Impact of Appropriate Use on the Prognostic Value of Single-Photon Emission Computed Tomography Myocardial Perfusion Imaging

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Background—Appropriate use criteria (AUC) have been developed to aid in the optimal use of single-photon emission computed tomography (SPECT)–myocardial perfusion imaging (MPI), a technique that is a mainstay of risk assessment for ischemic heart disease. The impact of appropriate use on the prognostic value of SPECT-MPI is unknown.

Methods and Results—A prospective cohort study of 1511 consecutive patients undergoing outpatient, community-based SPECT-MPI was conducted. Subjects were stratified on the basis of the 2009 AUC for SPECT-MPI into an appropriate or uncertain appropriateness group and an inappropriate group. Patients were prospectively followed up for 27±10 months for major adverse cardiac events of death, death or myocardial infarction, and cardiac death or myocardial infarction. In the entire cohort, the 167 subjects (11%) with an abnormal scan experienced significantly higher rates of major adverse cardiac events and coronary revascularization than those with normal MPI. Among the 823 subjects (54.5%) whose MPIs were classified as appropriate (779, 51.6%) or uncertain (44, 2.9%), an abnormal scan predicted a multifold increase in the rates of death (9.2% versus 2.6%; hazard ratio, 3.1; P=0.004), death or myocardial infarction (11.8% versus 3.3%; hazard ratio, 3.3; P=0.001), cardiac death or myocardial infarction (6.7% versus 1.7%; hazard ratio, 3.7; P=0.006), and revascularization (24.7% versus 2.7%; hazard ratio, 11.4; P<0.001). Among the 688 subjects (45.5%) with MPI classified as inappropriate, an abnormal MPI failed to predict major adverse cardiac events, although it was associated with a high revascularization rate. Furthermore, appropriate MPI use provided incremental prognostic value beyond myocardial perfusion and ejection fraction data.

Conclusions—When performed for appropriate indications, SPECT-MPI continues to demonstrate high prognostic value. However, inappropriate use lacks effectiveness for risk stratification, further emphasizing the need for optimal patient selection for cardiac testing. **(*Circulation*. 2013;128:1634-1643.)**

Key Words: myocardial perfusion imaging ■ outcome assessment (health care) ■ prognosis ■ tomography, emission-computed, single-photon

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The long-term prognostic value of stress myocardial perfusion imaging (MPI) with single-photon emission computed tomography (SPECT) is well established.[1–6] Numerous studies have demonstrated that abnormal MPI predicts a multifold increase in the risk of major adverse cardiac events (MACE).[1–6] Furthermore, the prognostic utility of MPI is incremental to clinical, treadmill stress test, and coronary angiography data.[7–9] The robust prognostic data, favorable diagnostic performance, and wide availability of SPECT-MPI have led to a great expansion in use with consequent excessive expenditure. This growth has caused increased scrutiny by regulators and payers, who have implemented various methods to reduce procedural volume.[10] The expansion of MPI use prompted professional societies to develop appropriate use criteria (AUC) to guide physicians on optimal use of SPECT-MPI in patient care.[11,12] With debate on healthcare costs intensifying, appropriate use is increasingly emphasized by professional societies, third-party payers, and accreditation agencies.[13–15] However, there has been no prospective evaluation of the impact of appropriateness of use on the prognostic value of cardiac testing such as MPI. In this investigation, we tested the hypothesis that inappropriate use limits the prognostic value of SPECT-MPI performed in a community environment.

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Methods

We conducted a prospective cohort study of consecutive patients referred for office-based, clinically indicated SPECT-MPI between August 15, 2007, and May 15, 2010, with a 2-year follow-up. A total of 22 physicians (20 primary care physicians and 2 cardiologists) from 11 practices encompassing 12 ZIP codes within the Chicago metropolitan area took part in the study. Exclusion criteria were missing/invalid address, missing/invalid telephone or Social Security number, or refusal of the referring physician to provide access to patient health records.

Clinical Data

Baseline patient demographics, referral diagnosis, risk factors, cardiovascular history, and medications were tabulated before the stress MPI. The referring physicians' clinical notes preceding MPI were reviewed to determine patient symptoms, rationale for testing, and type of surgery if used as part of a preoperative risk assessment. Framingham 10-year global coronary heart disease risk estimates were calculated.[16] Chest pain syndromes were classified as typical angina, atypical angina, and nonanginal chest pain on the basis of location, exacerbation with exercise, and resolution with rest or nitroglycerin.[17] If clinical notes did not describe the chest pain, it was considered nonanginal. Dyspnea was classified as nonanginal chest pain. Consequently, the pretest probability of obstructive coronary artery disease (CAD) was determined on the basis of age, sex, and chest pain classification according to Diamond and Forrester[17] tables.

Appropriate Use Criteria

Computer-based logic was applied to assign each patient a specific indication and subsequently to categorize the studies as appropriate, uncertain, or inappropriate on the basis of the 2009 AUC, in a fashion similar to previous reports.[12–14] To study the impact of inappropriate use on the prognostic value of MPI and in consideration of reimbursement rules recommended by the AUC,[12] patients with appropriate and uncertain appropriateness scans were combined, thus stratifying the study cohort into an appropriate/uncertain group and inappropriate group.

Stress MPI

A 1-day, rest/stress, technetium-99m sestamibi protocol was implemented, conforming to the American Society of Nuclear Cardiology guidelines.[18] One of 3 stress modalities was chosen as clinically appropriate: exercise Bruce protocol, standard 6-minute adenosine infusion, or adenosine stress with low-level exercise.[19,20] All MPI studies were acquired with a single mobile, upright-acquisition, dual-head, dedicated cardiac SPECT camera (MAIcam180, Mid-Atlantic Imaging Services, Inc, Columbia, MD) without attenuation correction.

