ORIGINAL RESEARCH

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Economic Outcomes With Anatomical Versus Functional Diagnostic Testing for Coronary Artery Disease

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Background: PROMISE (PROspective Multicenter Imaging Study for Evaluation of Chest Pain) found that initial use of at least 64-slice multidetector computed tomography angiography (CTA) versus functional diagnostic testing strategies did not improve clinical outcomes in stable symptomatic patients with suspected coronary artery disease (CAD) requiring noninvasive testing.

Objective: To conduct an economic analysis for PROMISE (a major secondary aim of the study).

Design: Prospective economic study from the U.S. perspective. Comparisons were made according to the intention-to-treat principle, and CIs were calculated using bootstrap methods. (ClinicalTrials.gov: NCT01174550)

Setting: 190 U.S. centers.

Patients: 9649 U.S. patients enrolled in PROMISE between July 2010 and September 2013. Median follow-up was 25 months.

Measurements: Technical costs of the initial (outpatient) testing strategy were estimated from Premier Research Database data. Hospital-based costs were estimated using hospital bills and Medicare cost–charge ratios. Physician fees were taken from the Medicare Physician Fee Schedule. Costs were expressed in 2014 U.S. dollars, discounted at 3% annually, and estimated out to 3 years using inverse probability weighting methods.

Results: The mean initial testing costs were $174 for exercise electrocardiography; $404 for CTA; $501 to $514 for pharmacologic and exercise stress echocardiography, respectively; and $946 to $1132 for exercise and pharmacologic stress nuclear testing, respectively. Mean costs at 90 days were $2494 for the CTA strategy versus $2240 for the functional strategy (mean difference, $254 [95% CI, −$634 to $906]). The difference was associated with more revascularizations and catheterizations (4.25 per 100 patients) with CTA use. After 90 days, the mean cost difference between the groups out to 3 years remained small.

Limitation: Cost weights for test strategies were obtained from sources outside PROMISE.

Conclusion: Computed tomography angiography and functional diagnostic testing strategies in patients with suspected CAD have similar costs through 3 years of follow-up.

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* For a list of the PROMISE investigators, see the **Appendix** (available at www.annals.org).

Nonacute chest pain is a common reason for patients to seek medical care and a continuing challenge for the medical practitioners who must determine what it represents. Clinicians typically rely on the patient's history and noninvasive tests to assess the possibility of obstructive coronary artery disease (CAD). To date, the evidence base on the effectiveness of the major testing alternatives has largely been limited to observational studies comparing diagnostic accuracy or prognostic significance (1–4). Consequently, little consensus exists among clinicians and testing experts on which strategy provides the best outcomes for patients.

PROMISE (PROspective Multicenter Imaging Study for Evaluation of Chest Pain) examined the effect of different diagnostic testing strategies for CAD on patient outcomes (5) (**Supplement**, available at www.annals.org). A detailed description of the overall PROMISE design has been published (5, 6). Briefly, between 27 July 2010 and 19 September 2013, PROMISE enrolled 10 003 symptomatic outpatients without known CAD at 193 North American sites (5). Patients were eligible if their physician believed that nonurgent, noninvasive stress testing was indicated for evaluation of their symptoms (6). Patients were randomly assigned to either initial computed tomography angiography (CTA) (anatomical strategy) or initial prespecified functional testing using stress electrocardiography (ECG), stress echocardiography, or stress nuclear methods, stratified by site (6). The choice of functional test was left to the patient's clinician, as was the interpretation of the test and all subsequent management after the test. Median follow-up was 25 months (interquartile range, 18 to 34 months). The primary study outcome, a composite of all-cause mortality, myocardial infarction, hospitalization for unstable angina, or major 72-hour complications from diagnostic tests or cardiovascular procedures, occurred in 3.3% of patients in the CTA group and 3.0% of those in the functional testing group (adjusted hazard ratio, 1.04 [95% CI, 0.83 to 1.29]; $P = 0.75$) (5). No individual components of the primary end point, combinations of components, or subgroup anal-

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Table 1. Estimated Costs of Noninvasive Tests*

Strategy	Tests, *n*	Mean Cost (SD), $	Median Cost (IQR) (Range), $
Stress nuclear testing			
Pharmacologic	3903	1132 (416)	1101 (864–1356) (432–4517)
Exercise	2396	946 (420)	898 (649–1189) (280–3052)
Stress echocardiography			
Pharmacologic	152	501 (135)	487 (408–562) (258–978)
Exercise	632	514 (151)	508 (403–612) (238–1261)
Exercise electrocardiography	455	174 (80)	152 (117–196) (61–465)
CTA with contrast	489	404 (122)	401 (307–486) (167–878)

CTA = computed tomography angiography; IQR = interquartile range.
* Based on data from the Premier Research Database on outpatient test encounters between 1 January and 30 June 2014 with admission diagnosis of chest pain or primary/secondary diagnosis of chest pain/acute coronary syndrome/ischemic heart disease/valve/dysrhythmias. Excludes 6 sites with inconsistent data.

yses differed significantly between groups. Economic analysis of these strategies was a major secondary objective of the PROMISE research program (6).

METHODS

Overview of the PROMISE Economic Study

The economic study design involved 3 major components: collection of empirical resource use data and hospital cost data, an intention-to-treat comparison of within-study medical costs, and a lifetime cost-effectiveness analysis (which was not performed because the hypothesized primary clinical benefits for CTA were not found).

Patients enrolled in PROMISE and cared for in the fee-for-service sector of the U.S. health care system (*n* = 9649 [96.5%]) were included in the economic study. Patients enrolled in the military or the Department of Veterans Affairs system (*n* = 39), an HMO (*n* = 166), or Canada (*n* = 131) were excluded. Eighteen patients were excluded because their enrolling sites declined to participate in this study outcome. Costs for hospital-based care were assigned using prospectively collected hospital billing data along with the relevant charge–cost correction factors, as described in the Statistical Analysis section. For the initial office-based diagnostic tests, no method exists for converting billed charges to costs. Thus, for these costs, we used cost weights from a secondary source, as described in the next section. We report total costs (fixed plus variable) discounted at 3% annually. Hospital-based costs were adjusted to 2014 U.S. dollars by using the Producer Price Index for hospital care. An overview of cost analysis methods and terminology is provided elsewhere (7).

All patients provided written informed consent, and the study protocol was approved by each site's institutional review board or a central institutional review board.

Index Diagnostic Testing Cost Estimation

Cost weights for the index testing procedures were derived from the Premier Research Database (www.premierinc.com), which contains discharge abstract and cost data for all inpatient and hospital-based outpatient encounters from more than 800 geographically diverse hospitals. Two thirds of these hospitals provide detailed, service-level data from resource-based cost-accounting systems, and the remainder provide itemized charges that are converted to costs by using department-level cost–charge ratios (RCCs). To estimate test costs, we extracted data on outpatient encounters for patients aged 45 years or older who were discharged between 1 January and 30 June 2014 with CPT (Current Procedural Terminology) codes for target noninvasive diagnostic tests and cardiac diagnoses.

We used testing cost data from Premier that were generated from bottom-up cost-accounting methods (rather than RCCs) because they provide a detailed resource-based estimate of testing costs in a large group of U.S. hospitals (7). The facility testing costs used in our base-case analyses were derived from the distribution of these costs (data are shown in Table 1).

Hospital Cost Estimation

Medical resource use through the first 60 days was recorded on the study case report form. Further follow-up information was collected from patients by using mail-based (46%) or telephone-based (54%) methods. Resource consumption data covered emergency department visits, days in the hospital, use of intensive care unit services, catheterization and coronary revascularization procedures, and major complications related to procedures. Hospitalizations and hospital-based testing and procedures were verified using medical billing information. Patient reports of hospitalizations that could not be verified were not counted in the analysis.

