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Patient Management After Noninvasive Cardiac Imaging

Results From SPARC (Study of Myocardial Perfusion and Coronary Anatomy Imaging Roles in Coronary Artery Disease)

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Objectives This study examined short-term cardiac catheterization rates and medication changes after cardiac imaging.

Background Noninvasive cardiac imaging is widely used in coronary artery disease, but its effects on subsequent patient management are unclear.

Methods We assessed the 90-day post-test rates of catheterization and medication changes in a prospective registry of 1,703 patients without a documented history of coronary artery disease and an intermediate to high likelihood of coronary artery disease undergoing cardiac single-photon emission computed tomography, positron emission tomography, or 64-slice coronary computed tomography angiography.

Results Baseline medication use was relatively infrequent. At 90 days, 9.6% of patients underwent catheterization. The rates of catheterization and medication changes increased in proportion to test abnormality findings. Among patients with the most severe test result findings, 38% to 61% were not referred to catheterization, 20% to 30% were not receiving aspirin, 35% to 44% were not receiving a beta-blocker, and 20% to 25% were not receiving a lipid-lowering agent at 90 days after the index test. Risk-adjusted analyses revealed that compared with stress single-photon emission computed tomography or positron emission tomography, changes in aspirin and lipid-lowering agent use was greater after computed tomography angiography, as was the 90-day catheterization referral rate in the setting of normal/nonobstructive and mildly abnormal test results.

Conclusions Overall, noninvasive testing had only a modest impact on clinical management of patients referred for clinical testing. Although post-imaging use of cardiac catheterization and medical therapy increased in proportion to the degree of abnormality findings, the frequency of catheterization and medication change suggests possible undertreatment of higher risk patients. Patients were more likely to undergo cardiac catheterization after computed tomography angiography than after single-photon emission computed tomography or positron emission tomography after normal/nonobstructive and mildly abnormal study findings. (Study of Perfusion and Anatomy's Role in Coronary Artery [CAD] [SPARC]; NCT00321399) (J Am Coll Cardiol 2012;59:462–74) © 2012 by the American College of Cardiology Foundation

The use of noninvasive cardiac imaging is recommended in numerous clinical scenarios by current guidelines and appropriate use documents as a diagnostic and prognostic tool to improve efficiency of further testing and enhance risk stratification for coronary artery disease (CAD), especially in patients with an intermediate likelihood of CAD (1–3). Nonetheless, critics have pointed out that despite the widespread use of noninvasive cardiac imaging, there is no clinical trial evidence that this practice results in improved health outcomes or a decrease in long-term medical costs (4). There is also concern about the potential risks associated with radiation exposure from medical imaging. On the other hand, advocates claim that incorporating imaging into a testing strategy results in superior diagnostic accuracy, improved cost-effectiveness of patient management, and enhanced patient benefit (5,6). Although these claims have been widely made, evidence is sparse that the use of these expensive modalities actually alters post-imaging patient management.

Abbreviations and Acronyms

CAD = coronary artery disease

CCTA = coronary computed tomography angiography

MPI = myocardial perfusion imaging

PET = positron emission tomography

SPECT = single-photon emission computed tomography

The goal of the current study was to examine post-imaging, short-term patient management as measured by referral to catheterization and changes in medical therapy at 90 days after the index study in patients without previous CAD referred for elective noninvasive cardiovascular imaging and recruited to the SPARC (Study of Myocardial Perfusion and Coronary Anatomy Imaging Roles in CAD).

Methods

Study design. The details of the SPARC design and methods of analyses were previously published (7). The current analysis is limited to patients without previous CAD with an intermediate to high CAD likelihood enrolled in the SPARC. Clinically stable patients presenting for elective, clinically indicated cardiac imaging (myocardial perfusion imaging [MPI], single-photon emission computed tomography [SPECT] or positron emission tomography [PET], and coronary computed tomography angiography [CTA]) were enrolled. Participating sites included hospitals and outpatient offices, academic and nonacademic sites, and community and tertiary care centers. A total of 1,717 consecutive patients without previous CAD were enrolled in the SPARC. At 90 days after the index study, 5 patients (0.3%) were lost to follow-up and 9 patients (0.5%) withdrew consent, leaving 1,703 patients with 90-day follow-up for analysis. No patients had missing data for any variable.

This study was approved by the institutional review committee at each study site, and all enrolled patients provided both written informed consent and HIPAA (Health Insurance Portability and Accountability Act) release before index study procedures for study endpoint records collection.

Performance, interpretation, and scoring of the index imaging study. All studies, image acquisition, and image processing followed each site's institutional protocol. As patient management decisions were based on the clinically reported interpretations, analyses of patient management were based on the reported site interpretation rather than a core laboratory interpretation of imaging results.

MYOCARDIAL PERFUSION IMAGES. SPECT and PET findings were assessed using semiquantitative visual assessment of regional myocardial perfusion using the recommended 17-segment/4-point scoring system, as previously described (7). Segmental scoring was performed by site readers following study guidelines (7).

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Summed scores were calculated from these segmental scores and converted to a percentage of myocardium fixed, abnormal, or ischemic (the percentage of total myocardium involved with stress, ischemic, or fixed defects), by dividing the summed scores by 51 and multiplying by 100, as previously described (7).

CCTA IMAGES. CTA study findings were interpreted and scored using the American College of Cardiology/American Heart Association–recommended segmentation schema, as previously described (7). For each coronary segment, segment accessibility, plaque presence, stenosis severity, plaque composition (calcified, predominantly noncalcified, or complex), and stent presence were recorded.

DERIVED INDICES. The pre-test likelihood of CAD as a continuous variable was calculated using the method of Pryor et al. (8). Hospital status was defined on the basis of whether the imaging center was located in a hospital and academic status on the basis of the site principal investigator's self-reporting. Dyspnea and type of chest pain were considered as separate variables.

To permit direct comparison of myocardial perfusion imaging (MPI) and CCTA data, a 3-category variable was predefined as follows: 1) normal/nonobstructive included CCTA with either normal coronary arteries or with nonobstructive CAD, and normal myocardial perfusion by SPECT or PET; 2) mildly abnormal included CCTA showing evidence of obstructive CAD (at least 1 epicardial coronary artery with ≥70%) but without high-risk anatomic features (i.e., left main stenosis ≥50%, ≥70% stenosis in the proximal left anterior descending artery, or 3-vessel CAD with ≥70% stenosis) (9), and a myocardial perfusion SPECT or PET study demonstrating mild abnormality (>0% but <10% myocardium abnormal); 3) moderate to severe abnormality included CCTA showing evidence of high-risk anatomic features as defined previously, and a myocardial perfusion SPECT or PET study showing a moderate to severe abnormality (≥10% myocardium abnormal). For purposes of dichotomization, categories 2 and 3 were included in the abnormal category and 1 in the normal category.

