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Economic Outcomes in the Study of Myocardial Perfusion and Coronary Anatomy Imaging Roles in Coronary Artery Disease Registry

The SPARC Study

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CME Objective for This Article: At the conclusion of this activity, the learner will be able to compare the economic outcomes of patients undergoing different non-invasive tests to evaluate suspected coronary artery disease.

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Objectives The goal of this study was to compare the economic outcomes of patients undergoing different noninvasive tests to evaluate suspected coronary artery disease (CAD).

Background Evaluation of noninvasive tests is shifting to an assessment of their effect on clinical outcomes rather than on their diagnostic accuracy. Economic outcomes of testing are particularly important in light of rising medical care costs.

Methods We used an observational registry of 1,703 patients who underwent coronary computed tomography angiography (CTA) (n = 590), positron emission tomography (PET) (n = 548), or single-photon emission computed tomography (SPECT) (n = 565) for diagnosis of suspected CAD at 1 of 41 centers. We followed patients for 2 years, and documented resource use, medical costs for CAD, and clinical outcomes. We used multivariable analysis and propensity score matching to control for differences in baseline characteristics.

Results Two-year costs were highest after PET ($6,647, 95% confidence interval [CI]: $5,896 to $7,397), intermediate after CTA ($4,909, 95% CI: $4,378 to $5,440), and lowest after SPECT ($3,965, 95% CI: $3,520 to $4,411). After multivariable adjustment, CTA costs were 15% higher than SPECT ($p < 0.01$), and PET costs were 22% higher than SPECT ($p < 0.0001$). Two-year mortality was 0.7% after CTA, 1.6% after SPECT, and 5.5% after PET. The incremental cost-effectiveness ratio for CTA compared with SPECT was $11,700 per life-year added, but was uncertain, with higher costs and higher mortality in 13% of bootstrap replications. Patients undergoing PET had higher costs and higher mortality than patients undergoing SPECT in 98% of bootstrap replications.

Conclusions Costs were significantly lower after using SPECT rather than CTA or PET in the evaluation of suspected coronary disease. SPECT was economically attractive compared with PET, whereas CTA was associated with higher costs and no significant difference in mortality compared with SPECT. (J Am Coll Cardiol 2014;63:1002–8) © 2014 by the American College of Cardiology Foundation

Evaluation of patients with symptoms suggestive of coronary artery disease (CAD) is an everyday clinical problem, but the diagnosis is often uncertain after a clinical history, physical examination, and resting electrocardiogram (ECG) have been performed. Noninvasive testing is typically used to refine the probability of CAD estimated from the initial clinical evaluation and to select patients for invasive coronary angiography. There are many options for noninvasive testing, including myocardial perfusion imaging with single-photon emission computed tomography (SPECT), positron-emission tomography (PET), and coronary computed tomography angiography (CTA). Results from series of patients evaluated with single modalities have been published by many investigators, but there are few head-to-head comparisons of the outcomes of alternative test strategies. Consequently, the comparative effectiveness of different noninvasive cardiac testing strategies has been difficult to assess.

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The SPARC (Study of Myocardial Perfusion and Coronary Anatomy Imaging Roles in Coronary Artery Disease) registry was a multicenter study designed to collect standardized clinical data on patients undergoing CTA, PET, or SPECT and to document their subsequent clinical outcomes (1). The 90-day clinical follow-up of patients in the SPARC registry showed that medications were often changed as a result of testing, and that invasive evaluation was usually prompted by abnormal test results (2). The purpose of the present study was to evaluate the economic outcomes of using CTA, PET, or SPECT to evaluate patients with suspected CAD.

Methods

The design (1) and initial results (2) of the SPARC registry have been reported previously. Briefly, SPARC was a prospective observational registry that between May 2006 and April 2008 enrolled patients undergoing clinically-indicated CTA (using multidetector CT scanners with ≥64 slices), PET, or SPECT at 1 of 41 study centers (40 in the United States, 1 in Canada). Data were collected prospectively on standardized forms about patient demographics, cardiac risk factors, prior medical history, symptoms, and medications. Results of the imaging study were recorded, as were the subsequent treatments, including use of invasive coronary angiography and coronary revascularization. Patients were followed at 90 days, and 6, 12, and 24 months to document outcomes: death, myocardial infarction (MI), invasive cardiac procedures (catheterization, coronary artery bypass graft surgery [CABG], and percutaneous coronary intervention [PCI]), noninvasive tests, and use of cardiac medications (aspirin, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, beta-blockers, calcium antagonists, clopidogrel, nitrates, and statins).