Hospital-based costs were calculated using hospital billing data (UB-04 forms), with charges converted to costs using the departmental charge–cost conversion factors available from each hospital's annual Medicare cost report. Of the 5863 hospital-based care episodes, we collected billing information for 4876 (83.2%). In all cases, uncollectible billing information from verified hospitalizations was missing due to administrative reasons (such as the hospital declining to provide requested bills) unconnected with the randomized diagnostic strategy, the actual tests received, subsequent care, or patient outcomes. Therefore, we assumed these data were missing at random and used linear re-

Table 2. Estimated Costs of Noninvasive Tests, by Cost Component*

Cost Component	Stress Nuclear Testing		Stress Echocardiography		Exercise Electrocardiography (*n* = 455)	CTA (*n* = 489)
	Pharmacologic (*n* = 3903)	Exercise (*n* = 2396)	Pharmacologic (*n* = 152)	Exercise (*n* = 632)		
Primary test (imaging, treadmill, or CTA)	502	538	210	252	137	221
Stress test	137	134	157	160	0	0
Stress agent	214	0	14	0	0	0
Isotope	152	151	0	0	0	0
Contrast	0	0	26	15	0	48
Laboratory	1	1	1	1	0	6
Other pharmacologic costs	3	2	7	0	0	10
Other nuclear medicine costs	7	3	0	0	0	0
Subtotal	1015	829	415	428	137	285
Physician fees†	117	117	86	86	37	119
Total	1132	946	501	514	174	404

CTA = computed tomography angiography.
* Costs are presented in U.S. dollars and may not sum to totals due to rounding. Costs are based on data from the Premier Research Database on outpatient test encounters between 1 January and 30 June 2014 with an admission diagnosis of chest pain or a primary/secondary diagnosis of chest pain/acute coronary syndrome/ischemic heart disease/valve/dysrhythmias. Excludes 6 sites with inconsistent data.
† Based on Medicare Physician Fee Schedule.

gression methods to impute cost weights for these records from the portion of the study cohort with complete cost data. The imputation models included reason for hospitalization, type of hospital visit (inpatient vs. emergency department), length of stay, intensive care unit admission during stay, coronary artery bypass grafting surgery (CABG), percutaneous coronary intervention (PCI), and peripheral vascular bypass or stenting. Some catheterization and revascularization procedures were performed on an outpatient basis or were captured as a clinical event but not as a hospitalization; costs for these services were imputed using average prices from services with billing records, as summarized in Appendix Table 1 (available at www.annals.org).

Physician Cost Estimation

Physician costs for the index testing strategy and for any follow-up care shown on the case report form or identified through billing data were estimated by mapping major procedures and physician services to appropriate CPT or Healthcare Common Procedure Coding System codes in the 2014 Medicare national reimbursement schedule. The physician fees assigned to the initial randomized tests in this study are shown in Table 2.

Statistical Analysis

Descriptive Analyses and General Considerations

All primary comparisons were performed according to the intention-to-treat principle. Descriptive statistics included percentages for discrete variables and medians with interquartile ranges plus means with SDs for continuous variables. The chi-square test was used for discrete variable comparisons, and nonparametric tests, such as the Wilcoxon–Mann–Whitney test, were used for continuous variable comparisons. Follow-up cost data on surviving patients lost to follow-up were assumed to be missing at random and were imputed using linear regression models developed on patients with complete cost data.

Estimation and Comparison of Cumulative Within-Trial Costs

A nonparametric partitioned estimator was used to estimate 3-year medical costs specific to the diagnostic strategy, with 12 partitions corresponding to 3-month intervals after randomization (8). Comparisons between testing strategies were made using a normal approximation, with SEs estimated using the bootstrap approach. To account for uncertainty in test prices, in each bootstrap repetition, we randomly sampled (with replacement) a price weight from the Premier database distribution for each test type and used these price weights to calculate costs during that bootstrap repetition. Bootstrapping was performed using 10 000 repetitions, with percentile-based CIs reported. The primary effect size was the mean cost difference and 95% CI between the groups. *P* values were calculated for selective comparisons, with a "significant" *P* value equivalent to a 95% CI that excluded 0. No adjustment in significance levels for multiple comparisons was planned or used. Differences in cost by diagnostic testing group were interpreted in the context of the trial clinical results; we looked for consistency and plausibility with respect to end points as well as measures of resource use.

In addition, we used bootstrap methods to plot the probability of differences in cost greater than arbitrary thresholds of interest (such as $500, $750, or $1000).

Subgroups

Prespecified subgroup analyses were based on age, sex, race, site-generated assessment of pretest probability of CAD, CAD risk equivalent (history of diabetes, peripheral vascular disease, or cerebrovascular disease), Diamond–Forrester/CASS (Coronary Artery Surgery Study) pretest probability of CAD (9), and prerandomization physician choice for functional stress test (5).

Sensitivity Analyses

To examine the sensitivity of our results to the specific testing cost weights chosen, we performed 2 sensitivity analyses. First, we replaced the bottom-up cost-accounting–based test costs with the top-down estimates of test costs from the Premier database, using the sample of hospitals that provided data in terms of charges and cost–charge correction ratios (Appendix Table 2, available at www.annals.org). Second, we used the 2014 Medicare reimbursements for hospital-based testing in place of the Premier cost weights (Appendix Table 2); this analysis did not substitute Medicare reimbursements for all follow-up tests and was not intended to represent a cost analysis from the Medicare perspective.

Role of the Funding Source

The PROMISE economic study was a prospectively designed part of the PROMISE trial and was funded through a separate R01 grant from the National Heart, Lung, and Blood Institute along with the parent trial. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Heart, Lung, and Blood Institute or the National Institutes of Health.

RESULTS

Baseline Characteristics

Baseline characteristics for the economic study cohort were well-balanced by randomized assignment (Appendix Table 3, available at www.annals.org). The mean age was 60.8 years, 53.1% of patients were female, 87.8% had a primary symptom of chest pain or dyspnea, and the average Diamond–Forrester/CASS pretest probability of CAD was 53.4%. Patients excluded from the economic study were about 1 year younger, less likely to be female, more likely to be a member of a minority group, and more likely to have noncardiac chest pain and had a slightly lower average pretest probability of CAD (Appendix Table 4, available at www.annals.org).