Study endpoints. The primary endpoints of this study are: 1) referral for catheterization within 90 days of the index study; and 2) change in cardiac medication use between baseline and 90 days (medication dose change [increase or decrease], discontinuation, or addition of a new medication). We limited our analysis to the use of aspirin, beta-blockers, and lipid-lowering agents. Referral to revascularization within 90 days after noninvasive procedures was a secondary endpoint. Information regarding invasive procedures and medication use were obtained directly from patient interview. The occurrence of catheterization and revascularization and the results of catheterization were ascertained from operative and procedural reports.

Cardiac catheterization results. CAD presence and extent were determined from catheterization reports by 2 independent readers, with discrepancies adjudicated by consensus. Obstructive CAD was defined as stenosis of ≥50% of the left main coronary artery or ≥70% of a major epicardial or branch vessel. Patients with definite atherosclerosis but with coronary stenosis of ≤50% of the left main coronary artery or ≤70% of a major epicardial or branch vessel were considered to have nonobstructive CAD. Patients without evidence of angiographic atherosclerosis were categorized as having normal coronary arteries.

Statistical analysis. Continuous variables are presented as mean ± 1 SD and categorical variables as percentages. Continuous variables were compared with a *t* test (pairwise comparisons) or analysis of variance (multigroup comparisons) and categorical variables with a chi-square test. A Bonferroni adjustment was applied as appropriate for multiple comparisons. Analysis of medication change as a function of study results and imaging modality was performed for aspirin, lipid-lowering agents, and beta-blockers. A Cochran-Mantel-Haenszel chi-square test was used to examine the association of time (baseline vs. 90 days) and study results with respect to frequency of medication use. Post-hoc comparisons across modalities were performed at each level of study result using a chi-square test of association with significance determined by a Bonferroni adjustment using 3 comparisons.

For each outcome, a generalized linear mixed model, a hierarchical model, was applied by including regions and sites as random effects to account for the possible variability of the regions and sites within each region. A logistic link was used for the binary outcome. All interesting covariates were considered as fixed effects, whereas regions and sites within each region as random effects. This analysis was done by the function of "glmer" in R library lme4 (The Comprehensive R Archive Network, The R Foundation for Statistical Computing). Contrasts were used to compare across modalities at each study result with significance determined by a Bonferroni corrected p value with 3 comparisons.

Results

Patient characteristics. Table 1 summarizes the baseline characteristics of patients in the study. The 1,703-patient cohort was evenly divided among the 3 imaging modalities. Risk factors were prevalent. More than three fourths of patients presented with angina; 30% of patients reported dyspnea. Aspirin, beta-blockers, and lipid-lowering agents were the most commonly used medications at baseline.

As part of the SPARC, sites collected data on 7,872 patients presenting for testing but not enrolling in the SPARC. Due to institutional review board constraints, the data collected on these patients were limited to age, race, and sex. Compared with the patients in the current study, patients in the SPARC screening registry were slightly older (age 63 ± 14 years), more frequently white (86%), and more frequently male (54%).

Overall, 26% of patients had abnormal noninvasive imaging results. Of these, 18% were mildly abnormal and 8% moderately to severely abnormal. Normal or nonobstructive

Table 1 Baseline Characteristics for Study Population

	Index Modality			
	SPECT (n = 565)	PET (n = 548)	CCTA (n = 590)	Total Patients (N = 1,703)
Demographics				
Age, yrs	60 ± 11	63 ± 11*	58 ± 11.4	62 ± 11
Male	49% (279)	41% (225)*	52% (308)	48% (812)
White race	68% (386)	80% (439)*	87% (513)	82% (1,396)
Body mass index, kg/m^2	30 ± 7	34 ± 10*	29 ± 6	31 ± 7
Baseline medical history				
Diabetes	31% (173)	41% (225)*	16% (94)*	29% (492)
Smoking, within 5 yrs	20% (110)	12% (64)*	16% (97)*	16% (271)
High/elevated cholesterol	60% (338)	65% (356)*	63% (370)*	62% (1,064)
Hypertension	66% (371)	73% (398)*	56% (328)*	64% (1,097)
Family history of premature CAD	29% (165)	24% (130)*	37% (220)*	30% (515)
Atrial fibrillation	5% (30)	8% (44)	5% (30)	6% (104)
Baseline medications				
Aspirin	41% (230)	47% (256)	47% (278)	45% (764)
Lipid-lowering drugs	44% (250)	53% (288)	50% (295)	49% (833)
Beta-blockers	30% (172)	39% (211)	29% (170)	32% (553)
ACE inhibitors	28% (158)	35% (193)	20% (116)	27% (467)
Angiotensin receptor blocker	9% (51)	13% (71)	10% (60)	11% (182)
Diuretics	23% (129)	35% (189)	18% (105)	25% (423)
Calcium channel blockers	16% (92)	18% (99)	11% (66)	15% (257)
Nitrates	5% (30)	4% (24)	5% (31)	5% (85)
Clopidogrel	2% (9)	3% (18)	3% (19)	3% (46)
Antiarrhythmic agents	1% (7)	2% (12)	2% (13)	2% (32)
Presenting cardiac symptoms				
Asymptomatic	11% (63)	11% (63)	10% (60)	11% (186)
Anginal symptoms	79% (449)	68% (370)*	85% (504)*	78% (1,323)
Noncardiac chest pain	4% (21)	5% (29)	2% (13)	4% (63)
Dyspnea	24% (136)	44% (239)*	23% (134)	30% (509)
Likelihood of CAD	0.38 ± 0.29	0.45 ± 0.33	0.41 ± 0.39	0.41 ± 0.33

Values are mean ± SD or % (n). *$p < 0.05$ versus SPECT based on *t* test using a Bonferroni adjustment of 0.025 for 2 comparisons.
ACE = angiotensin-converting enzyme inhibitor; CAD = coronary artery disease; CCTA = coronary computed tomography angiography; PET = positron emission tomography; SPECT = single-photon emission computed tomography.

imaging results were present in 82% undergoing CCTA, 62% undergoing PET, and 78% undergoing SPECT studies ($p < 0.001$). In the SPECT arm, 65% (n = 368) of patients underwent exercise stress, 28% (n = 158) underwent pharmacologic stress only, and an additional 7% (n = 40) underwent combined pharmacologic stress with adjunct exercise stress. All patients in the PET arm underwent pharmacologic stress.

Overall, 17% of patients in the study had stress and/or other imaging tests within 90 days before their index imaging study (Fig. 1). The frequency of previous testing among patients undergoing CCTA as their index study was twice as high as that of those undergoing PET and 6 times higher than those undergoing SPECT.