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Abbreviations and Acronyms

CABG = coronary artery bypass graft surgery

CAD = coronary artery disease

CI = confidence interval

CTA = coronary computed tomography angiography

ECG = electrocardiogram/electrocardiography

MI = myocardial infarction

PCI = percutaneous coronary intervention

PET = positron emission tomography

SPECT = single-photon emission computed tomography

In order to compare use of tests for diagnostic evaluation, we studied only the patients without a known history of coronary disease. We measured the cost of medical care for CAD by multiplying counts of resource use by standardized cost weights (Online Table 1). We used the 2008 Medicare fee schedule as the basis for the cost of tests (CTA, PET, and SPECT), procedures (invasive coronary angiography, CABG, and PCI) and subsequent events (MI, death). We used average wholesale prices to assign costs to cardiac medications. For the purpose of this analysis, we included all costs between study entry and 2 years of follow-up, which included the cost of the index study test.

We estimated cumulative radiation exposure from all cardiac tests and procedures performed on individual patients, based on the number of procedures in each patient and average radiation exposures per procedure: 13 mSV for CTA, 11 mSV for SPECT, 4 mSV for PET, 7 mSV for invasive coronary angiography, and 15 mSV for PCI (3).

Patients in this study underwent testing by physician choice, not as a result of randomization. In order to adjust for differences among patient groups, we developed a propensity score for use of CTA instead of SPECT, and a second propensity score for use of PET instead of SPECT. We developed these 2 propensity score models using multivariable logistic regression, based only on patients enrolled in centers that performed both tests of interest, using baseline clinical characteristics recorded on study data forms: age, sex, race, weight, height, diabetes, history of smoking, hypertension, family history of CAD, heart failure, atrial fibrillation, presence of a pacemaker, prior cardiac studies, and symptom status (angina, noncardiac pain, asymptomatic). We compared cumulative 2-year medical costs for CAD management between test groups after logarithmic transformation of the costs because of the skew in the data, using linear regression analysis that adjusted for the propensity score and other baseline characteristics.

We performed a cost-effectiveness evaluation using the observed survival times of patients who died and their projected remaining life expectancy (based on the age-sex-race–matched U.S. population) to estimate life-years lost. In a sensitivity analysis, we assigned 2 life-years lost to every patient who had an MI and survived the remainder of the follow-up time (4). In order to control for baseline clinical differences between test groups, we first matched on propensity score (within 0.01) patients undergoing CTA or SPECT, using a greedy matching algorithm (5). We calculated the incremental cost-effectiveness ratio as the difference among matched patients in 2-year costs divided by the difference in life-years lost in the 2 groups. We assessed the uncertainty in the cost-effectiveness estimate using 10,000 bootstrap resamplings of the CTA patients and SPECT patients, rematching patients on propensity score, and recalculating the incremental cost-effectiveness ratio after each resampling. We calculated the cost effectiveness of PET relative to SPECT in the same fashion, using patients matched on the PET versus SPECT propensity scores within 0.01.

Results

There were 1,703 patients without known CAD included in the SPARC registry, 565 of whom underwent SPECT, 590 of whom had a CTA, and 548 of whom had PET scanning. Overall, patients who underwent CTA were the youngest, and patients who underwent PET were the oldest (Table 1). Patients who underwent PET were more likely to have diabetes and hypertension, and less likely to have angina.

Over the subsequent 2 years of follow-up, patients who underwent CTA were more likely to undergo invasive coronary angiography and to receive coronary revascularization than patients who underwent SPECT, but were similar to patients who underwent PET; most of the differences in invasive procedures were evident at 90 days and persisted for 2 years (Table 2). Use of beta-blockers and statins was highest after PET and lowest after SPECT (Table 2). During the 2 years of follow-up, 4 patients who underwent CTA died (0.7%), 9 patients who underwent SPECT died (1.6%), and 30 patients who underwent PET died (5.5%); in addition, a nonfatal MI was documented in 2 patients (0.3%) who underwent CTA, 7 patients (1.2%) who underwent SPECT, and 6 patients (1.1%) who underwent PET.

