiography
DISCHARGE	Diagnostic Imaging Strategies for Patients With Stable Chest Pain and Intermediate Risk of Coronary Artery Disease
FFR_{CT}	computed tomography–derived fractional flow reserve
FORECAST	Fractional Flow Reserve Derived From Computed Tomography Coronary Angiography in the Assessment and Management of Stable Chest Pain
ICA	invasive coronary angiography
ISCHEMIA	International Study of Comparative Health Effectiveness with Medical and Invasive Approaches
PCI	percutaneous coronary intervention
PLATFORM	Prospective Longitudinal Trial of FFRCT: Outcome and Resource Impacts
PRECISE	Prospective Randomized Trial of the Optimal Evaluation of Cardiac Symptoms and Revascularization
PROMISE	Prospective Multicenter Imaging Study for the Evaluation of Chest Pain
SCOT-HEART	Scottish Computed Tomography of the Heart Trial
TARGET	Effect of On-Site CT-Derived Fractional Flow Reserve on the Management of Decision Making for Patients With Stable Chest Pain

Nonacute chest pain remains one of the most common symptoms prompting patients to seek medical care and one of the most challenging for clinicians to assess. Many patients will ultimately have a benign explanation for their symptoms, but an important minority will have prognostically significant coronary artery disease (CAD). For each patient, the clinician must decide whether diagnostic testing is indicated and, if so, which initial test to obtain. The first large outcome-based clinical trial of this question, the PROMISE (Prospective Multicenter Imaging Study for the Evaluation of Chest Pain), found that a functional testing–based strategy and a coronary computed tomographic angiography (cCTA)–based strategy provided equivalent short- and medium-term clinical outcomes for these patients.[1] These results were largely concordant with the SCOT-HEART (Scottish Computed Tomography of the Heart Trial), which compared a cCTA strategy to a stress testing strategy that primarily used stress electrocardiography without imaging.[2] These 2 trials established cCTA as a viable first-line test for nonacute chest pain that could be used instead of functional testing. However, they raised new questions about the efficiency of the strategies used, particularly related to the need for any testing in low-risk patients and the need for confirmatory invasive coronary angiography (ICA) in patients with ambiguous cCTA findings, about 30% of whom were found not to have obstructive CAD.[2]

The PRECISE clinical trial (Prospective Randomized Trial of the Optimal Evaluation of Cardiac Symptoms and Revascularization) was designed specifically to address these efficiency of care issues raised by PROMISE and SCOT-HEART.[3] The key innovation relative to PROMISE and SCOT-HEART was a novel precision medicine diagnostic testing strategy that matched the intensity of diagnostic evaluation with the risk level of each patient to improve the efficient identification of patients with actionable CAD while minimizing potentially harmful overtesting. The primary clinical outcomes of PRECISE have recently been reported.[4] Economic efficiency, assessed in terms of resource use and medical costs, was a major prespecified secondary outcome of the trial.[3]

METHODS

There are no plans to make a deidentified data set publicly available at present.

Overview of PRECISE Design and Primary Clinical Results

Details of the PRECISE trial rationale and design have been published.[3] Between December 3, 2018, and May 18, 2021, the trial randomized 2103 patients (53.5% United States) with stable chest pain and a clinical recommendation to test for suspected CAD to either an investigational precision diagnostic testing strategy or a usual diagnostic testing strategy. Patients randomized to the precision strategy underwent a risk assessment using the PROMISE Minimal Risk Tool,[5] and the 20% at lowest risk were assigned to an initial strategy of guideline-recommended care with deferred testing. Patients randomized to the precision strategy who had elevated risk or known nonobstructive plaque were assigned to undergo diagnostic testing using cCTA with selective use of computed tomography–derived fractional flow reserve (FFR_{CT}). Patients randomized to the usual testing arm underwent functional testing or went directly to catheterization. The trial's primary end point was a composite of major adverse cardiovascular events (all-cause death and nonfatal myocardial infarction) or invasive cardiac catheterization free of evidence of significant CAD (coronary stenosis ≥50%, FFR ≤0.80, or other actionable cardiac pathology).

The PRECISE trial cohort had a mean age of 58.4 years, 50% were female, and 16.0% were from an underrepresented racial or ethnic group.[4] Chest pain was the primary symptom for 83%, while 10% presented with dyspnea. The mean 10-year predicted risk of cardiovascular events using the 2013 American College of Cardiology/American Heart Association pooled cohort risk calculator was 12%. As reported previously, the primary end point occurred in 4.2% of the precision strategy participants and 11.3% of the usual testing strategy (hazard ratio, 0.35 [95% CI, 0.25–0.50]).[4] The end point of ICA without obstructive disease occurred in 2.6% of the precision strategy patients and 10.2% of the usual testing patients. Death occurred in 0.5% of precision strategy and 0.7% of usual testing patients. Nonfatal myocardial infarction occurred in 1.2% of precision strategy patients and 0.5% of usual testing patients. The effect size estimate for the death/myocardial infarction secondary end point had low precision, and the rates were statistically indistinguishable (hazard ratio, 1.52 [95% CI, 0.73–3.15]). About two-thirds of patients had frequent angina at baseline as assessed by the Seattle Angina Questionnaire. Chest pain/angina symptoms improved in both groups from baseline to a similar extent. The proportion of patients with frequent angina at 1 year was 15.8% for the precision strategy and 16.1% for usual testing.[4]

All patients provided written informed consent, and study protocol approval was obtained from each site or a central institutional review board. The trial work was funded by an investigator-initiated research grant from HeartFlow, Inc, to the Duke Clinical Research Institute.

Overview of the PRECISE Economic Study Design

Resource use and total medical costs were prespecified secondary end points of PRECISE.[3] The PRECISE economic study analysis involved 4 major components: (1) comparison of empirical within-trial resource use patterns between the 2 treatment arms; (2) estimation and comparison of within-trial medical costs between the 2 treatment arms; (3) comparison of within-trial resource use and medical cost data for key clinical subgroups; and (4) sensitivity analyses.