Medical Costs Analyzed by the Intention-to-Treat Principle

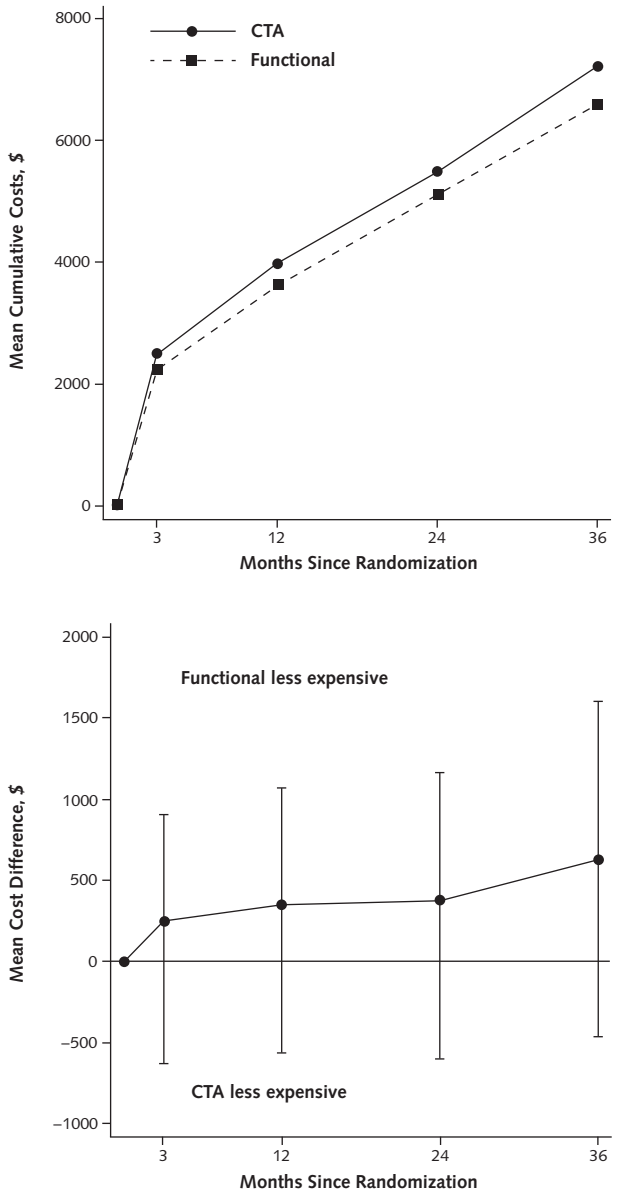
Among patients in the economic study cohort who were randomly assigned to CTA, 4523 (93.9%) had CTA as their initial test, 134 (2.8%) had a functional test, 9 (0.2%) had invasive angiography, and 152 (3.2%) had no diagnostic test. Among those randomly assigned to functional testing, 4523 (93.6%) had a functional test as their initial test, 46 (1.0%) had CTA, 20 (0.4%) had invasive angiography, and 240 (5.0%) had no test.

Costs to 3 Years

Within 90 days after randomization, 12.2% of CTA patients and 8.1% of functional testing patients had follow-up invasive catheterization, and 6.2% of patients in the CTA group versus 3.2% of those in the functional testing group had coronary revascularization. At 90 days, the mean cost for the CTA group was $2494 versus $2240 for the functional testing group, with a mean difference of $254 (95% CI, −$634 to $906).

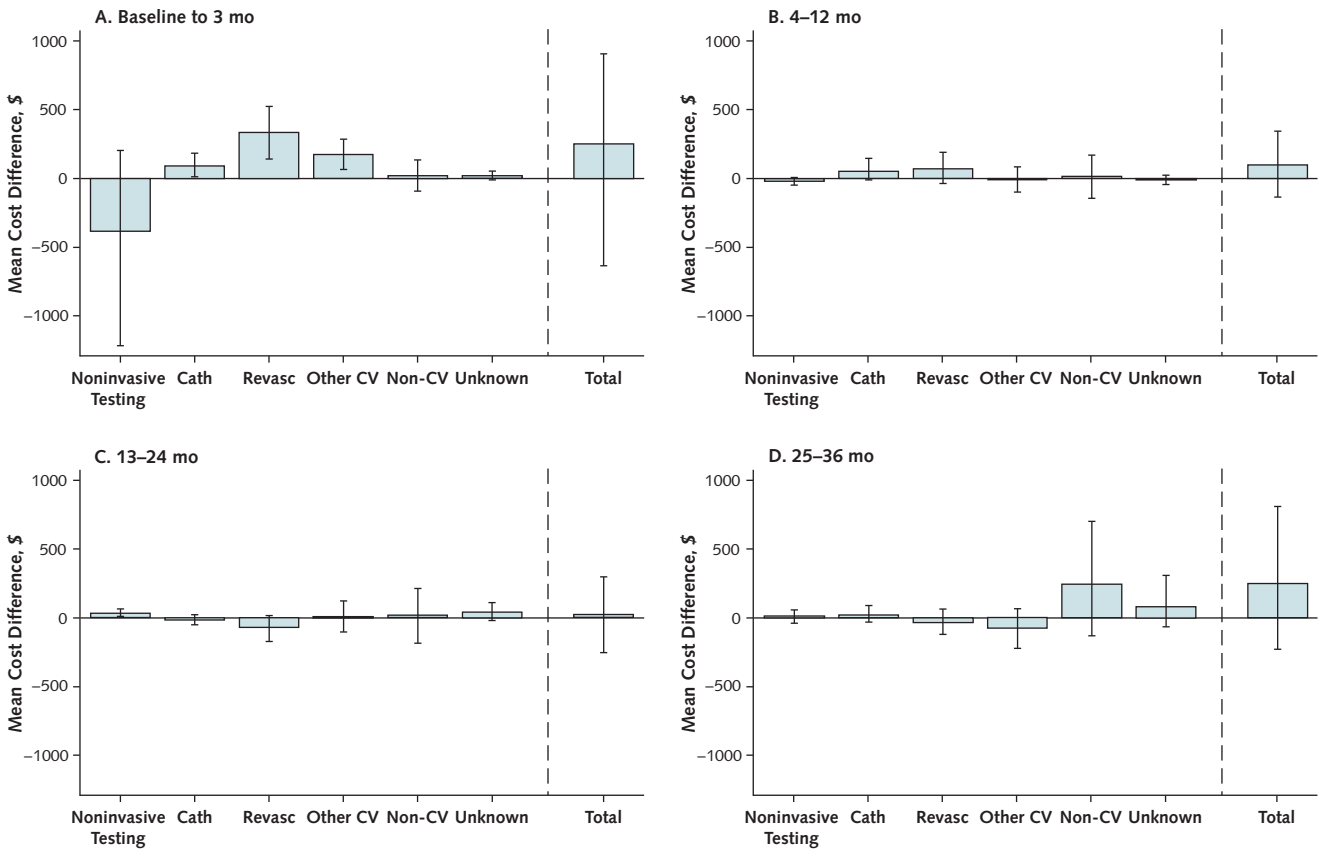
Between 91 and 365 days, the mean cost difference between the groups was $99 (CI, −$136 to $342). Thus, the cumulative 1-year cost difference was $353 (CI, −$568 to $1071). In year 2, the mean cost difference was $26 (CI, −$252 to $297), and in year 3, the mean difference was $249 (CI, −$227 to $811). The 3-year cumulative costs were $7213 for CTA and $6586 for functional testing, with a mean difference of $627 (CI, −$463 to $1609) (Figure 1). None of the 95% CIs excluded the null value (no cost difference).

Figure 1. Cumulative costs by random assignment (*top*) and mean cost differences with 95% CIs (CTA − functional) (*bottom*).



CTA = computed tomography angiography.

Figure 2. Mean cost differences, by cost category.



Values >0 indicate higher cost for CTA, and values <0 indicate higher cost for functional testing. Cath = cardiac catheterization; CTA = computed tomography angiography; CV = cardiovascular; Revasc = revascularization.

Year 3 results were skewed by an outlier in the CTA group that involved a hospitalization costing more than $300 000 for orthopedic care unrelated to the PROMISE testing question. When this observation was removed, the mean difference between the groups in year 3 was reduced to $91 and the cumulative difference was reduced to $469. Other approaches to addressing outliers reduced the mean difference at 3 years to $539, and winsorizing all outlier observations that were less than the first or greater than the 99th percentiles to the first and 99th percentiles, respectively, reduced the mean difference at 3 years to $493.

As shown in **Appendix Table 5** (available at www.annals.org), CTA testing costs were $332 lower than functional testing costs. However, by 90 days downstream costs after testing were about $600 higher for patients in the CTA group.

Sensitivity Analyses

The difference in cost between anatomical and functional testing was robust to various alternative price specifications. Using cost weights based on the Medicare Physician Fee Schedule for noninvasive tests, the 90-day cost difference favored CTA slightly (mean difference, −$32 [CI, −$314 to $256]), whereas use of the RCC-derived price weights created a larger difference (mean difference, −$401 [CI, −$2131 to $619]).