The 2-year costs were highest among the patients who had PET (mean $6,647, 95% confidence interval [CI]: $5,896 to $7,797), intermediate among the patients who had CTA (mean $4,909, 95% CI: $4,378 to $5,440), and lowest among the patients who had SPECT ($3,965, 95% CI: $3,520 to $4,411). The unadjusted costs among patients who had PET were significantly higher than those of patients who had SPECT ($p < 0.001$), and the unadjusted costs in patients who had CTA were significantly higher than those of patients who had SPECT ($p < 0.0001$). After multivariable adjustment for differences in baseline clinical characteristics, patients undergoing CTA had 15% higher costs than patients undergoing SPECT ($p < 0.01$), whereas patients undergoing PET had 22% higher costs than patients undergoing SPECT ($p < 0.0001$).

On the basis of the duration of observed survival and life expectancy of patients based on the U.S. life tables, patients in the CTA group lost a mean of 0.08 years of life, patients in the SPECT group lost 0.23 years, and patients in the PET group lost 0.76 years. After adjustment for baseline characteristics, the difference in survival between CTA and SPECT was not significant ($p = 0.07$), and the

Table 1 Baseline Characteristics

	CTA (n = 590)	SPECT (n = 565)	PET (n = 548)
Age, yrs	59 ± 11*	60 ± 11	63 ± 11§
Female	48	51	59†
White race	86§	68	80§
Diabetes	16§	30	41‡
Hypertension	56‡	66	73*
Hyperlipidemia	63	60	65
Smoker	16	19	12‡
Family history of CAD	37†	29	24*
Angina	84*	78	67‡
Heart failure	1§	5	3
Dyspnea	23	24	44§
Atrial fibrillation	5	5	8
Abnormal resting ECG	19	35	42
Prior cardiac testing	29§	4	15§
Likelihood of CAD	55†	51	47*

Values are mean ± SD or %. *p < 0.05 versus SPECT. †p < 0.01 versus SPECT. ‡p <0.001 versus SPECT. §p < 0.0001 versus SPECT.

CAD = coronary artery disease; CTA = coronary computed tomography angiography; ECG = electrocardiogram; PET = positron emission tomography; SPECT = single-photon emission computed tomography.

difference between PET and SPECT was also not significant (p = 0.07).

In order to estimate the cost effectiveness of CTA compared with SPECT, we matched patients on propensity score (Table 3). In the matched cohort of 388 pairs, patients who had CTA had $1,284 higher costs and 0.11 years longer survival, implying an incremental cost-effectiveness ratio of $11,700 per life-year added. This estimate was quite uncertain in the bootstrap analysis, however, with 13% of replications indicating lower survival and higher cost among CTA patients compared with SPECT, and another 10% of replications having a cost-effectiveness ratio >$50,000 per life year added (Fig. 1). In a sensitivity analysis that included life-years lost from a nonfatal MI, CTA added 0.12 life-years and had an incremental cost-effectiveness ratio of $10,700 per life-year added compared with SPECT; this estimate was also quite uncertain, with 11% of replications showing lower survival and higher costs after CTA, and another 7% with a cost-effectiveness ratio >$50,000 per life-year added.

In order to estimate the cost effectiveness of PET compared with SPECT, we matched on propensity score 372 pairs of patients undergoing either PET or SPECT (Table 3). In the matched group, the mean 2-year costs were higher among patients undergoing PET by $2,292, whereas survival was 0.36 years shorter among PET patients. Consequently, SPECT was the "dominant strategy," with lower costs and better survival. In the bootstrap analysis, 98% of replications yielded higher costs and poor survival among PET patients (Fig. 2). These results were essentially unchanged in the sensitivity analysis that incorporated life-years cost as a result of a nonfatal MI, with 96% of replications having higher costs and lower survival after PET compared with SPECT.