Referral for cardiac catheterization after noninvasive imaging tests. Catheterization was performed in 9.6% of patients (n =163), in 35 patients (2.8%) with normal/nonobstructive results, in 61 patients (20.3%) with mildly abnormal, and in 67 patients (48.2%) with moderately to severely abnormal study results ($p < 0.001$). Referral to catheterization within 90 days occurred in 24 patients (4.3%) after SPECT, in 61 patients (11.1%) after PET, and in 78 patients (13.2%) after CCTA ($p < 0.001$). The frequency of catheterization was greater after CCTA than after SPECT or PET across the entire spectrum of study results, although it was only statistically different in the setting of normal/nonobstructive or mildly abnormal study results (Fig. 2A). However, when normal CCTA findings were defined as the absence of any abnormality on CCTA, the referral for catheterization rate after normal CCTA results decreased from 5.2% to 1.7%, and the intermodality difference was no longer present. There were no significant changes in these results when the frequencies of catheterization were considered as a function of stress defects rather than ischemic defects.

MULTIVARIABLE MODELING OF CATHETERIZATION REFERRAL. Multivariable modeling using recruitment site and the site's geographic location as random effects revealed that after

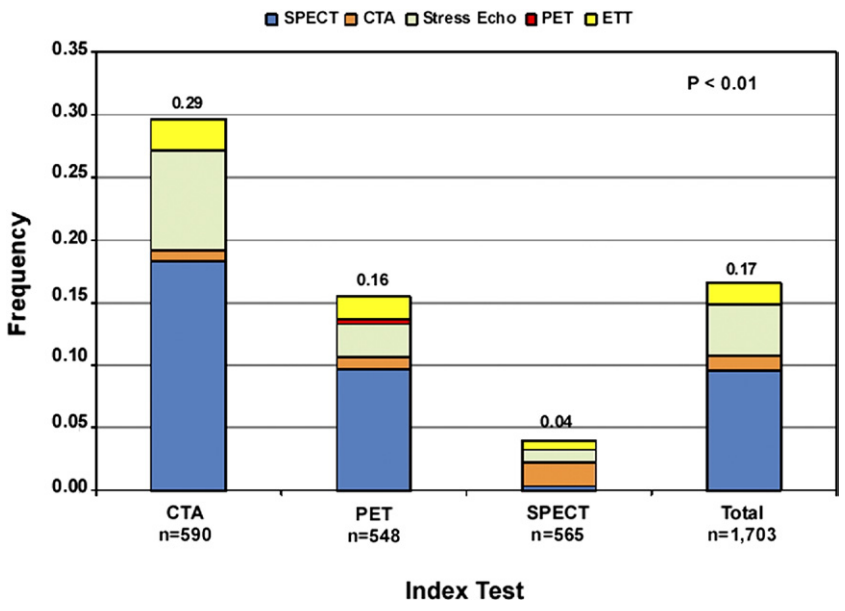

Figure 1 **Frequency of Testing Before Enrollment**

Relative frequency of stress test and/or imaging studies performed within 90 days before enrollment in the SPARC (Study of Myocardial Perfusion and Coronary Anatomy Imaging Roles in Coronary Artery Disease) by imaging arm. Comparisons of previous studies by modality are performed using the Cochran-Mantel-Haenszel chi-square test. The p value indicates that the frequency of previous studies differed by index study modality. CCTA = coronary computed tomography angiography; Echo = echocardiography; ETT = exercise treadmill test; PET = positron emission tomography; SPECT = single-photon emission computed tomography.

adjustment for patient age, sex, race, diabetes, and hospital status, both imaging results and the modality used were closely associated with referral for early catheterization (Wald chi-square test: 378.9, $p < 0.0001$) (Table 2). The effect of PET use was less than that of CCTA, but both were associated with increased referral for catheterization. A significant interaction between the modality used and study result was present such that referral for catheterization rates differed between MPI and CCTA in the setting of normal/nonobstructive and mildly abnormal test results but not in the setting of moderately to severely abnormal results (Fig. 2B).

The type of center where the study was performed or the occurrence of another imaging study before the index study was not associated with an increased referral for catheterization rate. In a separate model, the use of SPECT, CCTA, echocardiography, or exercise treadmill test in the 90 days preceding the index study was not associated with increased referral for catheterization. Finally, catheterization rates were greater in patients who were men, those with angina, and those of the white race.

We also repeated this analysis in the subset of 1,493 patients who did not undergo noninvasive procedures before their index SPARC imaging study. The results were very similar to the results of the analysis in the overall cohort. The global chi-square was reduced (from 379 to 324), whereas modality used, study result, and the modality used–study result interaction were all statistically significant. The odds ratios for these covariates were similar to those described earlier. Unlike this analysis of the overall cohort, the PET-SPECT difference in referral for catheterization was no longer significant ($p = 0.12$).

CARDIAC CATHETERIZATION RESULTS AND REFERRAL FOR REVASCULARIZATION. Overall, 62.6% of patients (n = 102) referred for catheterization had evidence of obstructive CAD. The frequency of obstructive CAD was 54.2% (n = 24), 67.2% (n = 61), 61.5% (n = 78) found on SPECT, PET, and CCTA, respectively ($p = 0.517$). The proportions of patients without obstructive disease at catheterization and a positive imaging study results was 39.1%, 28.3%, and 16.9%, respectively in SPECT, PET, and CCTA (SPECT vs. PET: p = NS, SPECT vs. CCTA: $p = 0.049$), and the proportions of patients with obstructive disease at catheterization and negative imaging study results were 0.0%, 3.3%, and 20.8%, respectively (SPECT vs. PET: p = NS, SPECT vs. CCTA: $p = 0.006$).

In the setting of an imaging study with moderately to severely abnormal findings, multivessel CAD was found in 49%, 27%, and 30% of PET, CTA, and SPECT patients, respectively. After an imaging study showing mildly abnormal findings, multivessel CAD was found in 12%, 24%, and 0% of patients after PET, CCTA, and SPECT, respectively. Due to small numbers, these differences did not reach statistical significance.