Costs were discounted at 3%. Hospital-based costs were adjusted to 2022 US dollars using the Centers for Medicare & Medicaid Services inpatient market basket update.[6] The US health care system perspective was used for this study.

Data Collection

Medical Resource Use Data

Participants had protocol-specified follow-up contacts at 45 days, 6 months, and 12 months. Follow-up at 45 days was done during a clinic visit by the sites. Follow-up outside the United States at 6 and 12 months was done via telephone contact by the sites. Follow-up in the United States at 6 and 12 months was done centrally by the Duke Clinical Research Institute Patient Reported Outcomes group via telephone. Health care resource use data were collected on the clinical trial electronic case report form and included hospitalizations (including length of stay and reason for admission), noninvasive diagnostic testing (both protocol and nonprotocol), major cardiac diagnostic tests, major cardiac therapeutic procedures, cardiac disease–related complications, and relevant medication use.

Bill Collection for Hospital-Based Care

For US participants, billing data for hospital admissions, emergency department visits, and same-day surgeries/major procedures reported by participants during the study follow-up were collected by Duke Clinical Research Institute Patient Reported Outcomes group personnel. The UB04, itemized bill, and summary ledger were requested for all hospitalizations. From the UB04 forms, charges by revenue center were extracted for conversion to costs using cost-center-level cost-to-charge ratios.[7]

Physician and Outpatient Cost Data

Physician service costs for inpatient care were estimated as a percentage of associated hospital costs based on previous work estimating this relationship.[8]

Our base-case analysis used a weighted average reimbursement for office- or hospital-based outpatient cardiac testing derived from reported 2019 use proportions.[9] Sensitivity analyses examined the alternatives of all office-based or all hospital–based testing reimbursement. Hospital-based outpatient testing costs were based on Medicare hospital outpatient prospective payment system reimbursement rates, with professional fees assigned using the Medicare Physician Fee Schedule rates. Office-based test costs were based on the technical and professional components of the Medicare Physician Fee Schedule, which were available online by current procedural terminology/health care common procedure coding system code. The Centers for Medicare & Medicaid Services price for FFR_{CT} ($950 in Medicare hospital outpatient prospective payment system and $930 in Medicare Physician Fee Schedule) was used for the base-case analysis, with sensitivity analysis using the HeartFlow published price ($1100), as well as the range of hospital payments requested from the Centers for Medicare & Medicaid Services.

Cost Estimation Methods

The cost of inpatient US hospital-based care was estimated by applying hospital-specific, revenue center-level cost-to-charge ratios to empirical billing data collected during the study. This approach, which has been used successfully in previous clinical trials including the PROMISE trial,[10] takes advantage of the objective, detailed account in hospital bills of services provided to participants and recalibrates hospital charges to more closely reflect costs. For participants without billing data, we imputed costs using a generalized linear model developed using study data.[11] In this model, the dependent variable was defined as total cost, including a percentage adjustment to account for inpatient professional fees. Independent variables included demographics (age, sex, and ethnicity), hospital length of stay, diagnoses, and high-cost cardiovascular procedures (coronary artery bypass grafting surgery, percutaneous coronary intervention (PCI), catheterization, and ablation), and hospital encounter type. Coefficients for model parameters were estimated from study data of participants with complete costs and then used to predict costs for participants without billing information. Hospital bills were available for 243 US patients (353 hospital encounters). Mean hospital bill costs were $11 603, and model-estimated costs were $11 571 for the 353 hospital encounters with bills.

Costs for outpatient testing and procedures were estimated by weighting resource use counts recorded in the electronic case report form with the Centers for Medicare & Medicaid Services reimbursement rates. Cost weights for the base case used a weighted mix of 2022 Medicare hospital outpatient prospective payment system reimbursement, using the mix ratios reported in Reeves.[9]

Outpatient medication costs were estimated by applying unit costs by medication type or class, based on the National Average Drug Acquisition Cost, to medication use recorded in the electronic case report form.[12]

Data Analyses

All primary analyses were performed with diagnostic strategy groups defined by the principle of intention-to-treat (as randomized). Descriptive statistics include percentages for discrete variables and medians with 25th and 75th percentiles and means with standard deviations for continuous variables.

Resource use rates and costs were compared between randomized diagnostic testing strategy arms by intention-to-treat at 45 days and at 12 months. Testing and procedure rates are presented as percent of patients (with ≥1 test/procedure) in the main article and mean number of each test/procedure per patient (with distributional parameters) in the supplement.

Comparisons between the 2 testing strategies were made using a normal approximation, with standard errors estimated using the bootstrap approach. Bootstrapping was performed with replacement using 1000 repetitions, with percentile-based CIs reported. The primary cost comparison was made for cumulative total costs at 12 months. The primary outcome was the mean cost difference between the 2 arms with 95% CIs. No adjustment in significance levels for multiple comparisons was used.

For illustrative purposes, costs were partitioned into 3 general categories: diagnostic, revascularization-related, and other therapeutic/hospitalization-related. In PRECISE, all PCIs were performed following catheterization in inpatient settings except for 1 PCI with coronary angiography performed at an outpatient setting. For inpatient PCIs, the cost for both the preceding coronary angiography and PCI was included in the total cost for the same hospitalization. Where both procedures were part of the same hospital bill, the granularity of the billing data was insufficient to allow us to reliably separate the diagnostic components. In such cases, the total procedure cost was assigned to the revascularization category with no catheterization cost counted in the diagnostic category.

To assess the precision/uncertainty in our total cost difference estimates, we used bootstrap methods to plot the proportion of 1000 replicates with a difference in total costs greater than arbitrary thresholds of interest (such as $0, $500, or $1000).