The mean total radiation exposure over the study period was significantly higher (p < 0.0001) for patients who underwent CTA (15.1 mSV) compared with propensity score–matched patients who underwent SPECT (11.7 mSV), both for the initial tests (13 mSV vs. 11 mSV) and for follow-up tests and procedures (2.1 mSV vs. 0.7 mSV, p < 0.0001). Mean total radiation exposure was significantly lower (p < 0.0001) after PET (6.0 mSV) than after SPECT

Table 2 Resource Use and Cost

	CTA (n = 590)	SPECT (n = 565)	PET (n = 548)
Invasive angiography			
90 days	13 (77)	4 (24)	11 (63)
2 yrs	16 (92)	7 (38)	15 (82)
PCI			
90 days	6 (37)	1 (8)	5 (25)
2 yrs	7 (43)	2 (11)	6 (31)
CABG			
0 days	2 (10)	0.4 (2)	2 (9)
Two yrs	2 (12)	0.4 (2)	2 (11)
Medications at 1 yr			
ACE/ARB	29 (171)	37 (209)	49 (269)
Beta-blocker	31 (181)	32 (178)	37 (203)
Calcium antagonist	11 (66)	16 (89)	20 (107)
Nitrate	6 (37)	6 (33)	5 (28)
Statin	49 (290)	45 (255)	55 (301)
Cost over 2 yrs			
Mean ± SD	$4,909 ± $6,575	$3,965 ± $5,404	$6,647 ± $8,962
Median (IQR)	$2,820 ($1,777–$4,585)	$2,810 ($1,692–$4,436)	$3,815 ($2,691–$5,585)

Values are % (n) unless otherwise indicated.

ACE/ARB = angiotensin-converting enzyme inhibitor/angiotension receptor blocker; CABG = coronary artery bypass graft surgery; IQR = interquartile range (25th to 75th percentile); PCI = percutaneous coronary intervention; other abbreviations as in Table 1.

Table 3 Baseline Characteristics of the Test Groups Matched by Propensity Score

	CTA–SPECT		PET–SPECT	
	CTA (n = 388)	SPECT (n = 388)	PET (n = 372)	SPECT (n = 372)
Mean age, yrs	59.4	59.9	62.6	61.6
Male	52	51	42	43
White race	85	75	78	70
Diabetes	18	20	37	34
Hypertension	60	59	67	72
Hyperlipidemia	67	60	65	61
Smoker	17	15	14	17
Family history of CAD	32	37	27	26
Angina	83	82	70	79
Heart failure	2	1	8	3
Dyspnea	22	21	28	41
Atrial fibrillation	6	3	7	6
Abnormal resting ECG	18	31	36	40
Prior cardiac testing	6	5	6	6
Likelihood of CAD	0.56	0.51	0.47	0.52

Values are %.
Abbreviations as in Tables 1 and 2.

(11.6 mSV) in propensity score–matched patients; exposure from the initial test was lower for PET (4 mSV) than for SPECT (11 mSV), but exposure from follow-up tests and procedures was higher after PET (2.0 mSV) than after SPECT (0.6 mSV) ($p < 0.0001$).

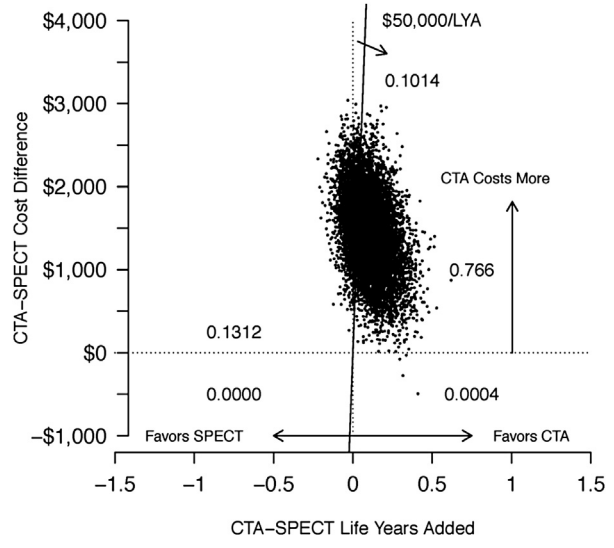

Figure 1 Bootstrap Analysis of the Incremental Cost-Effectiveness Ratio of CTA Compared With SPECT

Each **point** represents the results of a single bootstrap replication. The difference in 2-year costs between CTA and SPECT is displayed on the **vertical axis**, and the difference in life-years lost on the **horizontal axis**. The **solid line** indicates the $50,000 per life-year threshold, and the **numbers** indicate the proportion of replication falling within each sector of the cost-effectiveness plane. CTA = coronary computed tomography angiography; LYA = life-years added; SPECT = single-photon emission computed tomography.