Overall, there were 96 revascularization procedures within 90 days of the index study (Fig. 3). When

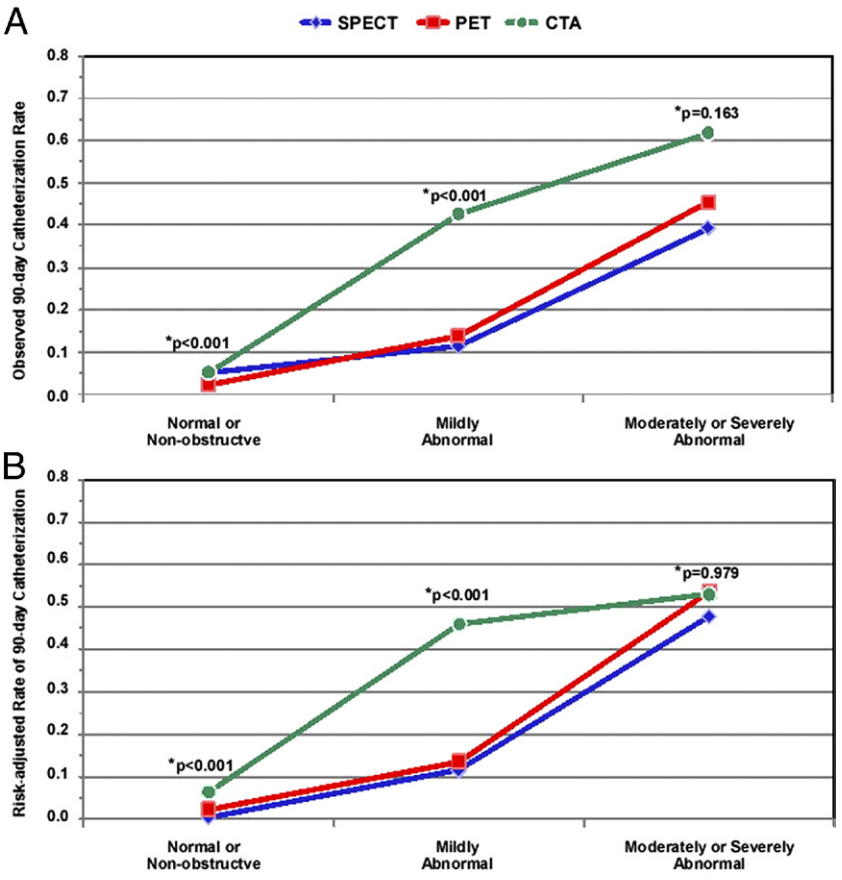

Figure 2 Post-Test Referral for Cardiac Catheterization

(A) Relative frequency of referral for cardiac catheterization within 90 days after SPECT, PET, and CCTA as a function of study result. Differences in catheterization rates across study results and modalities were significant (Cochran-Mantel-Haenszel chi-square test: $p < 0.001$). Results of statistical testing of differences in catheterization rates between modalities within study result categories are indicated by **asterisks**. Differences in catheterization rates among modalities in normal/nonobstructive and mildly abnormal are significant after Bonferroni adjustment for 3 multiple comparisons. **(B)** Risk-adjusted rate of referral for cardiac catheterization within 90 days after SPECT, PET, and CTA as a function of study result. Risk adjustment based on the results of general linear modeling using regions and sites as random effects (Table 4). Adjustment includes consideration of patients' age, sex, race, anginal symptoms, diabetes, hospital status, and previous imaging study. The p values shown represent contrasts between modalities. Contrasts assumed mean values of numeric predictors and modality values of categorical predictors. Differences in catheterization rates between modalities in normal/nonobstructive and mildly abnormal are significant after Bonferroni adjustment for 3 multiple comparisons. Abbreviations as in Figure 1.

expressed as a function of the overall cohort, the revascularization rate after an imaging study with normal findings was uniformly low across all modalities. Compared with SPECT and PET, revascularization rates were greater after CCTA, with the greatest differences in the setting of a mildly abnormal study result (3.1%, 4.6%, and 30.7%, respectively; $p < 0.001$), but more similar after studies with moderately to severely abnormal findings (28.6%, 35.1%, and 44.1%, respectively; $p = 0.43$). Among patients referred for cardiac catheterization, the frequency of revascularization tended to be higher in CCTA patients than in MPI patients.

Baseline and 90-day medication use. Baseline and 90-day medication use are summarized in Table 3. The frequency pattern of medication use was similar across all imaging arms, with the exception of the lipid-lowering agent use, which was slightly higher in patients referred for PET and CCTA (52.6% and 50.0%, respectively). Comparing baseline with 90-day medication use in the overall cohort, there were modest increases in the use of all 3 medications. Overall, a significant association was present between the number of medications used at the time of the study and the degree of abnormality found on the study (Cochran-Mantel-Haenszel chi-square test, $p = 0.0049$). In addition, there was an association between the degree of abnormality found on the study and the baseline use of aspirin and lipid-lowering agents (both $p < 0.01$), but not beta-blockers ($p = 0.0987$).

MEDICATION CHANGES, MODALITY USED, AND STUDY RESULTS. The frequency of use of each of the 3 medications increased from baseline to 90 days in almost all imaging modality

Table 2 Results of Multivariable Modeling of Referral for Cardiac Catheterization at 90 Days

Variable	Wald Chi-Square Statistic (p Value)	Adjusted Odds Ratio (95% CI)
Imaging modality (overall)	17.4 (<0.0001)	
CCTA*	13.4 (<0.0001)	14.92 (3.52–63.27)
PET*	4.0 (0.045)	5.03 (1.04–24.43)
Imaging results (overall)	58.5 (<0.0001)	
Mildly abnormal†	18.0 (<0.0001)	28.45 (6.06–133.62)
Moderately to severely abnormal†	40.5 (<0.0001)	199.23 (38.98–1,018.21)
Imaging modality × imaging results	12.4 (0.015)	
PET: mild abnormality‡	2.5 (0.11)	0.24 (0.04–1.42)
CCTA: mild abnormality‡	0.9 (0.34)	0.44 (0.08–38)
PET: moderate to severe abnormality‡	2.1 (0.14)	0.25 (0.04–1.59)
CCTA: moderate to severe abnormality‡	6.9 (0.009)	0.08 (0.01–0.53)
Age group (overall), yrs	13.4 (0.02	
40–49§	1.7 (0.24)	4.13 (0.49–34.50)
50–59§	2.8 (0.11)	5.88 (0.73–47.23
60–69§	3.4 (0.09)	7.03 (0.87–56.51)
70–79§	3.5 (0.079)	7.39 (0.90–60.7)
>80§	2.0 (0.25)	5.11 (0.54–48.39)
Male‖	8.2 (0.004)	1.82 (1.15–2.78)
White race‖	8.6 (0.003)	2.46 (1.35–4.50)
Angina‖	16.1 (<0.001)	3.11 (1.79–5.42)
Diabetes‖	0.2 (0.68)	1.11 (0.69–1.78)
Hospital status¶	2.1 (0.15)	1.52 (0.86–2.68)
Previous imaging study	0 (0.96)	0.99 (0.56–1.73)

*The odds ratios are for imaging modality (CCTA, PET) compared with single-photon emission computed tomography. †The odds ratios are for imaging results (mild abnormality, moderate to severe abnormality) compared with a normal/nonobstructive study result. ‡The odds ratios are for modality-study result pairing compared with normal findings on single-photon emission computed tomography. §The odds ratios are for age groups compared with the patient age group younger than 40 years. ‖The odds ratios are for the presence of this characteristic compared with its absence. ¶The odds ratios are for studies done in an imaging center located in hospital compared with out of hospital.