Using QPS/QGS software (Cedars-Sinai Cardiac Suite, Los Angeles, CA), MPI scans were interpreted semiquantitatively by a single expert nuclear cardiologist (R.D.) who was blinded to patients' clinical and outcome data. On a 17-segment model, the segmental radiotracer activity in the rest and stress scans were scored according to the standard 5-point scale (0=normal; 1=mild; 2=moderate; 3=severe; 4=absent).[21] The segmental scores within the stress and rest scans were summed to generate summed stress scores (SSS) and summed rest scores (SRS). The summed difference score (SDS) was calculated from the sum of the difference scores derived by subtracting the segmental resting scores from the segmental stress scores. Quantitative poststress gated SPECT left ventricular ejection fraction (LVEF) <50% was considered abnormal. Normal MPI was defined on the basis of perfusion as SSS of 0–3.[22] Perfusion abnormalities were further categorized on the basis of SSS into mild (4–8), moderate (9–13), or severe (>13).[22] Reversible perfusion abnormalities, signifying stress-induced myocardial ischemia, were defined as SDS ≥2 and further categorized on the basis of SDS as mild (2–4), moderate (5–7), or severe (>7).[23] Given the questionable diagnostic and prognostic value of transient ischemic dilatation of the left ventricle with otherwise normal perfusion, it was not taken into account in the definition of abnormal MPI.[24]

To ensure the reproducibility of the semiquantitative assessment of the perfusion data, a random sample of 151 scans (10%) were independently interpreted by 2 board-certified nuclear cardiologists who were blinded to the clinical and outcome data. The interrater interpretation agreement (normal, fixed, or reversible defect) between the main reader and the 2 control readers was excellent (κ=0.83 and 0.87; P<0.001).

Outcome Determination

Subjects were prospectively followed for events of death resulting from any cause, cardiac death, nonfatal myocardial infarction (MI), coronary angiography, percutaneous coronary intervention, and coronary artery bypass graft surgery. Outcome assessors were blinded to MPI findings and AUC classification. Four methods for ascertaining outcome events were uniformly applied: (1) review of patient health records (from July 2011 through February 2012) at the referring physician offices, (2) 2 identical questionnaires mailed to patient residences 6 months apart (July 2011 and January 2012), (3) telephone interviews for subjects who did not complete mail surveys, and (4) Social Security Death Index search (April 2012) with cause of death determined from death certificates. MI events were defined by the clinical determination of the treating cardiologist. Fatal MIs were considered cardiac deaths if death occurred within the same hospitalization. Social Security Death Index data was used to discern the date of death and to determine follow-up time for pure mortality end points (death and cardiac death). The follow-up time for the composite end points (death or MI and cardiac death or MI) and coronary interventions was determined on the basis of the last clinical encounter date as determined by surveys, phone interviews, or medical records. Revascularization procedures performed within 60 days after MPI were considered to be triggered by MPI findings, whereas those occurring late (>60 days) were considered to be prompted by clinical deterioration or poor response to medical therapy.

The primary end point was all-cause mortality. Secondary end points were a composite end point of death or MI and a composite end point of cardiac death or MI.

Statistical Analysis

On the basis of published preliminary data, we predicted an abnormal MPI rate of 12%.[25] Assuming a baseline annual mortality of 0.5% among subjects with normal MPI,[1] we determined that 1558 subjects would be needed to attain 80% power to detect a 4-fold increase in mortality associated with abnormal MPI after a 2-year follow-up using the unadjusted χ^2 test (2-tailed α=0.05). Furthermore, assuming an inappropriate use rate of 30%, it was determined that the projected sample size would attain >99% power to detect incremental predictive value of appropriate use beyond myocardial perfusion with an adjusted odds ratio of 2.0 (2-tailed α=0.05).[25] The nQuery Advisor 7.0 software (Statistical Solutions, Ltd, Cork, Ireland) was used for sample size estimations.

The χ^2 test was used to compare dichotomous variables, which were expressed as frequency (percentage). The Fisher exact test was used for dichotomous comparisons when the number of events was ≤5. The 2-tailed Student t test was used to compare normally distributed continuous variables, which were expressed as mean±SD. A multivariable logistic regression model was used to determine the independent predictors of early (<60 days) coronary revascularization events. The correlation coefficient (r) between skewed continuous variables was determined with the Spearman method. Cox proportional hazards models were used to compare hazards adjusted for covariates. The clinical covariates adjusted for were age, sex, diabetes mellitus, hypertension, dyslipidemia, tobacco use, known CAD (prior MI, coronary artery bypass graft surgery, or percutaneous coronary intervention), and stress modality. Proportionality of hazards assumption was confirmed by demonstrating parallel "log minus log" survival plots. Stepwise Cox regression models were used to evaluate the gain in the global χ^2 value and hence the predictive value of clinical and imaging predictors. Two-tailed values of P<0.05 were considered

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significant. PASW 18.0 software (SPSS, Inc, Chicago, IL) was used for statistical analyses.

The study was approved by the institutional review board of Rush University Medical Center. A HIPAA waiver was applied to the chart review aspect of the methods. Subjects had the right to decline participation in the study via the mailed questionnaire.

Results

We identified 1707 consecutive subjects referred for an office-based, 1-day, rest/stress, Tc-99m sestamibi SPECT-MPI study. Among those, 182 subjects met ≥1 exclusion criteria: 84 lacked a valid Social Security number; 172 were missing a valid address or telephone number; and a physician for 43 patients declined to collaborate with the study. Two-hundred and two subjects refused to participate in the study surveys; thus, their outcome determination was based on chart review and the Social Security Death Index. Fourteen subjects (0.9%) were lost to follow-up, none of whom were identified as deceased by the Social Security Death Index. The remaining 1511 subjects (99.1%) had complete (100%) clinical and Social Security Death Index follow-up for a mean of 27±10 months.

MPI referrals were found to be appropriate in 779 studies (51.6%), inappropriate in 688 (45.5%), and uncertain in 44 (2.9%). All subjects were classifiable according to the 2009 AUC. Inappropriate use rates for individual practitioners ranged from 10% to 77% ($P<0.001$) and were higher among primary care physicians than cardiologists (47% versus 28%; $P<0.001$). The study cohort was then stratified into 2 groups: an appropriate/uncertain group (823 subjects, 54.5%) and an inappropriate group (688 subjects, 45.5%). Baseline patient characteristics are summarized in Table 1. Patients in the inappropriate group were more likely to be asymptomatic with a lower likelihood of obstructive CAD and a lower 10-year Framingham coronary heart disease risk (Table 1). Notably, women made up 58.0% of the inappropriate group but only 31.3% of the appropriate/uncertain group ($P<0.001$). Furthermore, among patients who underwent exercise stress, those in the appropriate/uncertain group had a slightly lower Duke Treadmill Scores (mean, 7.4±4.0 versus 7.9±4.1; $P=0.04$), but no statistically significant difference in the incidence of stress-induced ischemic ST-segment deviation (10.5% versus 7.9%; $P=0.13$).