Cost Components

Analysis of costs according to the type of care (**Figure 2**, *A*) showed that during the initial 90 days, the CTA group saved an average of $378 in additional noninvasive testing costs but had an excess cost of $423 due to invasive catheterization and revascularization as well as $166 in other cardiovascular inpatient care. After 90 days, costs were low in all categories and equivalent between the 2 strategies. Most of the excess $249 cost for CTA in year 3 (**Figure 2**, *D*) was due to an average of $256 in extra noncardiovascular inpatient care.

In our base-case analysis, the cost distribution for the CTA patients shifted upward relative to the functional testing patients (**Figure 3**). Because of the outlier effects in year 3, we believed that year 2 data best represented the relevant probabilities. Specifically, our analysis indicated that costs in the CTA group would exceed those in the functional testing group by no more than $500 in 58.6% of 1000 bootstrap samples, by no more than $750 in 79.7% of samples, and by no more than $1000 in 93.4% of samples. When we sub-

stituted the Premier RCC cost weights in our sensitivity analysis, costs in the CTA group exceeded those in the functional testing group by no more than $500 in 89.9% of bootstrap samples, and 63.4% of samples had a cost difference of no more than $0 (that is, lower costs in the CTA group than the functional testing group) (**Appendix Figure 1**, *top*, available at www.annals.org). With Medicare cost weights for hospital-based testing, 94.7% of samples had a cost difference of no more than $500 and 38% of samples had a cost difference of no more than $0 (**Appendix Figure 1**, *bottom*).

Prespecified Subgroup Analysis

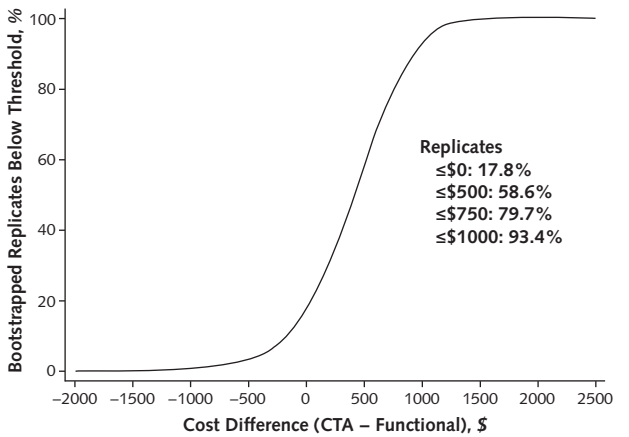
Five prespecified subgroups did not differ importantly from the overall result (**Figure 4**). For patients who had a high site-generated pretest probability of CAD (n = 431) or a high Diamond–Forrester pretest probability of CAD (n = 482), the CTA group had a mean cost difference in excess of $2000 at 90 days (**Figure 4**). The primary cost drivers for these differences were extra revascularization procedures, but costs were also higher for the categories of other cardiovascular care and noncardiovascular care (**Appendix Table 6**, available at www.annals.org). Mean cost differences (CTA minus functional testing) were similar in prespecified subgroups when Medicare pricing (**Appendix Figure 2**, *top*, available at www.annals.org) and RCC pricing (**Appendix Figure 2**, *bottom*) were used.

Discussion

In this economic analysis of PROMISE, we have shown that an initial CTA strategy had costs similar to those of a functional stress testing strategy, although the patterns of care differed. Specifically, the CTA group had less follow-up noninvasive testing and more invasive catheterization and revascularization. Our data suggest that, after 90 days, little happened to these patients out to 3 years that was driven specifically by which testing strategy they received.

Interpretation of empirical cost comparisons in which the clinical and cost outcomes are similar poses important challenges. One possible interpretation of our results is that the CTA strategy was modestly more costly than the functional testing strategy and our study had insufficient precision to exclude the null case (no cost difference). No criteria have been established for defining how small a numerical difference must be for costs to qualify as "similar" (a notion akin to "noninferior" in the comparison of clinical outcomes). Instead of using fixed decision rules to interpret cost data, as is typical for clinical outcome comparisons, health economics has developed methods that recognize that policymakers vary both in their willingness to tolerate uncertainty about the "true" cost difference and in the threshold cost difference they consider important. Four lines of evidence support the case that the costs for CTA and functional testing strategies are similar. First, the mean cost at 90 days was $254 higher for CTA, with an additional $99 in extra costs between 91 days and 1 year. Because the cumulative 1-year difference ($353)

Figure 3. 2-y cost threshold differences from bootstrap analysis.

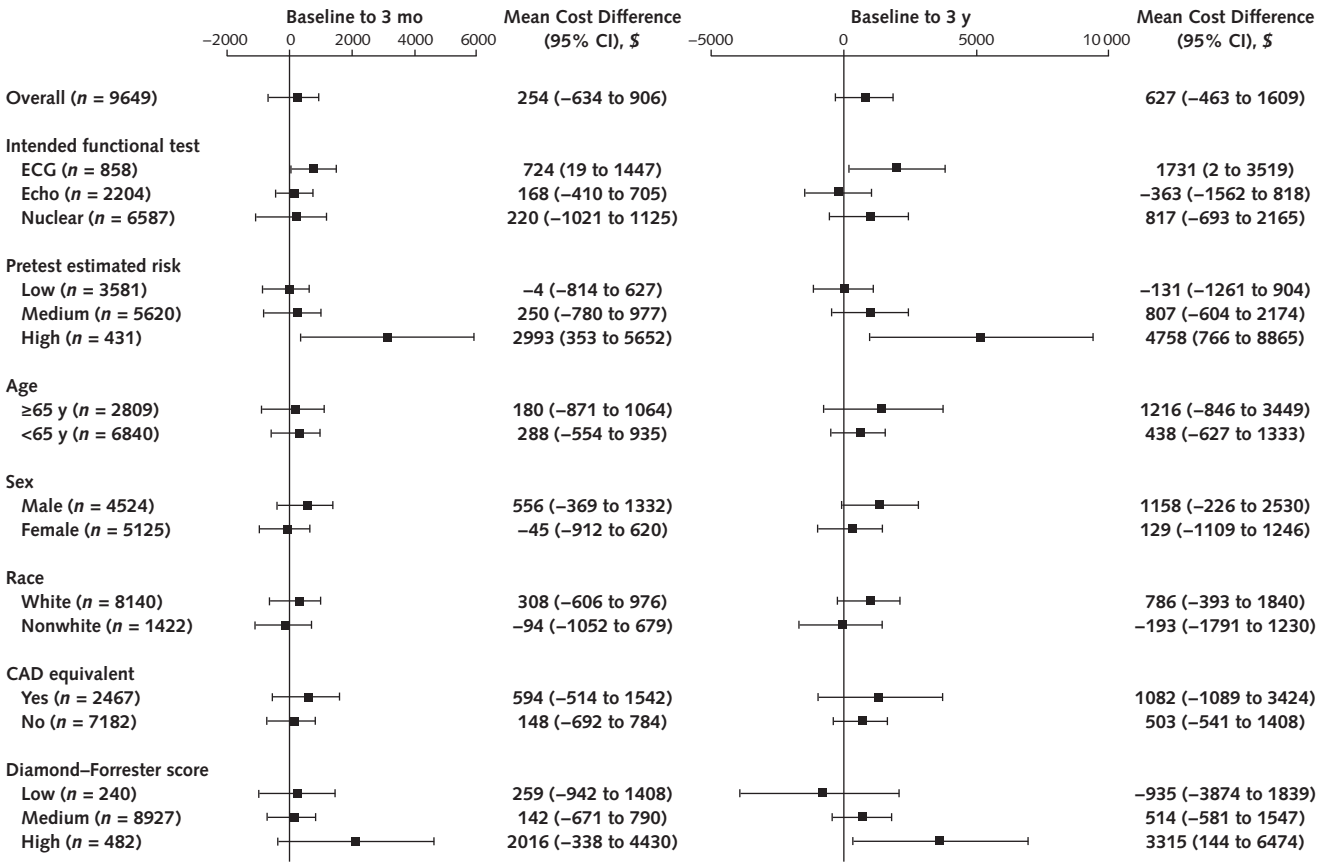


The curve shows the cumulative distribution function of the mean cost difference (CTA − functional) from 1000 bootstrap replications out to 24 mo. CTA = computed tomography angiography.