CI = confidence interval; other abbreviations as in Table 1.

subgroups. The absolute frequency in the use of aspirin, beta-blocker, and lipid-lowering agent increased as a function of study results in the overall cohort both at baseline and at 90 days. A similar trend was also observed in almost all imaging modality subgroups. In the overall cohort, there was an association between the study result and the 90-day

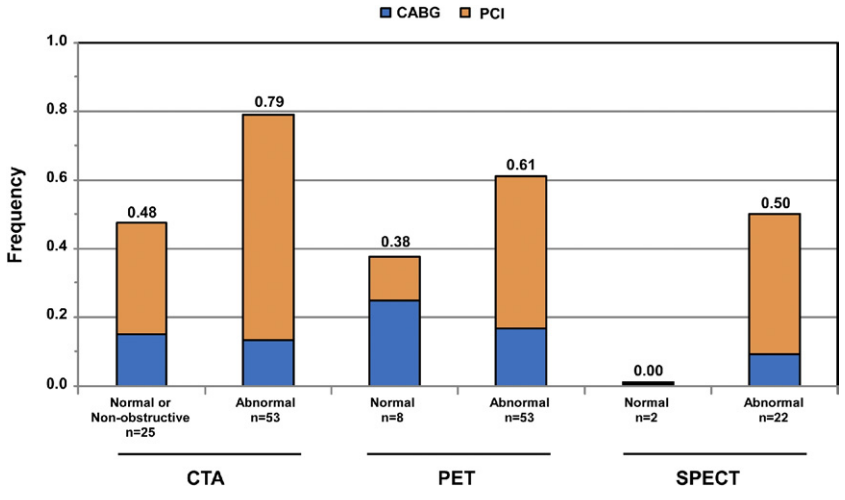

Figure 3 Post-Test Referral for Revascularization

Relative frequency of referral for coronary artery bypass graft (CABG) and percutaneous coronary intervention (PCI) within 90 days after normal or nonobstructive versus abnormal cardiac imaging study results in patients referred for cardiac catheterization in each of the 3 imaging arms. Revascularization rates were higher in patients with abnormal versus normal or nonobstructive CTA results (Cochran-Mantel-Haenszel, $p < 0.05$). Abbreviations as in Figure 1.

Table 3 Aspirin, Beta-Blocker, and Lipid-Lowering Agent Frequency: Baseline and 90 Days

	Aspirin, %		Beta-blocker, %		Lipid-Lowering Agent, %	
	Baseline	90 Days	Baseline	90 Days	Baseline	90 Days
All patients						
Overall	44.9	56.0*	32.5	37.8*	48.9	58.7*
Normal	43.2	52.7*	30.8	34.0	47.3	55.3*
Mildly abnormal	45.8	60.8*	35.2	44.9	49.2	64.5*
Moderate to severely abnormal	57.6†	76.3*†	41.7	57.6†	62.6	77.0†
p value	0.0002		<0.0001		0.2372	
SPECT						
Overall	40.7	48.7	30.4	33.3	44.2	51.7
Normal	37.4	45.4	29.9	31.5	43.5	49.9
Mildly abnormal	49.0	56.3	28.1	32.3	41.7	52.1
Moderately to severely abnormal	64.3†	75.0†	46.4	64.3†	64.3	78.6†
p value	0.6958		<0.0001		0.1089	
PET						
Overall	46.7	59.9*	38.5	44.5	52.6	62.2*
Normal	47.5	56.3	38.4	41.3*	51.0	58.1
Mildly abnormal	38.5	57.7*	38.5	46.2	51.5	65.4
Moderately to severely abnormal	57.1	79.2†	39.0	55.8	61.0	75.3†
p value	<0.0001		0.0777		0.1370	
CCTA						
Overall	47.1	59.5*	28.8	35.9	50.0	62.2*
Normal	45.5	56.8*	26.2	31.0	48.2	58.4*
Mildly abnormal	54.7	72.0	38.7	58.7	54.7	78.7*
Moderately to severely abnormal	52.9	70.6	44.1	55.9†	64.7	79.4
p value	0.0302		0.0015		0.1361	

Values from a Cochran-Mantel-Haenszel chi-square test statistic of general association of the distribution of medication change as a function of test result and imaging modality. *$p < 0.05$ for 90-day versus baseline frequency of medication use, overall and at each level of test result. †$p < 0.05$ across categories of test results within time category (baseline and 90 days). These comparisons are based on the chi-square test of association with a Bonferroni adjustment of 0.01 for 5 comparisons.

Abbreviations as in Table 1.

change (from baseline) in the frequency of use of aspirin and beta-blockers (Table 3) (Cochran-Mantel-Haenszel chi-square test, $p = 0.0002$ and $p < 0.0001$, respectively). A similar association was also present within a number of imaging modality subgroups (Table 3). Of note, among patients with moderately to severely abnormal study results, 24% were not receiving aspirin, 44% were not receiving a beta-blocker, and 23% were not receiving a lipid-lowering agent at 90 days after the index study, and 40% were on none of these medications or only taking 1 drug (Fig. 4). In addition, 49% of these patients were not referred for catheterization.

MULTIVARIABLE MODELING OF CHANGES IN MEDICAL MANAGEMENT. Multivariable modeling using recruitment site and the site's geographic location as random effects revealed that after adjustment for patient age, sex, race, diabetes, hospital status, and the use of previous imaging studies, the study result and, to a lesser degree, the use of CCTA and the use of aspirin at baseline were most closely associated with changes in the use of aspirin (change in dose, addition or removal of the medication, change in class of medication) (Table 4). Patient age and sex were also associated with this endpoint. When this analysis was limited to patients not taking aspirin at baseline, initiation of aspirin after imaging was most closely associated with the study result and the modality used (Table 5). With respect to this endpoint and patient subset, patients referred for both PET and CCTA were more likely to be started on aspirin compared with patients referred for SPECT.

Similar analysis of changes in the use of beta-blockers (Table 4) revealed that only study results and patient age to be associated with this endpoint; no such association was present for the modality used. Examination of patients not taking beta-blockers at baseline (Table 5) identified only patient age to be associated with initiation of beta-blockers and a borderline association with use of imaging before the index study.

Finally, analysis of changes in lipid-lowering agent use revealed the use of CCTA, study results, and patient age to be most closely associated with changes in lipid-lowering agent prescription (Table 4). With respect to patients not taking lipid-lowering agents at baseline, lipid-lowering agent initiation was most closely associated with these same factors (Table 5).