One hundred and sixty-seven subjects (11%) had myocardial perfusion defects (Table 1). Patients in the appropriate/uncertain group had significantly higher rates of abnormal MPI, more severe perfusion abnormalities (SSS), and greater ischemic burden (SDS), whereas the breakdown of perfusion abnormality type (fixed, reversible, or mixed) was not significantly different from that in the inappropriate group (Table 1).

Compared with subjects with complete follow-up, the patients excluded (n=182) or lost to follow-up (n=14) were younger (mean age, 55±15 versus 59±13 years; $P=0.001$) and had lower likelihood of obstructive CAD (15±13% versus 18±13%; $P=0.007$) but similar mean 10-year Framingham coronary heart disease risk (12.7±10.8% versus 12.8±10%; $P=0.88$) and CAD prevalence (19% versus 18%; $P=0.62$). The prevalence of depressed LVEF and abnormal perfusion was nearly identical ($P=0.97$ and 0.89, respectively), with a similar breakdown of reversible, fixed, and mixed defects ($P=0.64$). The excluded patients had a similar distribution of AUC classifications: 104 (53.1%) appropriate, 89 (45.4%) inappropriate, and 3 (1.5%) uncertain ($P=0.53$).

Coronary Angiography and Revascularization

During follow-up, 106 subjects (7.0%) underwent ≥1 coronary angiography, with subsequent percutaneous coronary intervention in 61 (4.0%) and coronary artery bypass graft surgery in 14 (0.9%; Table 2). Thirty-six (2.3%) coronary revascularizations (30 percutaneous coronary interventions and 6 coronary artery bypass graft surgeries) occurred within 60 days after MPI and thus were considered directly prompted by MPI findings.

When added to clinical covariates in Cox regression models, SDS provided a greater incremental value than SSS in predicting coronary interventions (gain in global χ^2 values, 237.8 versus 140.8 for angiography and 241.2 versus 118.3 for revascularization; $P<0.001$).

Multivariable logistic regression analysis demonstrated that SDS was a predictor for early post-MPI revascularization (odds ratio, 1.22 per 1-point SDS increment; 95% confidence interval [CI], 1.2–1.3; $P<0.001$] with adjustment for clinical covariates, appropriateness group ($P=0.75$), and depressed LVEF ($P=0.22$).

Patients with stress-induced ischemia (SDS ≥2) had significantly higher rates of coronary angiography and revascularization than those with no ischemia, regardless of appropriateness group (Table 2), and the rates of coronary angiography and revascularization were commensurate with the myocardial ischemia burden (SDS) after adjustment for clinical covariates (Figures 1A and 1B). Notably, a mild degree of myocardial ischemia (SDS=2–4) was associated with a significant increase in the rates of coronary angiography and revascularization (Figures 1A and 1B).

Patients in the appropriate/uncertain group had a higher overall rate of coronary angiography and revascularization than those in the inappropriate group (Table 2), but the difference was not statistically significant after adjustment for clinical covariates (angiography: hazard ratio [HR], 1.3; 95% CI, 0.8–2.1; $P=0.24$; revascularization: HR, 1.2; 95% CI, 0.6–2.1; $P=0.63$). The presence of myocardial ischemia by MPI was associated with significantly greater rates of coronary angiography and revascularization in both study groups (Figure 1C and 1D). Furthermore, the rates of coronary angiography and revascularization in patients with myocardial ischemia were not significantly different in the inappropriate versus the appropriate/uncertain group after adjustment for clinical covariates (angiography: HR, 1.2; 95% CI, 0.6–2.4; $P=0.66$; revascularization: HR, 1.1; 95% CI, 0.5–2.5; $P=0.87$; Figure 1C and 1D). Once performed, coronary angiography was followed by similar rates of nonintervention, percutaneous coronary intervention, and coronary artery bypass graft surgery, implying similar rates of no significant CAD, single- or 2-vessel disease, and multivessel or left main disease, respectively (Figure 2A).

During the entire follow-up, the median durations of time to angiography and time to revascularization in patients with myocardial ischemia were shorter in the inappropriate use group (0.8 versus 1.7 months and 0.6 versus 1.3 months, respectively), but these differences were not statistically significant

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Table 1. Baseline Clinical and Imaging Characteristics