represents a shift equivalent to about 4% of the SD of the 0-to-12–month partitioned cost estimator ($9436), it provides a useful, if imperfect, reference point for assessing the magnitude of the differences we observed. Second, the mean cost difference was $26 in year 2 and $249 in year 3 (which decreased to $91 after removal of 1 very-high-cost noncardiovascular outlier). These data provide strong evidence that the randomized diagnostic testing strategy had no discernable net effect on costs after the first year. Third, our bootstrap analysis of the 2-year cost difference (**Figure 3**) showed that 59% of bootstrap repetitions had a cost difference of $500 (4% of the SD of the 2-year partitioned estimator [$12 242]) or less, and 80% of repetitions had a difference of $750 (6% of the SD of the 2-year cost) or less. Finally, in sensitivity analyses where we used either Medicare Physician Fee Schedule cost weights or the top-down RCC method, costs in the CTA group were numerically lower than in the functional testing group.

To date, there have been few large multicenter empirical studies of the long-term costs and resource consumption effects of coronary CTA relative to alternative diagnostic imaging strategies. In a consecutive cohort study (2005 to 2007) from an academic institution in Ottawa, Canada, Chow and colleagues found that implementation of a cardiac computed tomography program (February 2006) was associated with a decrease in the frequency of normal invasive coronary angiography from 31.5% to 26.8% (10). A retrospective cohort study (2005 to 2008) from the U.S. Medicare population (aged ≥66 years) compared the effects of coronary CTA with functional stress testing options on subsequent catheterization, revascularization, and costs out to 180 days (11). Computed tomography angiography was associated with about a 2-fold increase in referral to invasive catheterization, a 2.5-fold increase in PCIs, and a 3-fold increase in CABG after adjustment. Coronary artery disease–related costs after CTA were almost

Figure 4. Forest plots for mean differences and 95% CIs of 3-y costs (CTA − functional testing) in prespecified subgroups.



CAD = coronary artery disease; CTA = computed tomography angiography; ECG = electrocardiography; Echo = echocardiography.

40% higher than with stress perfusion imaging at 180 days ($14 943 vs. $10 626). Finally, in a 41-center prospective cohort study (2006 to 2008) involving 1703 patients with suspected CAD, 2-year unadjusted costs for CAD management were about $1000 higher for CTA than for stress perfusion imaging (12). After adjustment for baseline differences, CTA costs remained 15% higher. The extra costs of CTA were driven by more frequent use of invasive catheterization (13% vs. 4% for stress nuclear testing at 90 days), as well as more PCIs (6% vs. 1% at 90 days) and CABG (2% vs. 0.4%).

Thus, observational studies reflecting data from 2005 to 2008 suggested that CTA would modestly reduce referral to catheterization for patients with normal coronary arteries but would increase use of invasive catheterization and revascularization overall, with an associated net increase in medical costs. These patterns were also seen in PROMISE, which enrolled patients from 2010 to 2013, but the magnitude of the effect on incremental medical costs compared with functional testing was much lower than these earlier studies predicted.

PLATFORM (Prospective Longitudinal Trial of FFR_{CT} Outcomes and Resource Impacts) recently reported an economic comparison of 204 European patients with stable chest pain who had intermediate likelihood for CAD and were managed either with stress testing or usual care or with fractional flow reserve (FFR) CTA imaging (13). Using Medicare reimbursement rates to estimate costs, Hlatky and colleagues found that 90-day costs did not significantly differ between strategies (mean difference, $542 [CI, −$1153 to $2237]). No difference was seen in the use of invasive catheterization, but the FFR_{CT} strategy resulted in about 6 more PCIs and 1 fewer CABG per 100 patients. Although these results are from a much smaller sample from a different geographic region (Europe vs. the United States), with a different CTA strategy (FFR in 60%) and a different usual care strategy (60% had CTA without FFR), they are reasonably concordant with our findings.

Of the 7 prespecified subgroup comparisons in PROMISE, 5 had cost results consistent with those in the overall comparison. Both measures of high pretest probability of CAD were associated with significantly higher cost at 90 days for CTA (**Figure 4**) due to greater use of invasive catheterization and revascularization among patients in that group. These high-probability subgroups are too small to allow reliable assessment of outcome differences produced by these different treatment patterns. However, this finding does show that the modest trend toward higher costs for CTA in our base-case cost comparison was due mostly to differ-

ences in management created among patients in the high pretest probability subgroup, in whom a higher rate of catheterization and revascularization would be most clinically justified.

Our study has limitations. The initial diagnostic test costs used in our analysis were derived from data from outside the trial, which was necessitated by the lack of suitable cost weights from the trial patients. There are no standard methods for converting the charges for an office-based test in the United States to the relevant resource-based cost. Thus, we used data from the Premier Research Database to provide these cost weights because the database reflects the input of many hospital-based testing laboratories and is provided in a cost-accounting format that shows not only the total facility cost of testing but also the key component costs. Also, we did not include the costs of outpatient medications, routine outpatient medical care, or patient and caregiver time because of budget constraints. Given the similarity in the costs of the 2 diagnostic strategies compared in PROMISE, regional variation in the relative costs of functional versus anatomical testing and in the type of functional testing preferred may result in net cost positions that differ from those reported for the trial overall.

In summary, in a large cohort of outpatients with stable chest pain referred for stress testing, we found similar net costs for the CTA and functional stress testing strategies out to 90 days. After 90 days, the choice of test had little effect on differential costs.

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Reproducible Research Statement: *Study protocol:* See the **Supplement**. *Statistical code:* Not available. *Data set:* Available according to National Institutes of Health requirements.

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Appendix Table 1. Cost Weights Used for Missing Catheterization and Revascularization Bills*

Procedure	Procedures Done, *n*	Mean (SD), $	Median (IQR) (Range), $
CABG	37	32 546 (11 181)	31 019 (23 934–37 957) (17 236–64 830)
Catheterization	172	3656 (1990)	3203 (2173–4656) (848–11 992)
PCI	325	12 779 (5498)	11 644 (8873–15 655) (1378–35 975)

CABG = coronary artery bypass grafting surgery; IQR = interquartile range; PCI = percutaneous coronary intervention.
* Derived from patients with medical bills for each procedure.