Referral for cardiac catheterization and/or changes in medication use after imaging. Overall, at 90 days after imaging, neither referral for cardiac catheterization nor medication changes occurred in 1,019 patients (59.8%), both occurred in 104 patients (6.1%), referral for cardiac catheterization without medication changes was observed in

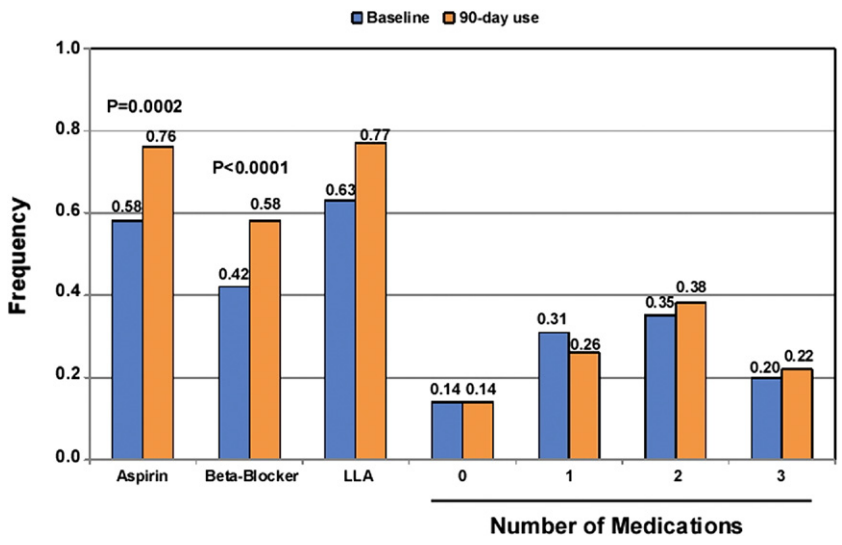

Figure 4 Medical Therapy Before and After Noninvasive Testing

Absolute frequency of medication use at baseline and 90 days in the subgroup of patients with moderately or severely abnormal imaging study results. Comparisons between frequencies of medication use are made using a chi-square test of association. The p values indicate differences in baseline versus 90-day medication use. LLA = lipid-lowering agent.

59 (3.5%), and medication changes without referral for cardiac catheterization was documented in 521 (30.1%). In the setting of normal or nonobstructive and mildly abnormal study results, the frequency of patients neither referred for catheterization nor having medication change was the most frequent finding, with smaller numbers having a medication change without a referral for cardiac catheterization, and few having both occur or only referral for catheterization (both $p < 0.05$) (Fig. 5). In the setting of moderately to severely abnormal test results, there were similar frequencies of patients in each category (p = NS).

Table 4 Modeling of Change in Medical Therapy With Adjustment for Baseline Medication Use

	Predictors of 90-Day Change in Aspirin		Predictors of 90-Day Change in Beta-Blockers		Predictors of 90-Day Change in Lipid-Lowering Agents	
Variable	Wald Chi-Square Statistic (p Value)	Adjusted Odds Ratio (95% CI)	Wald Chi-Square Statistic (p Value)	Adjusted Odds Ratio (95% CI)	Wald Chi-Square Statistic (p Value)	Adjusted Odds Ratio (95% CI)
Imaging modality (overall)	8.1 (0.017)		0.4 (0.82)		22.3 (<0.001)	
CCTA	7.6 (0.006)	1.62 (1.15–2.29)		0.96 (0.60–1.54)	22.3 (<0.001)	2.2 (1.59–3.05)
PET	0.5 (0.48)	1.14 (0.79–1.66)		0.86 (0.52–1.41)	0 (0.90)	1.02 (0.71–1.47)
Test result (overall)	16.7 (<0.001)		6.7 (0.035)		30.4 (<0.001)	
Mildly abnormal	4.3 (0.038)	1.45 (1.02–2.05)	0.5 (0.50)	0.89 (0.64–1.24)	11 (<0.001)	1.75 (1.26–2.45)
Moderate to severely abnormal	12.4 (<0.001)	2.24 (1.43–3.50)	6.2 (0.013)	1.82 (1.13–2.91)	19.4 (<0.001)	2.63 (1.71–4.04)
Age group (overall), yrs	15.6 (0.008)		13.9 (0.016)		30.9 (<0.001)	
40–49	0.4 (0.51)	1.41 (0.51–3.90)	3.7 (0.054)	0.42 (0.17–1.01)	4.1 (0.043)	3.57 (1.04–12.23)
50–59	3.9 (0.047)	2.68 (1.01–7.12)	0 (0.97)	1.01 (0.64–1.58)	9.1 (0.003)	6.39 (1.91–21.35)
60–69	5.5 (0.019)	3.23 (1.21–8.58)	6.1 (0.014)	1.69 (1.11–2.57)	8.6 (0.003)	6.12 (1.83–20.54)
70–79	4.5 (0.033)	2.96 (1.09–8.06)	3.2 (0.073)	0.69 (0.46–1.04)	7.3 (0.007)	5.41 (1.59–18.47)
Male	8.9 (0.003)	1.52 (1.15–1.96)	1.6 (0.20)	2.62 (0.61–1.42)	2.4 (0.12)	0.82 (0.64–1.06)
White race	0.3 (0.60)	0.91 (0.65–1.29)	2.3 (0.13)	3.14 (0.72–13.69)	1.0 (0.31)	1.19 (0.85–1.68)
Angina	0.2 (0.64)	1.08 (0.77–1.52)	2.4 (0.12)	3.26 (0.73–14.49)	3.6 (0.057)	1.37 (0.99–1.90)
Diabetes	0.3 (0.61)	0.92 (0.67–1.27)	1.6 (0.21)	0.61 (0.29–1.32)	0 (0.98)	1.00 (0.73–1.35)
Hospital status	2.9 (0.087)	0.68 (0.44–1.06)	0.9 (0.33)	2.24 (0.44–11.55)	0.3 (0.61)	0.89 (0.56–1.41)
Previous imaging study	0.8 (0.38)	1.19 (0.81–1.75)	1.0 (0.33)	1.23 (0.81–1.86)	0.3 (0.61)	0.91 (0.62–1.32)
Use of medication at baseline	16.5 (<0.001)	0.57 (0.44–0.75)	0.1 (0.76)	1.09 (0.63–1.89)	0.4 (0.53)	1.08 (0.84–1.40)

Abbreviations as in Tables 1 and 2.