	Overall Cohort (n=1511)	Appropriate/Uncertain (n=823, 54.5%)	Inappropriate (n=688, 45.5%)	*P* Value
Age, y	59±13	63±11	53±12	<0.001
Women, n (%)	657 (43.5)	258 (31.3)	399 (58.0)	<0.001
Primary indication for MPI, n (%)				<0.001
Chest pain	688 (45.5)	495 (60.1)	193 (28.0)	
Dyspnea	158 (10.5)	133 (16.2)	25 (3.6)	
Abnormal ECG	136 (9.0)	34 (4.1)	102 (14.8)	
Evaluation of known CAD	159 (10.5)	49 (6.0)	110 (16.0)	
Preoperative assessment	37 (2.4)	18 (2.2)	19 (2.8)	
Syncope	21 (1.4)	5 (0.6)	16 (2.3)	
Asymptomatic	262 (17.3)	70 (8.5)	192 (27.9)	
Hypertension, n (%)	841 (55.6)	538 (65.4)	303 (44.0)	<0.001
Diabetes mellitus, n (%)	333 (22.0)	244 (29.6)	89 (12.9)	<0.001
Dyslipidemia, n (%)	695 (46.0)	451 (54.8)	244 (35.5)	<0.001
Tobacco use, n (%)	181 (12.0)	100 (12.2)	81 (11.8)	0.82
Family history of CAD, n (%)	544 (36.0)	272 (33.0)	272 (39.5)	0.009
Framingham 10-y CHD risk, %	13±10	17±11	8±6	<0.001
Likelihood of obstructive CAD, %*	18±13	22±12	5±3	<0.001
Exercise stress (Bruce) protocol, n (%)	1164 (77.0)	554 (67.3)	610 (88.7)	<0.001
BMI, kg/m^2	30±5.7	29.9±5.4	29.4±6.0	0.12
Known CAD, n (%)	271 (17.9)	203 (24.7)	68 (9.9)	<0.001
Previous CABG, n (%)	76 (5.0)	76 (9.2)	0 (0)	<0.001
Previous PCI, n (%)	87 (5.8)	73 (8.9)	14 (2.0)	<0.001
Previous MI, n (%)	37 (2.4)	23 (2.8)	14 (2.0)	0.34
Statin, n (%)	580 (38.4)	390 (47.4)	190 (27.6)	<0.001
Antiplatelet, n (%)	370 (24.5)	273 (33.2)	97 (14.1)	<0.001
β-Blocker, n (%)	307 (20.3)	216 (26.2)	91 (13.2)	<0.001
ACE-I or ARB, n (%)	567 (37.5)	379 (46.1)	188 (27.3)	<0.001
Myocardial perfusion, n (%)				<0.001
Normal (SSS=0–3)	1344 (88.9)	704 (85.5)	640 (93.0)	
Mildly abnormal (SSS=4–8)	79 (5.2)	51 (6.2)	28 (4.1)	
Moderately abnormal (SSS=9–13)	47 (3.1)	38 (4.6)	9 (1.3)	
Severely abnormal (SSS >13)	41 (2.7)	30 (3.6)	11 (1.6)	
Myocardial ischemia, n (%)				0.03
None (SDS ≤1)	1399 (92.6)	742 (90.2)	647 (94.0)	
Mild (SDS=2–4)	38 (2.5)	27 (3.2)	11 (1.6)	
Moderate (SDS=5–7)	40 (2.6)	28 (3.4)	12 (1.7)	
Severe (SDS >7)	43 (2.8)	26 (3.2)	17 (2.5)	
Type of perfusion abnormality, n (%)				0.14
Reversible	87 (5.8)	58 (7.0)	29 (4.2)	
Fixed	61(4.0)	49 (6.0)	12 (1.7)	
Reversible and fixed	19 (1.3)	12 (1.5)	7 (1.0)	
Poststress LVEF <50%, n (%)	78 (5.2)	53 (6.4)	25 (3.6)	0.01

ACE-I indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CHD, coronary heart disease; LVEF, left ventricular ejection fraction; MI, myocardial infarction; MPI, single-photon emission computed tomography myocardial perfusion imaging; PCI, percutaneous coronary intervention; SDS, summed difference score; and SSS, summed stress score.

*Based on Diamond and Forrester[17] tables in patients with chest pain or dyspnea.

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(*P*=0.16 and 0.34, respectively). However, in the immediate period after myocardial ischemia was identified by MPI, the time to coronary angiography and time to revascularization were shorter in the inappropriate group after adjustment for SDS (Figure 2B and 2C). This difference dissipated during the remainder of the follow-up (Figure 1C and 1D).

Table 2. Intervention Decisions Based on the Presence of Myocardial Ischemia (SDS ≥ 2)

	Group	Total Events, n (%)	Ischemia (n=122, 8%), n (%)	No Ischemia (n=1389, 92%), n (%)	HR (95% CI)*	*P* Value*
Coronary angiography	Entire cohort	106 (7.0)	47 (38.5)	59 (4.2)	11.3 (7.6–16.9)	<0.001
	Appropriate/uncertain	72 (8.7)	32 (39.5)	40 (5.4)	9.9 (6.1–16.1)	<0.001
	Inappropriate	34 (4.9)	15 (36.6)	19 (2.9)	14.5 (7.0–30.2)	<0.001
Coronary revascularization	Entire cohort	61 (4.0)	29 (23.8)	32 (2.3)	11.8 (7.0–19.9)	<0.001
	Appropriate/uncertain	40 (4.9)	20 (24.7)	20 (2.7)	11.4 (6.0–21.8)	<0.001
	Inappropriate	21 (3.1)	9 (22.0)	12 (1.9)	12.1 (4.8–30.8)	<0.001

Entire cohort, n=1511; appropriate/uncertain group, n=823; inappropriate group, n=688. Each line represents a separate analysis. CI indicates confidence interval; HR, hazard ratio; MPI, myocardial perfusion imaging; and SDS, summed difference score.

*HR (95% CI) and *P* values are derived from Cox proportional hazards models adjusted for clinical covariates.

Furthermore, we identified a modest but statistically significant inverse correlation between the inappropriate use rate of individual physicians and the time to coronary angiography and revascularization (r=– 0.40, P=0.001; and r=– 0.36, P=0.01, respectively). In other words, physicians with higher inappropriate use rates were associated with shorter time to coronary interventions.

Outcomes

During follow-up, there were 34 deaths (2.3%), 12 cardiac deaths (0.8%), and 11 nonfatal MIs (0.7%). When added to the clinical covariates in Cox regression models, the SSS provided a greater incremental value than the SDS in predicting MACE (the gain in global χ^2 values: 20.1 versus 3.25 for death, 41.6 versus1.7 for death or MI, and 42.4 versus 2.3 for cardiac death or MI; P<0.001).

Patients with abnormal MPI had higher rates of all-cause mortality and cardiac death, as well as the secondary composite end points of death or MI and cardiac death or MI (Table 3). Rates of primary and secondary end points correlated with the severity of perfusion abnormality (SSS) after adjustment for clinical covariates (Figure 3).