RESULTS

Diagnostic Testing

At 45 days, 41.0% of the precision strategy patients had received a cCTA alone, 27.1% had received a cCTA with FFR_{CT}, 6.6% had an ICA, and 28.8% had received no diagnostic test (Figure 1A). At that same follow-up point, 28.8% of the usual testing strategy had received a single-photon emission computed tomography/positron emission tomography stress test, 23.6% had a stress echocardiogram, 10.2% had an exercise ECG, 7.0% had a stress cardiovascular magnetic resonance imaging, 11.7% had ICA, and 22.7% had no diagnostic test. At 12 months, the patterns were similar (Figure 1B): CTA with or without FFR_{CT} was done for 79.5% of precision strategy patients, while 62.2% of usual testing strategy had received stress echo or stress single-photon emission computed tomography/positron emission tomography imaging. ICA had been performed in 12.8% of the precision strategy arm and 16.8% of the usual testing arm, while no test had been done for 16.7% of the precision strategy patients and 7.6% of the usual testing patients. Testing rates expressed as mean values per patient with mean differences between strategy arms are shown in Table S1.

Revascularization Procedures

PCI was done in 3.9% of precision strategy patients at 45 days versus 2.0% of usual testing patients (Figure 2). At 1 year, the rates had increased to 7.2% for precision strategy patients and 3.5% for usual testing. Of the 120 total PCIs done in the PRECISE cohort within 12 months, 112 were first PCIs, while 8 were second PCIs (3 in precision strategy and 5 in usual testing).

In the precision strategy arm, 9 PCIs were unplanned (6 within 45 days and 3 after 45 days), while, in the usual testing arm, 7 PCIs were unplanned (4 within 45 days and 3 after 45 days). Each arm had one 2nd PCI that was unplanned, in both cases after 45 days.

Rates of coronary artery bypass grafting surgery were low and similar in the 2 arms (Figure 2).

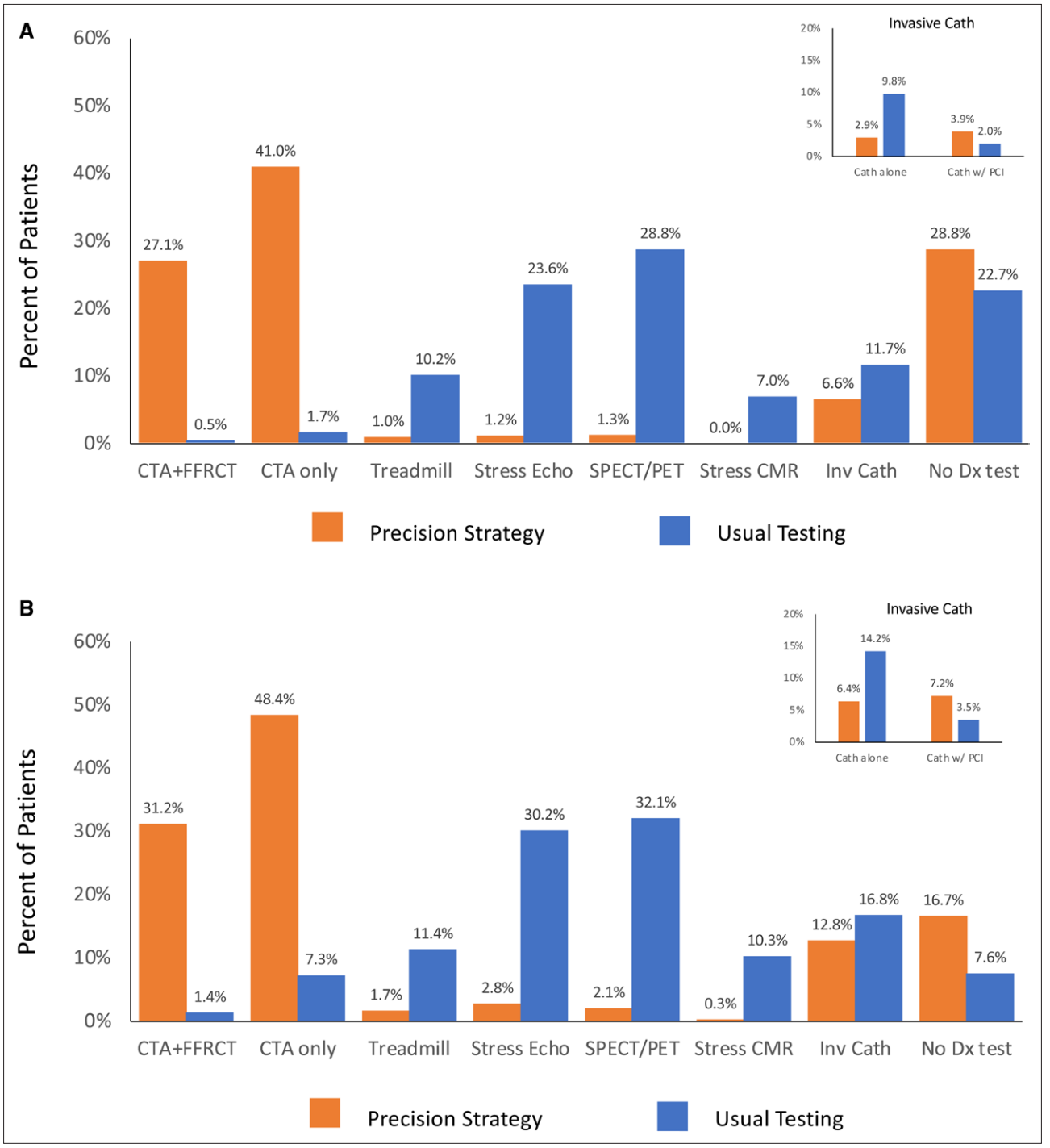

Figure 1. Percent of patients receiving diagnostic testing by technology.
Panel **A** represents testing done by day 45. Panel **B** represents testing done by 1 year. Cath indicates coronary catheterization; CMR, cardiovascular magnetic resonance imaging; CTA, computed tomographic angiography; Dx, diagnostic; Echo, echocardiography; FFR_{CT}, compute tomography fractional flow reserve; Inv Cath, Invasive catheterization; PCI, percutaneous coronary intervention; PET, positron emission tomography; and SPECT, single-photon emission computed tomography.