Table 5 Results of Multivariable Modeling of Change in Medical Therapy in Patients Not Taking Medication at Baseline

Variable	Predictors of 90-Day Change in Aspirin		Predictors of 90-Day Change in Beta-Blockers		Predictors of 90-Day Change in Lipid-Lowering Agents	
	Wald Chi-Square Statistic (p Value)	Adjusted Odds Ratio (95% CI)	Wald Chi-Square Statistic (p Value)	Adjusted Odds Ratio (95% CI)	Wald Chi-Square Statistic (p Value)	Adjusted Odds Ratio (95% CI)
Imaging modality (overall)	17.9 (<0.001)		1.9 (0.39)		15.2 (<0.001)	
CCTA	11.1 (<0.001)	2.14 (1.37–3.34)		1.01 (0.55–1.85)	13.8 (<0.001)	2.42 (1.52–3.85)
PET	6.8 (0.009)	1.87 (1.17–2.98)		0.62 (0.31–1.23)	1.4 (0.24)	1.35 (0.82–2.25)
Test result (overall)	19.3 (<0.001)		2.5 (0.29)		25.9 (<0.001)	
Mildly abnormal	4.1 (0.044)	1.59 (1.01–2.49)		0.93 (0.58–1.49)	14.3 (<0.001)	2.41 (1.53–3.79)
Moderately to severely abnormal	15.2 (<0.001)	3.41 (1.84–6.32)		1.78 (0.86–3.68)	11.6 (<0.001)	3.24 (1.65–6.38)
Age group (overall), yrs	10.3 (0.067)		17 (0.004)		16.6 (0.005)	
40–49		1.63 (0.52–5.11)	1.2 (0.27)	0.55 (0.19–1.60)	1.6 (0.20)	2.69 (0.59–12.3)
50–59		2.38 (0.79–7.18)	3.0 (0.082)	1.88 (0.92–3.85)	4.7 (0.03)	5.16 (1.17–22.63)
60–69		3.44 (1.13–10.44)	11.8 (<0.001)	3.1 (1.62–5.91)	4.2 (0.041)	4.74 (1.06–21.13)
70–79		2.48 (0.79–7.83)	0.3 (0.57)	0.84 (0.47–1.53)	3.9 (0.05)	4.58 (1.00–20.89)
>80		1.17 (0.28–4.83)	0.7 (0.39)	2.49 (0.31–20.07)	2.2 (0.14)	3.57 (0.65–19.49)
Male	4.9 (0.027)	1.47 (1.04–2.08)	1.0 (0.31)	2.9 (0.37–22.40)	0.9 (0.35)	0.84 (0.59–1.21)
White race	0 (0.93)	0.98 (0.63–1.51)	1.4 (0.23)	3.5 (0.45–27.04)	0.6 (0.44)	1.21 (0.75–1.94)
Angina	3.0 (0.083)	1.50 (0.95–2.38)	2.0 (0.16)	4.43 (0.56–35.33)	0.6 (0.42)	1.23 (0.74–2.03)
Diabetes	0.4 (0.53)	1.15 (0.75–1.75)	1.8 (0.18)	0.54 (0.22–1.34)	1.2 (0.28)	1.29 (0.81–2.04)
Hospital status	3.8 (0.05)	0.59 (0.35–1.00)	0.5 (0.47)	2.37 (0.23–24.89)	0.0 (0.89)	1.04 (0.60–1.81)
Previous imaging study	0.6 (0.43)	1.23 (0.74–2.05)	3.1 (0.078)	1.77 (0.94–3.35)	0.0 (0.98)	0.99 (0.59–1.66)

N for predictors of aspirin use was 939, for changes in beta-blocker, 1,150, and for changes in lipid-lowering agents, 870.
Abbreviations as in Tables 1 and 2.

Because assessing changes in medication use can underestimate the thoroughness of medical therapy if multiple medications are initiated before imaging, we examined the number of medications used before imaging studies by patients in the subgroup with moderately to severely abnormal study results who had no changes in medication at 90 days. In total, 24% of these patients were taking all 3 of the medications (aspirin, beta-blocker, lipid-lowering agent) and 32% were taking 2 of these medications. Interestingly, 16% of these patients were taking none of the medications,

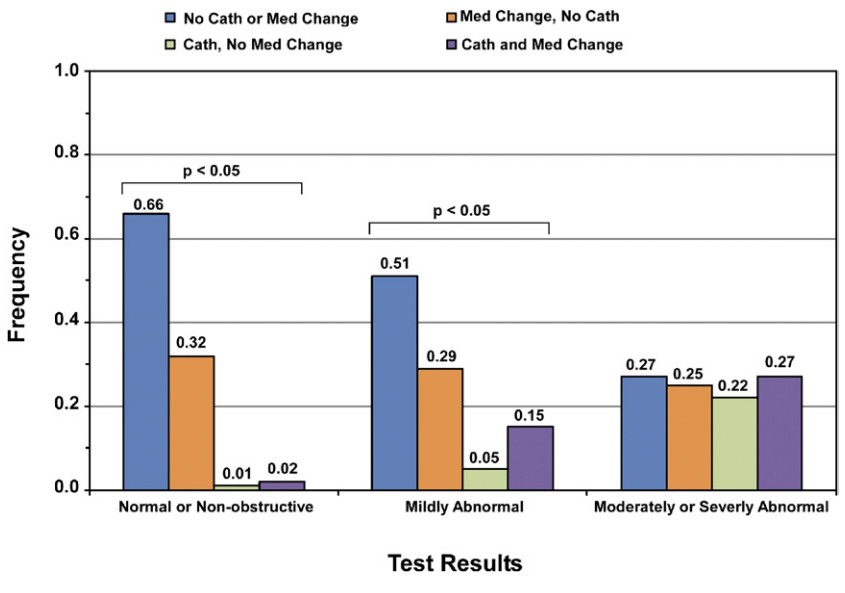

Figure 5 Post-Test Changes in Patient Management

Frequency of referral for catheterization (Cath), medication (Med) change, both, or neither at 90 days as a function of cardiac imaging study results. Comparisons made with chi-square tests of association within each test result.

and 29% was taking 1 of them; thus, 45% were taking fewer than 2 medications. These rates did not differ from those in the overall group of patients with moderately to severely abnormal study results (Fig. 4).

Discussion

In the current study, we examined patient management after noninvasive cardiovascular imaging, as measured by catheterization referral and medical therapy changes at 90 days after testing, in a prospective, multicenter registry of patients without previous CAD with a balanced representation of nonacademic and academic practice settings. There are several important findings. Overall, we found that cardiovascular imaging results had only a modest impact on clinical management. Although the frequency of post-imaging referral for catheterization and changes in medical therapy increased in proportion to the degree of abnormality found on imaging, we found that quantitatively the intensity of change in patient management was relatively limited, especially after moderately to severely abnormal test results. In the latter group, the frequency of referral for catheterization was only 62% after CCTA and <50% after MPI. Likewise, cardioprotective medication use among patients with the most abnormal study results was not uniformly high; 24% were not taking aspirin, 23% were not taking a lipid-lowering agent, and 43% were not taking a beta-blocker. Moreover, a medication change occurred only in approximately half of these patients, and both a referral for catheterization and a change in medical therapy were observed in only one-fourth of patients.

Second, we observed intermodality differences in catheterization referral rates, with a greater observed referral frequency after CCTA than after MPI (SPECT or PET) in the setting of normal/nonobstructive and mildly abnormal study results. Angiographically determined obstructive CAD rates was highest after abnormal CCTA findings (82%) and lower after abnormal findings on PET (74%) or SPECT (59%), although the differences were not statistically significant.