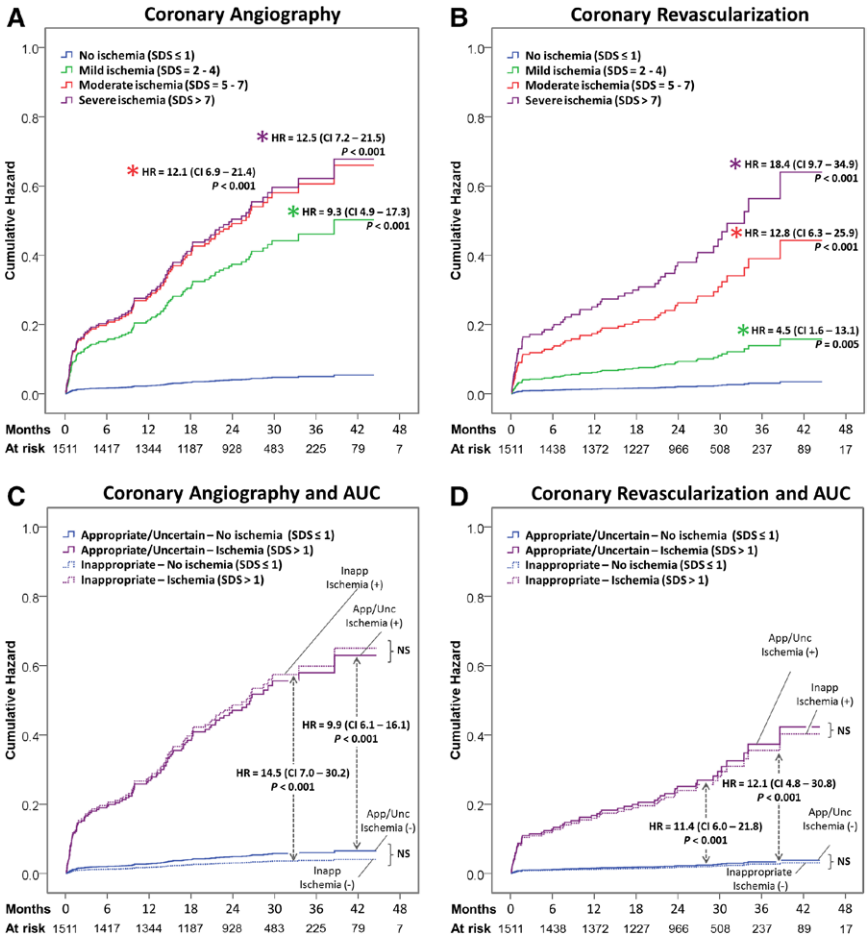

Figure 1. Coronary angiography and revascularization after myocardial perfusion imaging. **A** and **B**, Time-to-angiography and time-to-revascularization Cox proportional hazards curves based on severity of myocardial ischemia (summed difference score [SDS]). The hazard ratios (HRs) are calculated relative to the no ischemia group and adjusted for clinical covariates. **C** and **D**, Time-to-angiography and time-to-revascularization Cox proportional hazards curves of patients with vs without myocardial ischemia within the appropriate/uncertain (App/Unc) and Inappropriate (Inapp) groups. HRs (ischemia vs no ischemia) were calculated separately within each appropriateness group and adjusted for clinical covariates. AUC indicates appropriate use criteria; and NS, not significant (P>0.05).

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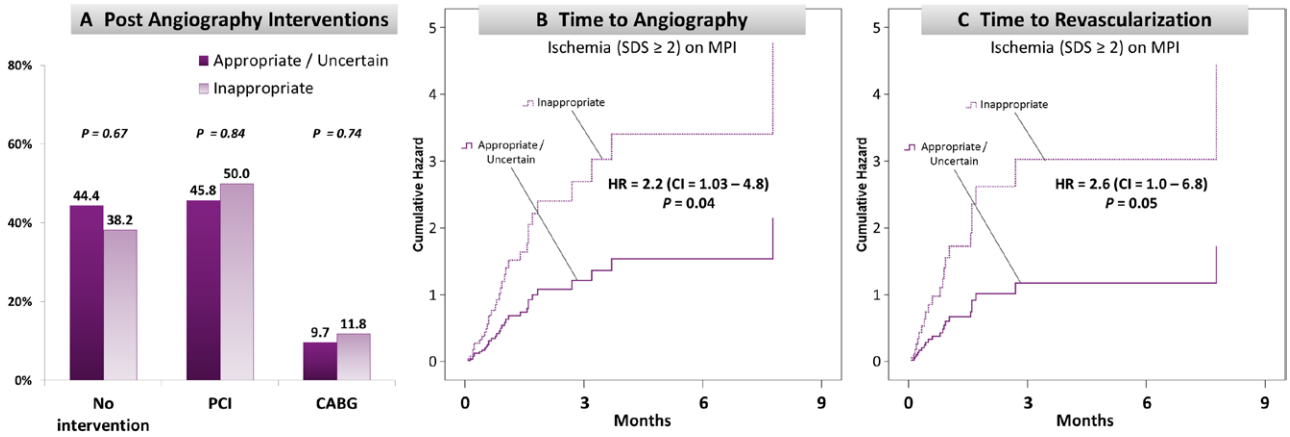

Figure 2. Decision-making after myocardial perfusion. **A**, Interventions performed after coronary angiography. **B** and **C**, Time-to-angiography and time-to-revascularization Cox proportional hazards curves of patients with myocardial ischemia in the inappropriate group vs appropriate/uncertain group (adjusted for summed difference score [SDS]). CABG indicates coronary artery bypass graft surgery; CI, confidence interval; HR, hazard ratio; and PCI, percutaneous coronary intervention.

Patients in the appropriate/uncertain group experienced significantly higher overall rates of death (HR, 2.9; 95% CI, 1.05–8.0; *P*=0.04), the composite of death or MI (HR, 1.04; 95% CI, 1.01–1.07; *P*=0.03), and the composite of cardiac death or MI (HR=5.7; 95% CI, 1.3–25.6; *P*=0.02) after adjustment for clinical covariates. Among patients in the appropriate/uncertain group, abnormal MPI continued to predict a multifold increase in the risk of death, cardiac death, composite of death or MI, and composite of cardiac death or MI (Figure 4). However, in the inappropriate group, there were no statistically significant differences in MACE rates between subjects with abnormal versus normal MPI (Figure 4). Furthermore, using Cox regression models, no interaction was identified between the study group and MPI finding in predicting death, the composite of death or MI, or the composite of cardiac death or MI (*P*=0.91, 0.70, and 0.43, respectively).