Hospital and Emergency Department Care

At 45 days, 9.8% of the precision strategy and 14.6% of the usual testing strategy patients had a hospitalization or emergency department visit or same-day hospital stay for an invasive cardiovascular procedure (Table S2). By 1 year, the rates were 24.7% for the precision strategy group and 28.2% for usual testing.

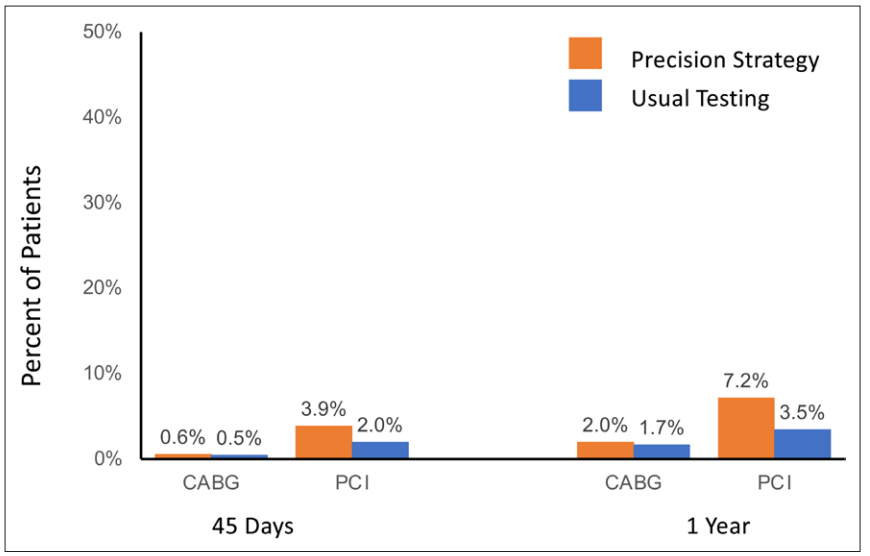

Figure 2. Percent of patients receiving revascularization procedures at 45 days and 1 year.
CABG indicates coronary artery bypass grafting surgery; and PCI, percutaneous coronary intervention.

Medical Costs

Of a total of 805 hospitalizations, 381 were incurred by US patients. Hospital bills were obtained from 353 (93%) of these hospitalizations and were used in the cost analysis.

Mean diagnostic costs at 45 days were $648 for the precision strategy and $897 for the usual testing strategy (mean difference, −$249 [95% CI, −$374 to −$111]; Figure 3; Table). At 1 year, the corresponding figures were $912 and $1247 with a mean difference of −$335 (95% CI, −$448 to −$125). Mean revascularization costs at 45 days were $1079 for the precision strategy and $506 for the usual testing strategy with a mean difference of $573 (95% CI, $15–$863; Figure 3; Table). The corresponding 1-year costs were $2380 and $1425, respectively, with a mean difference of $955 (95% CI, −$126 to $1457). Other costs involving therapies and hospitalizations were similar between the 2 strategies (Figure 3; Table). Hospital-based costs are shown in Table S3.

Total costs at 45 days were $1978 for the precision strategy and $1796 for usual testing (mean difference, $182 [95% CI, −$555 to $661]; Table). At 1 year, the corresponding costs were $5299 and $4821, respectively, with a mean difference of $478 (95% CI, −$889 to $1437).