Appendix Table 2. Estimated Costs of Noninvasive Diagnostic Tests

Strategy	Tests, *n*	Mean Cost (SD), $	Median Cost (IQR) (Range), $
Based on cost-charge ratio sites (Premier Research Database)			
Pharmacologic stress nuclear testing	2850	1534 (659)	1470 (989–1970) (373–5314)
Exercise stress nuclear testing	2139	1427 (795)	1303 (879–1573) (399–4964)
Pharmacologic echocardiography	110	1108 (469)	1335 (534–1450) (194–1778)
Exercise echocardiography	420	991 (557)	812 (562–1296) (191–2437)
Exercise electrocardiography	258	201 (97)	157 (150–226) (97–496)
CTA with contrast	66	568 (326)	413 (358–943) (236–1356)
Based on Medicare reimbursements in 2014*			
Pharmacologic stress nuclear testing	10 000	1234 (35)	1234 (1210–1257) (1109–1354)
Exercise stress nuclear testing	10 000	1234 (35)	1234 (1211–1257) (1079–1376)
Pharmacologic echocardiography	10 000	681 (26)	681 (663–699) (590–779)
Exercise echocardiography	10 000	681 (26)	681 (664–699) (574–778)
Exercise electrocardiography	10 000	281 (17)	281 (270–293) (217–342)
CTA with contrast	10 000	341 (19)	341 (329–354) (265–412)

CTA = computed tomography angiography; IQR = interquartile range.
* For the number of tests, uncertainty was created using 10 000 draws from Poisson distribution. Pharmacologic and exercise stress test costs were equal given outpatient facility-based pricing.

Appendix Table 3. Selected Baseline Characteristics, by Randomized Assignment*

Characteristic	Randomized Testing Group		
	Overall (*n* = 9649)	Functional (*n* = 4831)	Anatomical (*n* = 4818)
Age, *y*			
Median (IQR)	60.0 (54.5–66.0)	60.2 (54.6–66.0)	59.9 (54.3–66.0)
Mean (SD)	60.8 (8.3)	60.9 (8.3)	60.7 (8.3)
Female	5125 (53.1)	2601 (53.8)	2524 (52.4)
Racial or ethnic minority	2108 (22.0)	1015 (21.2)	1093 (22.8)
Cardiac risk factor			
Body mass index, kg/m^2			
Median (IQR)	29.8 (26.4–34.0)	29.8 (26.4–34.0)	29.7 (26.4–34.0)
Mean (SD)	30.6 (6.2)	30.6 (6.2)	30.6 (6.2)
Hypertension	6326 (65.6)	3165 (65.5)	3161 (65.6)
Diabetes	2088 (21.6)	1052 (21.8)	1036 (21.5)
Dyslipidemia	6502 (67.4)	3265 (67.6)	3237 (67.2)
Family history of premature CAD	3131 (32.6)	1543 (32.0)	1588 (33.1)
Peripheral or cerebrovascular disease	540 (5.6)	283 (5.9)	257 (5.3)
CAD risk equivalent	2467 (25.6)	1253 (25.9)	1214 (25.2)
Metabolic syndrome	3668 (38.0)	1849 (38.3)	1819 (37.8)
Current or past tobacco use	4908 (50.9)	2471 (51.2)	2437 (50.6)
Sedentary lifestyle	4761 (49.4)	2384 (49.5)	2377 (49.4)
History of depression	2015 (20.9)	1054 (21.8)	961 (20.0)
Risk burden			
No risk factors	251 (2.6)	132 (2.7)	119 (2.5)
Risk factor burden, *n*			
Median (IQR)	2.0 (2.0–3.0)	2.0 (2.0–3.0)	2.0 (2.0–3.0)
Mean (SD)	2.4 (1.1)	2.4 (1.1)	2.4 (1.1)
Risk score (combined Diamond–Forrester and CASS)			
Median (IQR)	51.0 (31.0–72.0)	51.0 (31.0–72.0)	51.0 (31.0–72.0)
Mean (SD)	53.4 (21.3)	53.3 (21.4)	53.6 (21.3)
Relevant medication			
β-Blocker	2347 (25.4)	1169 (25.3)	1178 (25.5)
ACE inhibitor or ARB	4087 (44.2)	2049 (44.3)	2038 (44.2)
Statin	4234 (45.8)	2100 (45.4)	2134 (46.2)
Aspirin	4128 (44.7)	2037 (44.1)	2091 (45.3)
Primary presenting symptom			
Chest pain	7027 (72.9)	3483 (72.1)	3544 (73.6)
Dyspnea on exertion	1436 (14.9)	748 (15.5)	688 (14.3)
Other	1179 (12.2)	597 (12.4)	586 (12.1)
Type of angina			
Typical	1145 (11.9)	566 (11.7)	579 (12.0)
Atypical	7515 (77.9)	3772 (78.1)	3743 (77.7)
Noncardiac	989 (10.2)	493 (10.2)	496 (10.3)

ACE = angiotensin-converting enzyme; ARB = angiotensin-receptor blocker; CAD = coronary artery disease; CASS = Coronary Artery Surgery Study; IQR = interquartile range.
* Values are numbers (percentages) unless otherwise indicated.

Appendix Table 4. Selected Baseline Characteristics, by Economic Study Inclusion*

Characteristic	In Economic Study?			*P* Value†
	Overall (*n* = 10 003)	No (*n* = 354)	Yes (*n* = 9649)	
Age, *y*				0.009
Median (IQR)	60.0 (54.4–65.9)	58.7 (53.6–64.4)	60.0 (54.5–66.0)	
Mean (SD)	60.8 (8.3)	59.5 (7.7)	60.8 (8.3)	
Female	5270 (52.7)	145 (41.0)	5125 (53.1)	<0.001
Racial or ethnic minority	2248 (22.6)	140 (39.5)	2108 (22.0)	<0.001
Cardiac risk factor				
Mean body mass index (SD), kg/m^2	30.5 (6.1)	28.7 (4.8)	30.6 (6.2)	<0.001
Hypertension	6501 (65.0)	175 (49.4)	6326 (65.6)	<0.001
Diabetes	2144 (21.4)	56 (15.8)	2088 (21.6)	0.009
Dyslipidemia	6767 (67.7)	265 (74.9)	6502 (67.4)	0.003
Family history of premature CAD	3202 (32.1)	71 (20.1)	3131 (32.6)	<0.001
Peripheral or cerebrovascular disease	552 (5.5)	12 (3.4)	540 (5.6)	0.07
CAD risk equivalent	2531 (25.3)	64 (18.1)	2467 (25.6)	0.001
Metabolic syndrome	3772 (37.7)	104 (29.4)	3668 (38.0)	<0.001
Current or past tobacco use	5104 (51.0)	196 (55.4)	4908 (50.9)	0.10
Sedentary lifestyle	4866 (48.7)	105 (29.7)	4761 (49.4)	<0.001
History of depression	2058 (20.6)	43 (12.1)	2015 (20.9)	<0.001
Risk burden				
No risk factors	263 (2.6)	12 (3.4)	251 (2.6)	0.36
Risk factor burden, *n*				<0.001
Median (IQR)	2.0 (2.0–3.0)	2.0 (1.0–3.0)	2.0 (2.0–3.0)	
Mean (SD)	2.4 (1.1)	2.2 (1.1)	2.4 (1.1)	
Risk score (combined Diamond–Forrester and CASS)				<0.001
Median (IQR)	51.0 (31.0–72.0)	51.0 (31.0–65.0)	51.0 (31.0–72.0)	
Mean (SD)	53.3 (21.4)	49.0 (22.4)	53.4 (21.3)	
Relevant medication				
β-Blocker	2399 (25.1)	52 (15.7)	2347 (25.4)	<0.001
ACE inhibitor or ARB	4194 (43.8)	107 (32.3)	4087 (44.2)	<0.001
Statin	4389 (45.9)	155 (46.8)	4234 (45.8)	0.72
Aspirin	4280 (44.7)	152 (45.9)	4128 (44.7)	0.66
Primary presenting symptom				0.16
Chest pain	7272 (72.7)	245 (69.2)	7027 (72.9)	
Dyspnea on exertion	1490 (14.9)	54 (15.3)	1436 (14.9)	
Other	1234 (12.3)	55 (15.5)	1179 (12.2)	
Type of angina				<0.001
Typical	1166 (11.7)	21 (5.9)	1145 (11.9)	
Atypical	7773 (77.7)	258 (72.9)	7515 (77.9)	
Noncardiac	1064 (10.6)	75 (21.2)	989 (10.2)	