Comparison with previous studies. Several previous retrospective studies examined post-test catheterization referral, reporting unadjusted catheterization rates ranging between 40% and 70% in patients with significant ischemia, with higher rates in patients with anginal symptoms, more extensive ischemia, and higher clinical risk (5,10–15). To date, limited data exist regarding changes in medication use after routine imaging, although a randomized trial in a lower risk cohort showed similar rates of medical management (16). However, we are not aware of other comparisons among cardiovascular imaging modalities with respect to post-test patient management with regard to either endpoint.

In the National Cardiovascular Data Registry, the yield (defined as obstructive CAD prevalence in patients with abnormal noninvasive study findings) of elective catheterization in patients without previous CAD was low (37.6%) and showed a modest increase after a "positive" stress test result (17). The current results differ from those of this previous report, including differences in cohort composition (National Cardiovascular Data Registry is an invasive registry; SPARC is a registry of noninvasive testing) and in the manner in which data were recorded and submitted. The National Cardiovascular Data Registry is a very large national registry with many sites submitting various types of data, but with relatively crude imaging results. SPARC, a far smaller registry, includes detailed imaging data based on careful, uniform interpretative and reporting criteria.

Clinical implications. In light of the enormous costs associated with cardiovascular imaging, efforts have been made to improve the appropriate use of medical imaging (2–5). Many justify the use of these tests on grounds that they play a central role in patient management and, although an unproven hypothesis, improve patient outcomes. The assumed paradigm is that in the setting of abnormal study results—particularly high-risk results—patients undergo intervention. The relatively limited changes in management after abnormal study results, especially high-risk findings, undermine this paradigm, especially because in our diagnostic cohort, these abnormalities represented a de novo CAD diagnosis. Although the observed catheterization rates can be explained by the perception of equipoise on the part of referring physicians, it is more difficult to understand or explain the patterns of medication use, especially among patients with high-risk study results. In light of the costs associated with cardiovascular imaging (4), it is problematic to justify the use of testing that will not be incorporated into subsequent patient care. A noninvasive procedure, the results of which have no impact on subsequent management, must be considered an inappropriate study; the current study suggests that a significant amount of inappropriate noninvasive procedures are currently performed.

There are several possible explanations for these findings. Physicians may have perceived equipoise between invasive and conservative approaches, thus not referring many patients for catheterization. However, this would not explain the frequency of medication use. Studies may have been ordered for confirmatory purposes, validating physicians' previous assessments, and optimal medical management was initiated before imaging. This is consistent with the association between study results and the frequency of pre-study medication use. Nonetheless, the fact that approximately one-third of patients with high-risk study results were not taking key medications after imaging suggests that a component of patient undertreatment is present as well. One cannot exclude the possibility that in a proportion of cases, physicians ordered the tests "defensively," feeling obligated to document a response to a patient's symptoms. However, it would seem that action on study results would be more likely justified in this scenario. Also, financial incentives on the part of physicians ordering studies cannot be excluded. Finally, it is possible that patients declined to undergo

catheterization or were noncompliant with medications. The former, however, was not reported in any interview. It is also possible that at the time of follow-up, the patients failed to fully inform the interviewer.

POST-IMAGING PATIENT MANAGEMENT AS A QUALITY METRIC. Quality of care has become a central issue in health care. Recently, patient selection, image acquisition, image interpretation, and results communication have been identified as important components of imaging quality (18). However, a well-performed imaging study in a high-quality laboratory reported to the ordering physician is not a quality study if it does not alter patient management, especially when the study results constitute new findings or diagnoses. Hence, referring physicians, implicated in this process via patient selection, must also come under scrutiny to determine their actions after notification of the study results. Although impact on clinical management is a stated quality goal, clinical outcomes were not considered feasible as a quality measure (18). Results communication per se does not necessarily ensure optimal patient care (19). The results of the current study suggest that patient management after noninvasive cardiac imaging should be considered a necessary component of the definition of imaging quality.

Understanding intermodality differences. We found an increased catheterization referral rate after CCTA compared with PET and SPECT after mildly abnormal study results, a category generally not associated with high clinical risk or potential benefit with revascularization (5,20–22). Nonetheless, the appropriateness of the referral for catheterization pattern after abnormal imaging study results is unclear. Whether this represents a relative catheterization overuse or underuse will require prospective, randomized clinical trial data.

The observed intermodality differences may be due to differences in physician comfort and experience with these modalities. Lower post-MPI catheterization rates may be due to greater physician experience with post-MPI patient management, understanding of post-test risk, and available observational data on the lack of revascularization benefit in patients with mild ischemia. Conversely, greater post-CCTA catheterization and revascularization rates may be due to the greater sensitivity of the test, the occulostenotic reflex, overestimation of stenoses on CCTA, and less familiarity with managing patients on the basis of CCTA results.

Study strengths and limitations. The most important limitation of the current study is the issue of whether the findings in our current cohort are unique or generalizable to outside populations. Unfortunately, we were not able to collect extensive data on patients presenting for testing at our recruitment sites who were not enrolled in the SPARC, information that would have informed us regarding the SPARC cohort's generalizability. Thus, we cannot say with certainty whether the SPARC cohort and the findings reported in the current paper are unique or characteristic of widespread practice. Nonetheless, previous single-site studies report catheterization referral rates similar to those that we observed in the SPARC (5,10–13).

Although randomized clinical trials enhance the validity of comparisons among imaging modalities, a prospective registry design enhanced our ability to observe patterns of care in daily clinical practice. Similarly, we used sites' clinical interpretations of imaging studies rather than those of core laboratories. Other than the collection of semiquantitative scoring data, all recruiting centers adhered to their routine practice with respect to all aspects of testing and reporting.

Although cardiac SPECT is an established imaging modality, PET and CCTA are relatively newer modalities and physicians' use patterns may not yet be established. With more experience, catheterization and medical therapy use after testing may change. Issues of heterogeneity in payer policies for these 3 modalities may further obfuscate comparisons of post-test management. Nonetheless, these issues should have less of an impact on post-test referral for catheterization or changes in medication use than on the composition of who is referred for imaging. It is possible that the results of the index study may have resulted in referral for additional noninvasive studies. It was a limitation of the study design that this information was not collected. However, we did collect data on pre-index study noninvasive procedures and used those data to examine the role and impact of sequential testing.

The characteristics of the patients enrolled in each of the 3 arms differed, as did the frequency of abnormal study results. Although every effort was made to adjust for these potential differences using multivariable modeling, this approach is not without limitations including that of unmeasured covariates.

Conclusions

Overall, noninvasive studies had only a modest impact on the clinical management of patients referred for clinical testing. Although post-imaging use of cardiac catheterization and medical therapy increase in proportion to the degree of abnormal study results, the frequency of catheterization and medication use suggest possible undertreatment of higher-risk patients. Compared with stress MPI, catheterization referral rates and subsequent need for revascularization are greater after CCTA, but the rates of medication use are similar.

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