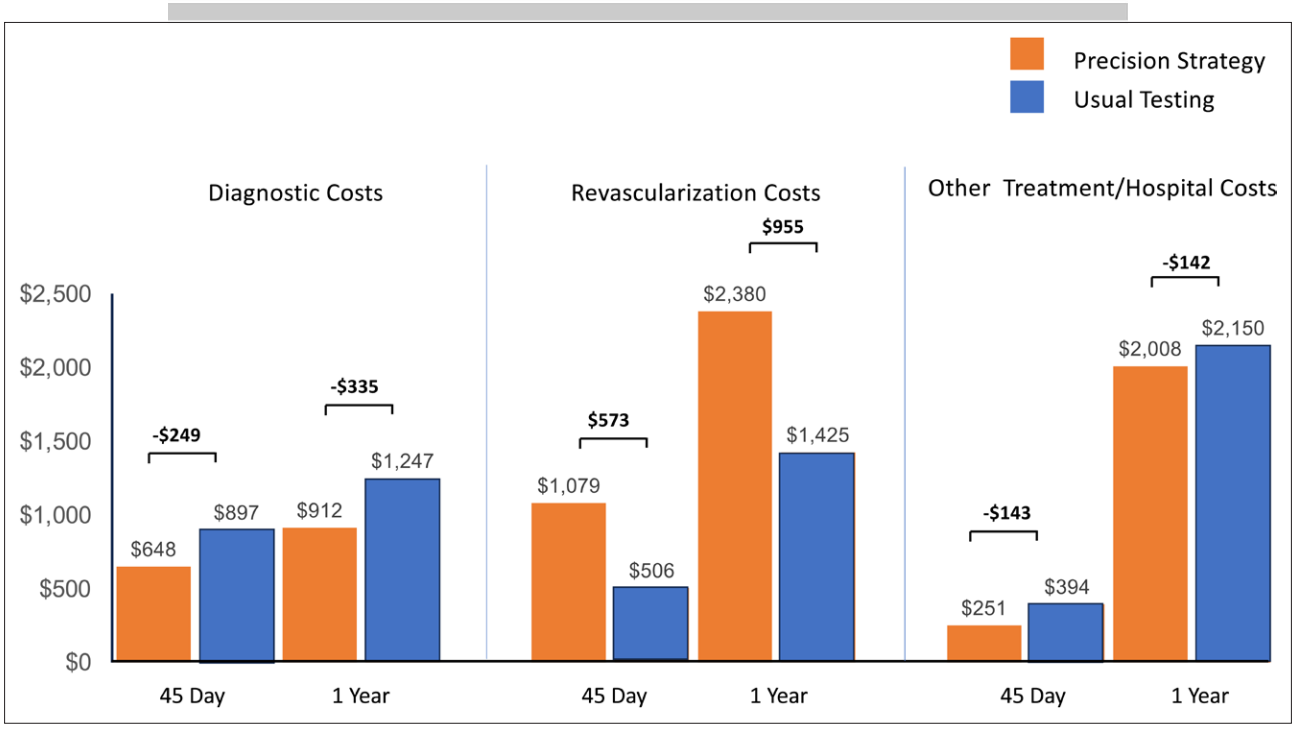

Figure 3. Mean costs categorized by diagnostic, revascularization, and other treatment/hospital costs at 45 days and at 1 year.

Table. Total Therapeutic and Diagnostic Costs* by Intention-to-Treat

Mean (SD)	Precision strategy (n=1057)	Usual testing (n=1046)	Difference (mean, PS-UT)
Within 45 d	1978 (7233)	1796 (6228)	182 (−555 to 661)
Diagnostic	648 (1185)	897 (1279)	−249 (−374 to −111)
Therapeutic	1330 (6989)	900 (6069)	430 (−266 to 857)
Revascularization	1079 (6332)	506 (4065)	573 (15 to 863)
Other Rx/ hospitalization	251 (1899)	394 (4330)	−143 (−471 to 157)
Beyond 45 d	3321 (11 042)	3025 (10 716)	296 (−755 to 1179)
Diagnostic	264 (1081)	350 (1183)	−86 (−161 to 72)
Therapeutic	3058 (10 748)	2675 (10 524)	383 (−694 to 1217)
Revascularization	1301 (7294)	920 (6114)	381 (−415 to 913)
Other Rx/ hospitalization	1756 (7370)	1756 (8105)	0 (−629 to 703)
1 y	5299 (13 247)	4821 (12 875)	478 (−889 to 1437)
Diagnostic	912 (1608)	1247 (1641)	−335 (−448 to −125)
Therapeutic	4388 (12 781)	3575 (12 529)	813 (−577 to 1629)
Revascularization	2380 (9513)	1425 (7463)	955 (−126 to 1457)
Other Rx/ hospitalization	2008 (7841)	2150 (9702)	−142 (−845 to 669)

PS indicates precision strategy; Rx, treatment; and UT, usual testing.
*Costs adjusted to 2022 US dollars.

Uncertainty assessed with bootstrap replications (with replacement) showed that 32% of replicates had a 12-month total cost difference (precision strategy arm minus usual testing arm) ≤$0, 65% had a cost difference ≤$500, and 89% had a cost difference ≤$1000 (Figure 4).

Subgroup Analyses

Patients designated as minimal risk with the PROMISE Minimal Risk Score (n=422) had a mean 12-month cost difference (precision strategy minus usual testing) of −$163 (95% CI, −$1175 to $988), while the difference for the nonminimal-risk patients (n=1676) was $656 (95% CI, −$1011 to $1787; Figure 5; Table S4). Subgrouping by geographic region demonstrated similar overlapping distributions of estimated cost difference by randomized group. Patients aged <65 years (n=1430) had a mean $1041 higher 12-month cost with the precision strategy (95% CI, −$233 to $2048), while patients aged≥65 years (n=673) had a $346 lower cost with the precision strategy (95% CI, −$3278 to $2107). Men (n=1056, 50%) had a $1678 higher 1-year cost with the precision strategy (95% CI, −$296 to $3204), while women (n=1047, 50%) had an $850 lower cost (95% CI, −$2450 to $525; Table S4). White non-Hispanic patients (n=1767, 84%) had an $813 (95% CI, −$664 to $1968) higher 1-year cost with the precision strategy, while racial or ethnic minority patients (n=336, 16%) had a $1378 (95% CI, −$4453 to $470) lower cost with the precision strategy (Table S4).

In patients for whom the intended first test was prespecified by their clinician as invasive (n=210), randomization to the precision strategy was associated with a mean $5684 lower 12-month cost (95% CI, −$12 319 to −$327), while those whose initial test designation was noninvasive (n=1893), and the precision strategy mean 12-month costs were $1169 higher than usual testing (95% CI, −$46 to $2134). Partitioning these costs into diagnostic/therapeutic illustrative categories (Table S5) shows that for the planned noninvasive testing subgroup, diagnostic cost differences between the 2 arms were small, and the net 1-year cost difference came primarily from incremental revascularization costs ($790 in the first 45 days and $596 additional out to 1 year). In the much smaller subgroup with planned initial invasive testing, both diagnostic and revascularization components contributed to the net $5684 higher costs for usual testing at 1 year.

Sensitivity Analyses

The base-case cost comparison was a weighted average of 2 methods of assigning costs to testing and outpatient care using Medicare reimbursements, hospital-based, and free-standing office-based. When using exclusively the hospital-based costing weights, the total cost difference at 12 months was $328 (95% CI, −$1036 to $1291). Using exclusively the office-based costing weights, the 12-month total cost difference was $658 (95% CI, −$710 to $1611; Table S6).