A Cox regression model demonstrated that inappropriate MPI use was a negative predictor of all-cause mortality (HR, 0.26; 95% CI, 0.10–0.67; *P*=0.005) after adjustment for myocardial perfusion finding (normal versus abnormal; HR, 2.5; 95% CI, 1.1–5.9; *P*=0.04) and depressed LVEF (<50%; HR, 3.7; 95% CI, 1.5–9.3; *P*=0.006); undergoing early coronary revascularization was not predictive of mortality (*P*=0.98). Similarly, in separate models, we demonstrated that inappropriate use was an independent negative predictor of the secondary end points of death or MI (HR, 0.31; 95% CI, 0.14–0.70; *P*=0.005) and cardiac death or MI (HR, 0.16; 95% CI, 0.04–0.71; *P*=0.02) after adjustment for depressed LVEF, myocardial perfusion findings, and early revascularization. In these models, MPI and depressed LVEF independently predicted the composite end points of death or MI and cardiac death or MI, whereas undergoing early coronary revascularization after MPI was not predictive of these end points (*P*≥0.97). Finally, in forward stepwise Cox regression models, appropriate use was shown to have incremental prognostic value to perfusion imaging and depressed LVEF in predicting

Table 3. Outcomes Based on MPI Abnormality (SSS ≥ 4)

	Group	Total Events, n (%)	Abnormal MPI (n=167, 11%), n (%)	Normal MPI, (n=1344, 89%), n (%)	HR (95% CI)*	*P* Value*
Death	Entire cohort	34 (2.3)	12 (7.2)	22 (1.6)	3.3 (1.6–6.8)	0.001
	Appropriate/uncertain	29 (3.5)	11 (9.2)	18 (2.6)	3.1 (1.4–6.6)	0.004
	Inappropriate	5 (0.7)	1 (2.1)	4 (0.6)	2.3 (0.25–21.1)	0.46
Cardiac death	Entire cohort	12 (0.8)	5 (3.0)	7 (0.5)	1.05 (1.01–1.1)	0.02
	Appropriate/uncertain	12 (1.5)	5 (4.2)	7 (1.0)	3.7 (1.1–12.1)	0.03
	Inappropriate	0 (0)	0 (0)	0 (0)	NA	NA
Death or MI	Entire cohort	44 (2.9)	16 (9.6)	28 (2.1)	3.5 (1.8–6.6)	<0.001
	Appropriate/uncertain	37 (4.5)	14 (11.8)	23 (3.3)	3.3 (1.6–6.5)	0.001
	Inappropriate	7 (1.0)	2 (4.2)	5 (0.8)	4.0 (0.7–21.8)	0.11
Cardiac death or MI	Entire cohort	22 (1.5)	9 (5.4)	13 (1.0)	4.4 (1.8–10.6)	0.001
	Appropriate/uncertain	22 (2.4)	8 (6.7)	12 (1.7)	3.7 (1.5–9.3)	0.006
	Inappropriate	2 (0.3)	1 (2.1)	1 (0.2)	11.8 (0.6–231.1)	0.10

Entire cohort, n=1511; appropriate/uncertain group, n=823; inappropriate group, n=688. Each line represents a separate analysis. CI indicates confidence interval; HR, hazard ratio; MI, nonfatal myocardial infarction; MPI, myocardial perfusion imaging; and SSS, summed stress score.

*HR (95% CI) and *P* values are derived from Cox proportional hazards models adjusted for clinical covariates.

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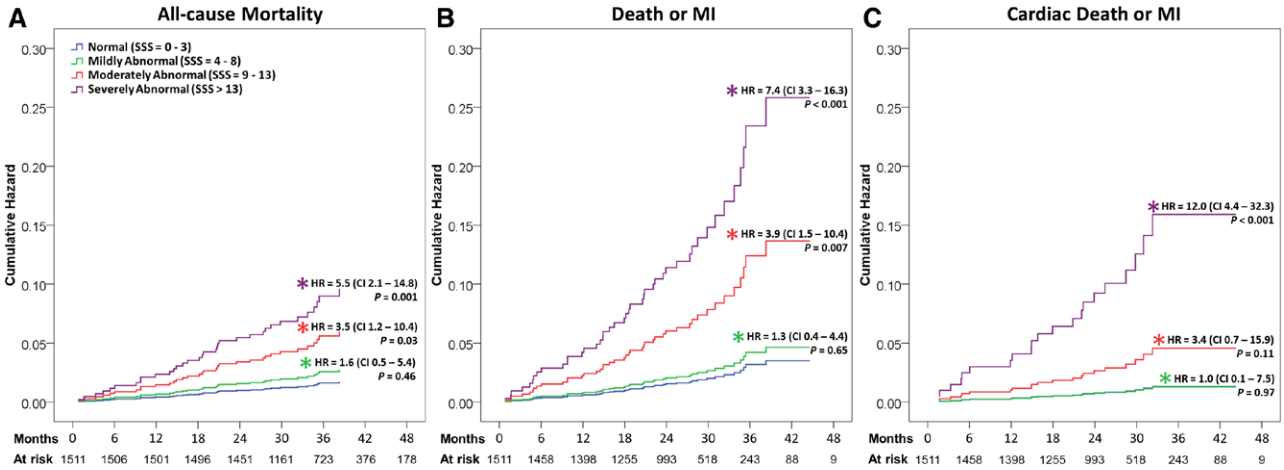

Figure 3. Major adverse cardiac events (MACE) based on myocardial perfusion imaging findings. Time-to-MACE Cox proportional hazards curves based on severity of perfusion abnormality (summed stress score [SSS]). The hazard ratios (HRs) are calculated relative to the normal group and adjusted for clinical covariates. CI indicates confidence interval; and MI, myocardial infarction.

MACE; undergoing early revascularization (<60 days) did not provide significant additional predictive value (Figure 5).