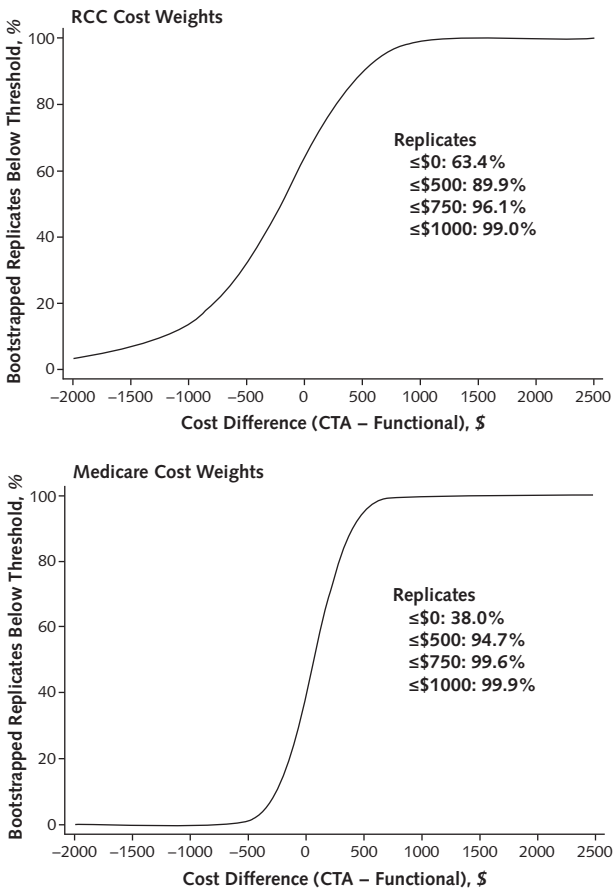
ACE = angiotensin-converting enzyme; ARB = angiotensin-receptor blocker; CAD = coronary artery disease; CASS = Coronary Artery Surgery Study; IQR = interquartile range.
* Values are numbers (percentages) unless otherwise indicated.
† Wilcoxon rank-sum test for continuous variables and chi-square test for binary/categorical variables.

Appendix Table 5. Downstream Cost Difference (CTA − Functional)

Months	Mean Cost Difference (95% CI), $		
	Total	First Test	All Other Services
0–3	254 (−634 to 906)	−332 (−364 to −299)	585 (−279 to 1236)
0–12	353 (−568 to 1071)	−333 (−366 to −300)	686 (−232 to 1403)
0–24	378 (−602 to 1162)	−333 (−366 to −300)	711 (−236 to 1505)
0–36	627 (−463 to 1609)	−333 (−366 to −300)	960 (−127 to 1962)

CTA = computed tomography angiography.

Appendix Figure 1. 2-y cost threshold differences from bootstrap analysis.



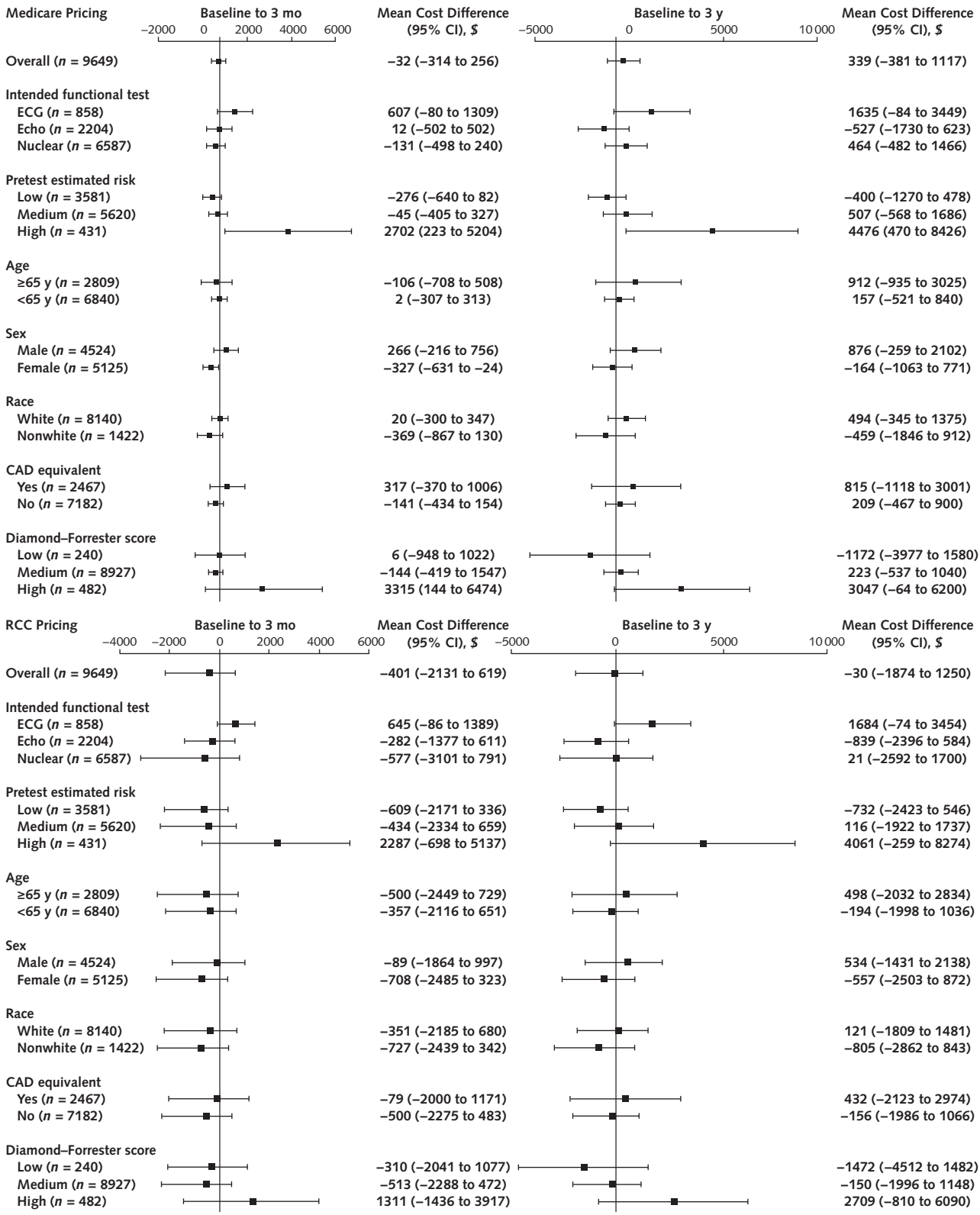
CTA = computed tomography angiography; RCC = cost–charge ratio.