To examine the effects of the cost of FFR_{CT} analysis of the cCTA images, we reduced the base-case cost weight on our results by 25%, 50%, and 100%. With a 25% reduction, the mean cost difference was $404, with a 50% reduction, it was $329. If we assigned the FFR_{CT} analysis no separate cost, the mean 12-month cost difference was $181.

DISCUSSION

In this prospective economic analysis of the PRECISE trial, our primary finding was that the improved clinical efficiency of the precision strategy was achieved at a total cost similar to that of the usual testing strategy. To understand this result, 3 additional points from the analysis are particularly helpful. First, the precision strategy reduced mean per-patient 12-month diagnostic

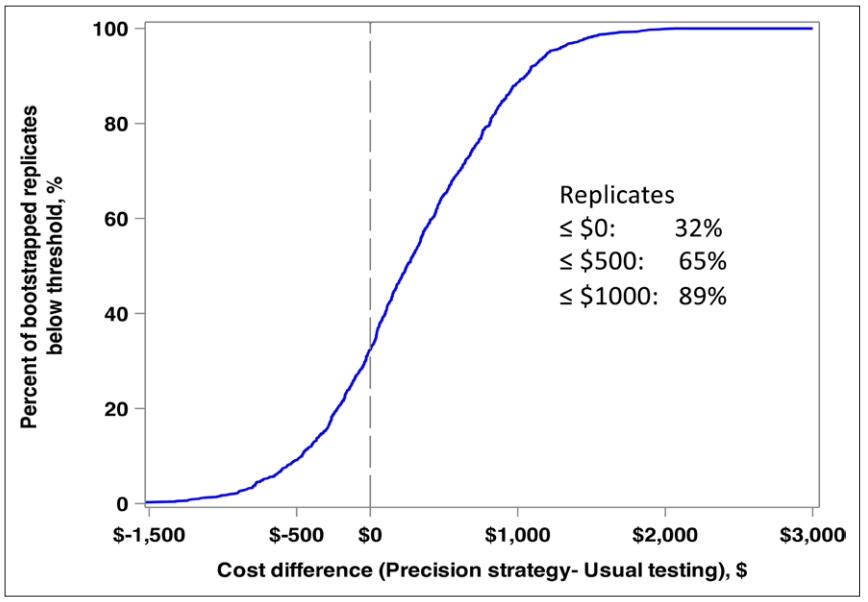

Figure 4. Percent of 1000 bootstrapped replicates below various thresholds.

testing costs by 27% relative to usual testing. This was achieved primarily by testing fewer patients and reducing the use of ICA, particularly ICA procedures not leading to revascularization. Second, the precision strategy increased mean 12-month per-patient revascularization costs by 67% due to a doubling in the 12-month rate of PCI use (from 3.5% in the usual testing arm to 7.2% in the precision strategy arm). The mean 12-month total cost difference of $478 in the base-case analysis reflects the blended average effect of these 2 patterns. Finally, our results were relatively robust to variations in cost weights used and to clinical and regional subgroup variation in the trial cohort. However, the clinician's prespecified intended first test (invasive versus functional) if