Discussion

This study represents the first large prospective evaluation of appropriate use of SPECT-MPI in terms of its prognostic value in a patient population with known or suspected ischemic heart disease. The patient population and healthcare providers in this study represent typical community-based practices within a major metropolitan area. The study demonstrates higher inappropriate use rates than most previous reports (10%–24%), particularly among primary care physicians (47%).[13,26–29] However, the majority of previously published data were based on single tertiary-care center experiences in which higher-risk populations, greater AUC awareness, less prominent self-referral bias, publication bias, and historic context can explain this disparity. Moreover, there were few referrals with uncertain appropriateness in this community-based cohort, probably because of the low complexity level of the clinical presentations (chest pain, dyspnea, asymptomatic, etc), for which the 2009 AUC document has decisive recommendations. Of note, the majority of the MPI scans evaluated were performed before the publication and wide-scale adoption of the 2009 AUC. Hence, this study was not intended to be a report on current appropriate use rates but rather an investigation of the impact of appropriateness of use on the prognostic value of MPI.

This investigation confirmed the excellent prognostic value of SPECT-MPI performed in community-based practice.[4] We demonstrated that SDS is better than SSS in predicting coronary angiography and revascularization decisions, whereas SSS is the better predictor for MACE. Furthermore, in the overall study cohort, revascularization and MACE rates were commensurate with the severity of myocardial ischemia (SDS) and perfusion abnormality (SSS), respectively. Notably, abnormal MPI was associated with similarly high rates of coronary angiography and revascularization, regardless of appropriateness. This is not surprising because the decision-making process for coronary angiography and revascularization after abnormal MPI often does not take into account the initial appropriateness for MPI. However, when

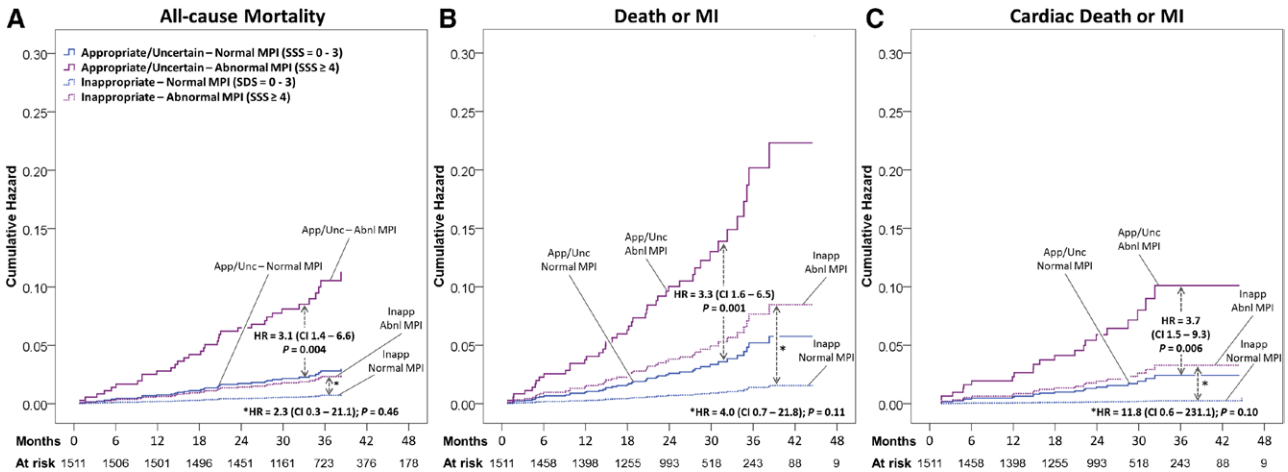

Figure 4. Adverse cardiac events based on myocardial perfusion imaging (MPI) and appropriateness. Time to major adverse cardiac events Cox proportional hazards curves of patients with abnormal (Abnl) vs normal MPI within the appropriate/uncertain (App/Unc) and Inappropriate (Inapp) groups. Hazards ratios (HRs; abnormal vs normal) were calculated separately within each appropriateness group and adjusted for clinical covariates. CI indicates confidence interval; SDS, summed difference score; and SSS, summed stress score.

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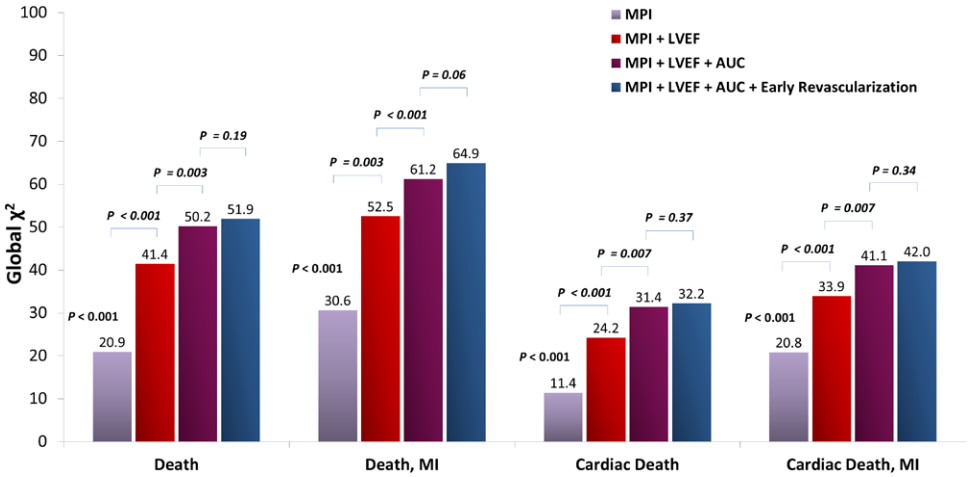

Figure 5. The incremental prognostic value of appropriate myocardial perfusion imaging (MPI) use. Outcome predictors were incrementally introduced in a stepwise fashion into Cox regression models: myocardial perfusion (normal vs abnormal), left ventricular ejection fraction (LVEF; ≥50% vs <50%), appropriate use criteria (AUC) group (appropriate/uncertain vs inappropriate), and then coronary revascularization performed within 60 days after MPI. The gain in the global χ^2 value was used to determine whether each sequentially introduced predictor provided an incremental prognostic value. MI indicates myocardial infarction.

the study population was stratified on the basis of AUC, the value of abnormal MPI in predicting MACE in the inappropriate use group was significantly diminished. Conversely, the prognostic value of MPI was maintained or slightly enhanced in the appropriate/uncertain group. Moreover, the study demonstrates that appropriate use provides incremental prognostic value, beyond myocardial perfusion and LVEF. However, early coronary revascularization after MPI did not provide additional protective or predictive value (Figure 4).