Appendix Table 6. Service Use, Stratified by Provider Pretest Risk Assessment*

Variable	Service Use per 100 Patients (95% CI)				
	Revascularization or Catheterization	Noninvasive Testing	Other CV	Non-CV	Unknown
Low					
Months 1–3	2.24 (0.28 to 4.12)	1.95 (0.65 to 3.26)	0.90 (−0.26 to 2.08)	−0.20 (−2.01 to 1.60)	0.29 (−0.16 to 0.77)
CTA	9.06 (7.64 to 10.50)	97.81 (96.98 to 98.57)	2.94 (2.10 to 3.89)	5.60 (4.39 to 6.90)	0.63 (0.29 to 1.03)
Functional	6.82 (5.57 to 8.16)	95.85 (94.81 to 96.88)	2.05 (1.36 to 2.82)	5.80 (4.52 to 7.12)	0.34 (0.11 to 0.63)
Months 4–12	0.99 (−0.47 to 2.44)	−2.69 (−7.30 to 1.87)	0.38 (−1.05 to 1.81)	0.11 (−2.17 to 2.39)	0.59 (−0.57 to 1.99)
CTA	5.01 (3.93 to 6.12)	26.82 (23.91 to 29.94)	3.92 (2.92 to 4.97)	9.54 (7.99 to 11.17)	1.90 (0.97 to 3.17)
Functional	4.02 (3.09 to 5.00)	29.52 (26.15 to 33.06)	3.54 (2.60 to 4.60)	9.43 (7.85 to 11.09)	1.31 (0.76 to 1.95)
Months 13–24	0.67 (−0.59 to 1.90)	2.54 (−2.24 to 7.31)	0.04 (−1.83 to 1.89)	0.59 (−2.14 to 3.36)	0.63 (−0.50 to 1.80)
CTA	2.28 (1.35 to 3.33)	21.02 (17.66 to 24.59)	4.66 (3.40 to 6.01)	11.64 (9.71 to 13.70)	2.29 (1.45 to 3.24)
Functional	1.61 (0.89 to 2.42)	18.49 (15.25 to 21.87)	4.62 (3.37 to 5.95)	11.05 (9.15 to 13.04)	1.66 (0.95 to 2.46)
Months 25–36	0.81 (−1.00 to 2.55)	8.27 (0.96 to 15.51)	−0.59 (−2.98 to 1.67)	−3.30 (−8.56 to 1.68)	−0.78 (−3.16 to 1.57)
CTA	2.44 (1.28 to 3.74)	26.21 (20.79 to 31.83)	3.89 (2.45 to 5.45)	12.00 (9.12 to 15.13)	2.27 (0.92 to 3.97)
Functional	1.63 (0.52 to 3.02)	17.95 (13.34 to 23.02)	4.48 (2.80 to 6.40)	15.30 (11.56 to 19.55)	3.05 (1.45 to 4.97)
Medium					
Months 1–3	4.85 (2.94 to 6.77)	1.25 (0.05 to 2.42)	0.86 (−0.13 to 1.88)	−0.74 (−2.01 to 0.55)	0.05 (−0.48 to 0.58)
CTA	14.33 (12.88 to 15.81)	97.87 (97.21 to 98.51)	3.46 (2.74 to 4.24)	4.76 (3.92 to 5.65)	0.87 (0.51 to 1.26)
Functional	9.47 (8.26 to 10.72)	96.62 (95.64 to 97.64)	2.60 (1.97 to 3.29)	5.50 (4.58 to 6.44)	0.82 (0.45 to 1.23)
Months 4–12	1.77 (0.29 to 3.20)	−3.84 (−7.87 to 0.27)	0.54 (−0.62 to 1.68)	−0.34 (−2.19 to 1.57)	−0.97 (−2.02 to 0.03)
CTA	7.62 (6.55 to 8.68)	29.89 (27.28 to 32.56)	4.16 (3.36 to 5.01)	10.22 (8.95 to 11.58)	1.49 (0.99 to 2.07)
Functional	5.85 (4.86 to 6.86)	33.72 (30.60 to 36.80)	3.62 (2.83 to 4.46)	10.56 (9.22 to 11.93)	2.46 (1.63 to 3.38)
Months 13–24	−0.93 (−2.17 to 0.30)	4.33 (0.22 to 8.57)	0.94 (−0.47 to 2.39)	1.24 (−1.45 to 4.02)	1.03 (−0.60 to 2.69)
CTA	2.54 (1.81 to 3.33)	25.58 (22.61 to 28.72)	4.99 (3.97 to 6.09)	15.55 (13.66 to 17.50)	3.94 (2.78 to 5.26)
Functional	3.47 (2.55 to 4.46)	21.26 (18.49 to 24.15)	4.05 (3.12 to 4.99)	14.31 (12.36 to 16.33)	2.91 (1.92 to 4.03)
Months 25–36	0.15 (−1.53 to 1.83)	2.19 (−4.72 to 8.69)	−2.03 (−4.35 to 0.31)	1.08 (−2.48 to 4.66)	2.17 (−1.74 to 7.66)
CTA	2.93 (1.77 to 4.22)	27.59 (22.98 to 32.37)	4.32 (2.97 to 5.87)	13.26 (10.87 to 15.74)	5.10 (1.96 to 10.24)
Functional	2.78 (1.68 to 4.01)	25.41 (20.92 to 30.37)	6.35 (4.55 to 8.24)	12.18 (9.60 to 14.87)	2.92 (1.27 to 5.04)
High					
Months 1–3	14.98 (4.49 to 25.75)	−0.71 (−4.57 to 3.02)	2.34 (−3.09 to 7.81)	4.54 (0.88 to 8.42)	2.02 (−0.80 to 5.29)
CTA	40.20 (31.74 to 48.95)	96.08 (93.26 to 98.52)	7.84 (4.00 to 12.28)	6.37 (3.24 to 9.88)	2.94 (0.50 to 6.02)
Functional	25.22 (19.07 to 31.77)	96.79 (94.01 to 99.16)	5.51 (2.28 to 9.39)	1.84 (0.44 to 3.81)	0.92 (0.00 to 2.37)
Months 4–12	6.31 (−1.97 to 14.32)	6.71 (−9.07 to 22.61)	−2.20 (−7.29 to 3.07)	7.20 (1.81 to 12.85)	0.03 (−1.95 to 2.03)
CTA	17.33 (11.56 to 23.44)	45.21 (33.81 to 57.79)	4.00 (0.99 to 8.01)	11.06 (6.48 to 16.11)	1.01 (0.00 to 2.59)
Functional	11.03 (5.82 to 17.06)	38.50 (28.12 to 49.84)	6.20 (2.72 to 10.28)	3.86 (1.46 to 6.77)	0.97 (0.00 to 2.50)
Months 13–24	−0.81 (−5.44 to 4.00)	1.46 (−13.19 to 16.45)	1.13 (−4.20 to 6.75)	2.94 (−6.85 to 12.84)	−1.77 (−6.43 to 2.85)
CTA	3.70 (0.72 to 7.30)	27.86 (17.90 to 39.03)	6.36 (2.56 to 10.99)	14.90 (8.21 to 22.70)	2.05 (0.00 to 5.59)
Functional	4.51 (1.39 to 8.06)	26.40 (16.78 to 36.79)	5.23 (1.98 to 8.93)	11.96 (6.12 to 18.66)	3.82 (0.72 to 7.69)
Months 25–36	−3.47 (−11.32 to 2.86)	1.30 (−25.34 to 27.51)	2.34 (−2.99 to 8.17)	6.87 (−4.49 to 19.02)	0.46 (−7.08 to 8.50)
CTA	2.99 (0.00 to 6.84)	42.38 (25.95 to 60.74)	4.58 (0.77 to 9.67)	16.03 (7.36 to 26.52)	4.63 (0.00 to 11.46)
Functional	6.46 (1.02 to 13.77)	41.08 (22.27 to 61.79)	2.23 (0.00 to 5.78)	9.16 (2.95 to 16.91)	4.17 (0.00 to 9.61)

CTA = computed tomography angiography; CV = cardiovascular.
* The first row for each time point shows the difference between the CTA and functional groups.

Appendix Figure 2. Forest plots for mean differences and 95% CIs of costs (CTA − functional testing) in prespecified subgroups.



CAD = coronary artery disease; CTA = computed tomography angiography; ECG = electrocardiography; Echo = echocardiography; RCC = cost-charge ratio. **Top.** Using Medicare pricing. **Bottom.** Using RCC pricing.