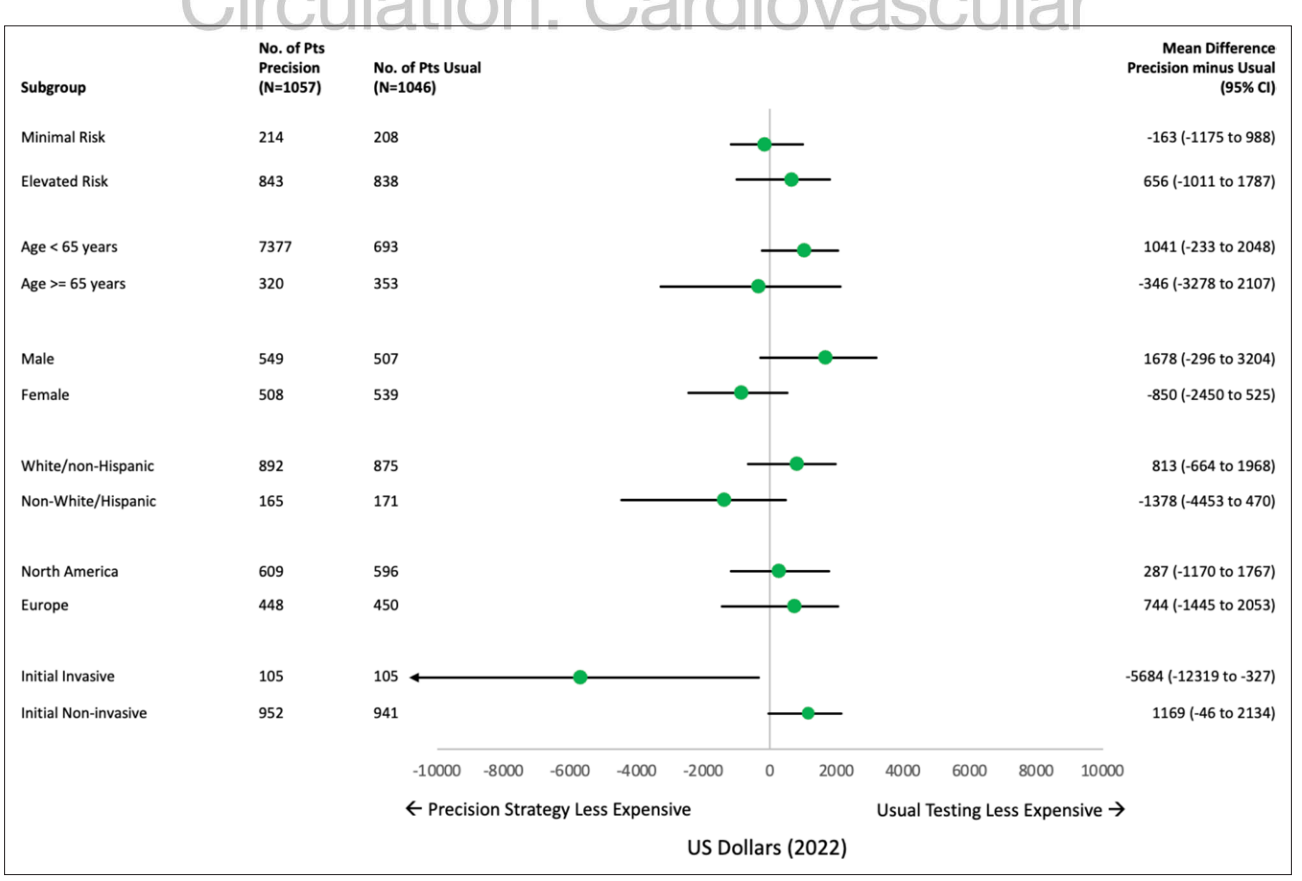

Figure 5. Total 1-year costs (2022 US dollars) by subgroup.

randomized to usual testing did identify heterogeneous resource use and cost patterns, as suggested by prior work in this area.[13–15]

The precision strategy added 2 key new elements to the routine cCTA strategy tested in PROMISE and SCOT-HEART: (1) deferred testing in minimal-risk patients and (2) selective use of cCTA-derived fractional flow reserve (FFR_{CT}) as a method for clarifying the significance of intermediate lesions on cCTA that might otherwise all require confirmatory ICA. PRECISE recently reported that this modified cCTA–based strategy improved the clinical efficiency of care with no adverse effects on safety relative to usual functional testing strategies.[4] Economic analysis and comparison of these strategies were a major secondary objective of the PRECISE research program.[3]

Interpretation of a medical cost analysis where total costs for the strategies being compared are numerically similar can be challenging.[10] Statistics is generally focused on testing whether things being compared are sufficiently different, but the absence of a statistically significant difference does not automatically default to not different. In addition, *P* values are sensitive to sample size (with a sufficiently large sample, almost any nonzero difference can be statistically significant) and to the underlying variability at the study cohort level of the outcomes being compared.[16] Thus, the assessment of similar costs must also include an assessment of plausibility, of whether there are coherent changes in the patterns of care that quantitatively account for the observed differences in costs. In PRECISE, the mean 12-month cost difference can be understood as the weighted average of 2 separate (but related) cost streams: diagnostic testing and coronary revascularization. On the diagnostic side, at 12 months, 16.7% of precision strategy patients had received no diagnostic test compared with 7.6% of usual testing patients, and this difference, together with the differences in the cost weights for the mix of noninvasive diagnostic tests used, accounts for about 75% of the 12-month diagnostic testing mean diagnostic cost reduction of $335, with much of the remainder related to the lower use of diagnostic ICA not immediately preceding PCI.

In contrast, the precision strategy doubled the use of PCI from 3.5% in the usual testing arm to 7.2% in the precision strategy arm, with extra procedures and associated medical costs at 12 months of $995. In most previous trials, the use of a cCTA-based diagnostic strategy has been associated with a small but fairly consistent increase in PCI use. In PROMISE, coronary revascularization was used in 6% of the cCTA strategy and 3% of the functional testing strategy.[10] In the SCOT-HEART trial, PCI was used in 8.9% of cCTA patients versus 7.7% of standard care patients.[2] In the FORECAST trial (Fractional Flow Reserve Derived From Computed Tomography Coronary Angiography in the Assessment and Management of Stable Chest Pain), the rates of PCI were 11% in the cCTA arm and 10% in the standard care arm. One unique feature of FORECAST is that 63% of the standard group patients had cCTA as their initial test.[14] In the DISCHARGE trial (Diagnostic Imaging Strategies for Patients With Stable Chest Pain and Intermediate Risk of Coronary Artery Disease), a randomized comparison of cCTA versus routine ICA in patients with stable chest pain found that cCTA had a lower rate of PCI than ICA (10.8% versus 14.4%).[17] In the TARGET trial (Effect of On-Site CT-Derived Fractional Flow Reserve on the Management of Decision Making for Patients With Stable Chest Pain), patients with stable chest pain and an intermediate stenosis on cCTA were randomized to further analysis with FFR_{CT} versus usual care.[18] The cCTA-FFR_{CT} group had a higher 90-day rate of revascularization than standard care (49.7% versus 42.8%) with a similar difference at 1 year.[18] Taken together, these trials support a small but relatively consistent effect of cCTA use to lead to slightly more use of PCI compared with usual care/usual testing strategies but a lower rate compared with routine ICA as the initial test.

As shown in Figure 3, about half of the extra revascularization-associated costs in the precision strategy arm occurred in the first 45 days of trial follow-up, while the other half occurred between 45 days and 12 months. If additional costs associated with revascularization were to continue accruing for the precision strategy patients after 12 months, our cost comparison could represent an underestimate of the actual long-term difference. Although PRECISE did not collect data after 12 months, both PROMISE and SCOT-HEART provide long-term results that are relevant to this issue. In PROMISE, year 2 costs were low, and the difference between the anatomic/cCTA arm and the functional testing arm was $26. Revascularization costs in years 2 and 3 were almost identical in the 2 arms.[10] SCOT-HEART 5-year results showed similar cumulative rates of revascularization: 13.5% in the cCTA arm and 12.9% in the standard care arm.[19] The PCI rates were 10.6% and 10.2%, respectively. Using a 12-month landmark analysis, SCOT-HEART found that after 12 months, the cCTA arm actually had a lower rate of both ICA and revascularization relative to standard care. In addition, the revascularization procedures done within the first year were done largely before any clinical events had occurred, while the revascularization procedures done after the first year were often in response to an acute coronary event.[20] These data provide reasonable reassurance that the 12-month PRECISE cost comparison is not underestimating the long-term incremental cost of the precision strategy due to unaccounted late revascularization procedures.