Discussion

This analysis of the SPARC registry suggests that the choice of noninvasive tests to evaluate patients with suspected CAD affects subsequent medical costs, with the lowest costs over 2 years follow-up among patients evaluated by SPECT. The significantly higher costs among patients undergoing CTA or PET were primarily due to higher rates of subsequent invasive cardiac procedures, because there was little difference in initial costs of testing. The higher costs among patients evaluated with CTA or PET do not appear to be explained by differences in baseline characteristics, because costs remained significantly higher even after multivariable adjustment.

Clinical strategies that lead to higher costs may nevertheless provide good value for the added expenditures if patient outcomes are improved sufficiently. Cost-effectiveness analysis provides a framework within which to weigh costs and outcomes, and thereby assess value. Quantifying improvement in clinical outcomes is unfortunately more difficult than measuring costs, and in this study, the differences in clinical outcomes were too small and uncertain to allow any firm conclusions about the relative cost effectiveness of CTA, PET, and SPECT. Larger and more definitive studies, such as the ongoing PROMISE (Prospective Multicenter Imaging Study for Evaluation of Chest Pain) trial (NCT01174550), are needed to assess the value and cost effectiveness of these strategies.

The higher rate of invasive coronary angiography after CTA has been documented previously in some studies (6), but not in others (7–9). The use of invasive procedures

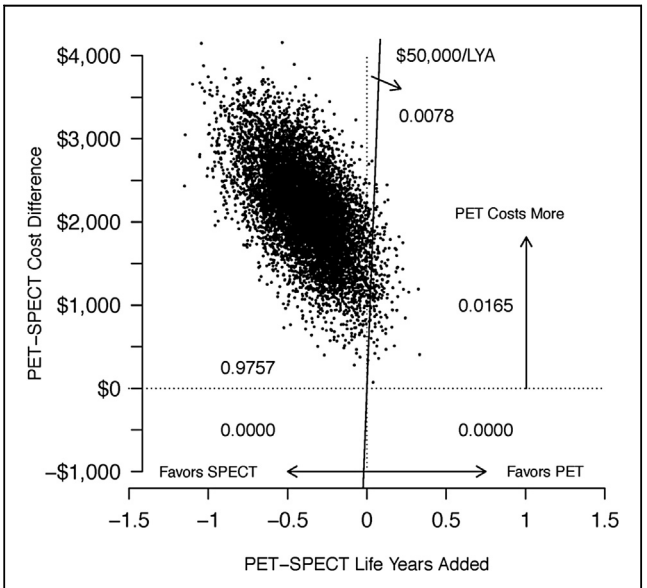

Figure 2 Bootstrap Analysis of the Incremental Cost-Effectiveness Ratio of PET Compared With SPECT

Format as in Figure 1. PET = positron emission tomography; other abbreviations as in Figure 1.

varied with the degree of abnormality seen on the CTA (2), with very few cardiac catheterizations done in patients with normal or near-normal CTA findings, but with a higher rate of catheterization among patients with an abnormal CTA (2). This observation suggests that the differences in the composition of the patient population and in the prevalence of underlying CAD may explain differences between prior studies in subsequent use of invasive testing after CTA. Studies that enrolled younger and lower-risk patient populations (9) should have more normal CTA studies and, consequently, fewer invasive tests than studies with patient populations that are older, have a higher risk, or both.

Patients undergoing PET in this study were older and had a number of adverse prognostic factors (e.g., diabetes and hypertension); they had the highest costs in follow-up and the worst clinical outcomes. The costs among PET patients remained higher after adjustment for clinical characteristics, although the statistical methods we used could not adjust for unmeasured factors, such as frailty, that might have increased overall costs. PET scanning has not been studied as intensively as other noninvasive testing methods, and is used uncommonly to evaluate suspected CAD. It is important to note that none of the patients in this study had a prior history of CAD, and that PET testing was not performed to assess myocardial viability. Our findings suggest that PET should be evaluated carefully in larger studies with contemporary controls, ideally in a randomized trial, to assess its impact on clinical and economic outcomes.