It is clear from our analyses that ischemic burden (SDS) was an independent determinant of the decision for early revascularization regardless of appropriateness group. Furthermore, the analyses of time to coronary intervention (Figure 2) reveal that patients in the inappropriate group were referred sooner for coronary angiography and revascularization despite the low clinical risk, perhaps with little time to evaluate response to medical therapy. Our analysis also indicates that physicians with a low threshold for MPI testing tended to have a low threshold for coronary evaluation after an abnormal MPI, suggesting a nondiscriminative approach to MPI findings. It is plausible that early coronary interventions are responsible for the lower event rates observed in the inappropriate use group. Nonetheless, this would be contradictory to the findings of the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (*COURAGE*) trial, which demonstrated that an initial revascularization strategy does not improve the outcome of patients with stable CAD.[30]

This investigation was not intended to be powered to detect differences in MACE rates on the basis of MPI findings within either appropriateness subgroup. However, it was designed and powered to detect incremental prognostic value with appropriate MPI use. This incremental risk prediction attained with appropriate use enhanced the excellent prognostic value of MPI in the appropriate/uncertain group, whereas inappropriate use was detrimental to the predictive value of MPI. This phenomenon is unlikely to be attributable to an interaction between appropriateness and MPI finding because formal statistical interaction analyses were clearly negative. Nevertheless, the incremental prognostic value of appropriate use is not surprising because robust clinical predictors such as Framingham coronary heart disease risk, likelihood of CAD, and ability to exercise are major determinants of appropriateness.[12] Thus, the low event rate observed in the inappropriate use group rendered MPI less effective in risk stratifying these already low-risk patients. It is likely that in a larger inappropriate use cohort a "statistically significant" difference in MACE rate based on MPI findings could be identified. However, the absolute difference in MACE rate would be very small and thus clinically insignificant.

Additionally, the downstream coronary angiography and revascularization procedures after inappropriate testing would increase cost without clear benefit. Therefore, the economic consequences of inappropriate use of SPECT-MPI are significant, considering that ~5.8 million MPI studies are performed annually in the United States, nearly 85% of which are performed in the outpatient setting,[31,32] at a cost ranging from $800 to $1000 per study according to the 2013 Medicare reimbursement schedule.[33] Thus, although MPI is considered cost-effective overall,[34] the diminished prognostic value with inappropriate testing could have serious implications on the overall cost-effectiveness of MPI, not to mention unnecessary radiation exposure. In fact, minimizing inappropriate use is probably the best and most cost-efficient way to limit the radiation exposure in the community.

This investigation represents the first community-based validation of the AUC for MPI. It reveals surprisingly high levels of inappropriate use with a wide range of disparity between practitioners. The study confirms that patients with appropriate indications receive excellent risk stratification with MPI, whereas those with inappropriate indications receive limited or ineffective risk stratification at high cost and unnecessary radiation exposure. Additionally, this study further emphasizes the role of AUC as an important quality measure in the laboratory accreditation process.[15] Furthermore, it stresses the need for national organizations of primary care and cardiology to educate their members about the AUC.

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This study is limited by AUC determination using chart review. However, this method has been used in many other reports.[26–29] A prospective AUC determination may introduce a different bias: In addition to the bias inherent in using preselected practices and physicians with higher awareness of AUC than is commonplace, physicians' mindfulness of being "scored" for AUC adherence could artificially lower inappropriate use.[13] Additionally, because this investigation was designed as an outcomes study, detailed coronary angiography findings were not collected. Furthermore, a significant number of patients were either excluded from the study (182, 12%) or lost to follow-up (14, 0.9%). Nevertheless, we demonstrated that the clinical, AUC, and imaging characteristics of these patients were similar to those who underwent final analysis. Therefore, it is unlikely that the excluded patients would have changed the conclusions of the investigation. Finally, the study findings cannot be generalized to patient populations not well represented in this cohort such as individuals presenting with acute coronary syndrome, preoperative assessment, syncope, cardiac dysrhythmias, or high-risk tertiary-care patients.

Conclusions

This community-based prospective study demonstrates that the inappropriate use of SPECT-MPI severely impairs its value for risk assessment of patients with known or suspected ischemic heart disease, negatively impacting cost-effectiveness and radiation exposure. However, when performed for appropriate indications, SPECT-MPI maintains its robust prognostic value, even in contemporary community-based settings. This report describes the first prognostic validation of AUC for SPECT-MPI, thus solidifying their role in clinical practice, policy making, and reimbursement decisions.

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Disclosures

Dr Doukky serves on the Advisory Board of Astellas Pharma US. Dr Hendel serves on the Advisory Board for Astellas Pharma US and Bayer (Leverkusen, Germany). The other authors report no conflicts.

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CLINICAL PERSPECTIVE

Single-photon emission computed tomography (SPECT) myocardial perfusion imaging (MPI) is a mainstay of risk assessment for ischemic heart disease. The expansion of MPI use prompted the development of appropriate use criteria to guide physicians on optimal implementation of SPECT-MPI in patient care. The impact of appropriateness of use on the prognostic value of stress MPI has never been evaluated. In this prospective, community-based, cohort study, we followed up for >2 years 1511 patients who were classified according to the 2009 appropriate use criteria. Among subjects with MPI classified as appropriate or uncertain, abnormal scans predicted a multifold increase in the rates of death, death or myocardial infarction, cardiac death or myocardial infarction, and revascularization procedures. However, among subjects with MPI classified as inappropriate, abnormal MPI failed to predict major adverse cardiac events, although it was associated with a high revascularization rate. Appropriate MPI use provided an incremental prognostic value beyond myocardial perfusion and ejection fraction. We concluded that the inappropriate use of SPECT-MPI severely impairs its value for risk assessment and negatively impacts cost-effectiveness. However, when performed for appropriate indications, SPECT-MPI maintains its robust prognostic value. This report describes the first prognostic validation of the appropriate use criteria for SPECT-MPI, thus solidifying their role in clinical practice, policy making, and reimbursement decisions.

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