A Markov microsimulation model based on patient-level data from the PROMISE trial found that over

a lifetime horizon, the cCTA strategy improved life expectancy by 6 months and reduced late ICA and revascularization procedures after 5 years.[21] These results were driven primarily by assumptions of long-term benefits associated with increased statin use observed in the cCTA arm of PROMISE. Compared with functional testing over the lifetime horizon, the model estimated that a strategy of cCTA in low-risk stable patients with chest pain would be economically dominant (increased quality-adjusted life years and lower cost).

Increasing the rate of PCI in stable patients with chest pain based primarily on anatomic severity supplemented by evidence of ischemic physiology might be regarded as an undesirable feature of a diagnostic strategy, given that PCI in stable CAD has not proven clearly prognostically beneficial. However, the large trials comparing PCI with medical therapy have actually compared a routine invasive strategy (with about 90% receiving PCI in the ISCHEMIA trial [International Study of Comparative Health Effectiveness with Medical and Invasive Approaches] invasive arm) with a selective invasive strategy (with about 30% receiving PCI in the ISCHEMIA trial conservative arm).[22] Thus, every large trial testing the prognostic effects of PCI has assumed that some moderate rate of PCI is necessary even with a conservative strategy centered on the use of prognostically active medical therapies. Patients in PRECISE who have both active symptoms and evidence on cCTA of obstructive CAD with ischemic physiology may, in fact, represent the appropriate group to receive PCI for symptom management in the context of a conservative management strategy.[20,23]

The differential effects of the physician's initial anticipated management strategy (invasive versus noninvasive) on the cost differences between a cCTA strategy and a usual testing (functional) strategy have been previously observed. In the PLATFORM study (Prospective Longitudinal Trial of FFR_{CT}: Outcome and Resource Impacts), among patients in the invasive testing stratum, a cCTA with selective FFR_{CT} (used in 61%) led to ICA in 42%, a strategy lowered costs by 32% ($3391 absolute difference) relative to usual testing (100% ICA), with cost differences driven primarily by the extra costs of ICA and follow-up hospital-based care.[13] Coronary revascularization rates were similar: 28% in the cCTA arm and 32% in the usual care arm with a 90-day mean cost difference of $707. In the noninvasive testing strata of PLATFORM, the cCTA arm 90-day total costs were $542 higher with $362 attributable to more revascularization (10% in the cCTA arm versus 5% in the usual care arm). In the FORECAST trial US cost analysis, for the planned invasive stratum, assignment to the experimental cCTA with provisional FFR_{CT} arm was associated with a $547 lower mean cost at 9 months, equivalent costs in the planned stress test stratum (mean $65 lower costs for cCTA arm), and $627 higher costs in the planned cCTA stratum.[15]

Limitations

Several caveats should be considered in the interpretation of our study. First, we applied US cost weights to the patients enrolled outside the United States. Our objective was to compare costs from the US health care system perspective. Although there was relatively little heterogeneity between regions in the 12-month cost difference estimates (Figure 5), samples of patients from other regions or different mixtures of component countries from PRECISE might display larger differences. Second, moderate variations in the rates of no initial testing and initial testing with ICA between the 2 arms from the rates in PRECISE would likely alter the mean cost difference estimates. Third, the partitioning of costs into categories of diagnostic- and revascularization-related provides estimates that depend on the granularity of the available cost and resource use data and represents an approximation provided primarily for illustrative purposes. Fourth, as noted earlier, the small differences in the use of PCI observed in PRECISE could be interpreted either as increased appropriate care or as increased unnecessary revascularization. Given the small absolute difference in PCI use in the 2 arms, empirical PRECISE data are insufficient in terms of both sample size and length of follow-up to have any expectation of providing support for either perspective. Fifth, the precision strategy deferred testing for those classified as minimal risk by the PROMISE Minimal Risk Score. A similar strategy of deferred testing for minimal-risk subjects is also possible as part of usual testing but was not included in the PRECISE design. Consequently, the clinical care effects and outcomes of modifying the usual testing strategy in that way cannot be derived from the trial data. Finally, the PRECISE trial results are most relevant to eligible stable patients with chest pain appropriate for elective diagnostic testing. The trial is not applicable to patients with high-risk features including severe, progressive, or unstable symptoms

Conclusions

In summary, we found that the precision strategy, a risk-based approach endorsed by current American College of Cardiology/American Heart Association clinical practice guidelines, had similar costs to usual testing at 45 days and a nonsignificant $478 cost difference at 1 year in the PRECISE trial. The precision strategy improved the clinical efficiency of testing for stable symptomatic patients with suspected CAD in PRECISE with a small increase in the use of percutaneous revascularization, little net effect on medical costs, and no significant

differences in major clinical outcomes in the year following evaluation.

ARTICLE INFORMATION

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Affiliations

Libin Cardiovascular Institute and O'Brien Institute for Public Health, University of Calgary, Calgary, Canada (D.S.C.). Duke Clinical Research Institute, Duke University, Durham, NC (D.B.M., Y.L., M.D.K., M.R.D., L.D.-R., K.N.B., M.R.P., S.V., P.S.D.). Division of Cardiology, Duke University Medical Center, Durham, NC (D.B.M., M.D.K., M.R.P., S.V., P.S.D.). Section of Cardiovascular Medicine, Yale University School of Medicine, New Haven, CT (M.G.N.). HeartFlow, Inc, Mountain View, CA (C.R.). Gillings School of Global Public Health, University of North Carolina, Chapel Hill (K.J.A.). Faculty of Medicine, University of Southampton, Cardiothoracic Unit, University Hospital Southampton, United Kingdom (N.C.).

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Supplemental Material

Tables S1–S6

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