The optimal approach to the evaluation of patients with suspected CAD has been difficult to define, in part because there are many alternative test strategies. Direct clinical comparisons of the outcomes of different strategies are limited to 2 or 3 alternatives, whereas decision-modeling studies have been able to assess a larger number of choices. A decision model by Garber and Solomon (10) compared exercise treadmill testing, stress echocardiography, planar thallium imaging, SPECT, and PET imaging with a strategy of immediate invasive angiography. They found SPECT to be much more cost effective than PET for noninvasive diagnosis, and SPECT to be a better option than immediate invasive coronary angiography. Their study did not evaluate CTA, which had not yet been developed. A similar decision model by Kuntz et al. (11) found exercise echocardiography and SPECT to be reasonable choices for patients with intermediate probability of CAD, but invasive coronary angiography to be optimal for patients with high pre-test probability of CAD; their study did not evaluate PET or CTA. Hunink et al. (12) used a decision model to determine parameters that would indicate a new noninvasive test could be cost effective compared with stress echocardiography or SPECT, and suggested the cost would have to be <$1,000 with sensitivity and specificity of 95% or more. A systematic review and economic evaluation by Mowatt et al. (13) suggested that SPECT imaging could be cost effective compared with exercise ECG. The model of Hernández and Vale (14) also suggested that SPECT was cost effective compared with exercise ECG or invasive angiography without noninvasive testing, but did not consider CTA (or PET) as alternatives. Min et al. (15) used a decision model to assess 5 strategies using CTA or SPECT, and projected that strategies based on CTA might be more cost effective than strategies based on SPECT (15).

Empirical comparisons of outcomes after alternative noninvasive tests have been performed infrequently, and of necessity, have been limited to fewer choices. Shaw et al. (16) found that patients who underwent initial SPECT with selective cardiac catheterization had lower costs than patients who underwent routine coronary angiography. Sharples et al. (17) randomized 898 patients to SPECT, stress echocardiography, magnetic resonance imaging, or direct invasive coronary angiography, and found SPECT to be as useful as immediate invasive angiography with similar costs.

Long-term studies of clinical and economic outcomes such as the SPARC registry of necessity require prolonged observation, and hence may not reflect contemporary practice—the so-called "moving target problem" (18). All of the imaging tests we studied have continued to evolve, particularly CTA, which was performed in this study using 64-slice scanners between 2006 and 2008, when there was less experience in interpreting the images than today. In addition, newer approaches, such as noninvasive fractional flow reserve (19), can now provide information on the functional significance of lesions seen on CTA, which may alter the subsequent use of invasive cardiac procedures (20). Methods for performing PET and SPECT have also evolved over time. The ongoing evolution of medical knowledge and clinical practice underscores the value of maintaining prospective clinical registries that collect data on practice and outcomes continuously, and allow tracking of the "moving target."

Study limitations. This study has a number of additional limitations, primarily that mode of testing was chosen by physicians and not assigned randomly. Consequently, any differences in outcomes could be the result of residual selection bias that was uncorrected by careful statistical adjustment. The propensity score method we used cannot adjust for data that were not recorded on study forms, such as renal function, or that was not assessed uniformly, such as left ventricular function. Patients were from multiple different centers, and despite the use of a common protocol and data standards, differences in clinical practice patterns among centers might have affected the clinical and economic outcomes assessed here. The sample size in this study was not large enough to define reliably the effects of the alternative tests on subsequent rates of survival and MI, and consequently, the cost-effectiveness analysis has a wide range of uncertainty. We do not have data on symptoms or quality of life during follow-up, so our measure of clinical effectiveness could not account for any improvements in these outcomes as the result of treatments initiated based on test results. Finally, this study was performed among stable outpatients, and the results should not be extrapolated to other

settings, such as evaluation of patients presenting to an emergency department with acute chest pain.

Conclusions

The use of SPECT myocardial perfusion imaging seems to be associated with lower costs over 2 years of follow-up than does the use of CTA or PET, primarily because of fewer subsequent invasive procedures. Further studies are needed to compare the cost effectiveness of alternative noninvasive testing approaches for patients with symptoms suggestive of CAD.

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Key Words: costs and cost analysis ■ health services research ■ outcomes research.

APPENDIX

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