The Impact of Appropriate Use on the Prognostic Value of SPECT Myocardial Perfusion Imaging

Running title: Doukky et al.; AUC and the Prognostic Value of Cardiac SPECT

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Abstract

Background—Appropriate use criteria (AUC) have been developed to aid in the optimal use of 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 based on the 2009 AUC for SPECT-MPI into appropriate or uncertain appropriateness group and inappropriate group. Patients were prospectively followed for 27±10 months for major adverse cardiac events (MACE) of death, death or myocardial infarction (MI), and cardiac death or MI. In the entire cohort, the 167 (11%) subjects with abnormal scan expectedly experienced significantly higher rates of MACE and coronary revascularization than those with normal MPI. Among the 823 (54.5%) subjects whose MPIs were classified as appropriate [779 (51.6%)] or uncertain [44(2.9%)], abnormal scan predicted a multi-fold increase in the rates of death [9.2% vs. 2.6%;HR=3.1;P=0.004], death or MI [11.8% vs. 3.3%;HR=3.3;P=0.001], cardiac death or MI [6.7% vs. 1.7%;HR=3.7;P=0.006], and revascularization [24.7% vs. 2.7%;HR=11.4;P<0.001]. However, among the 688 (45.5%) subjects with MPI classified as inappropriate, abnormal MPI failed to predict MACE, although was associated with a high revascularization rate. Furthermore, appropriate MPI use provided an 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.

Key words: myocardial perfusion imaging, appropriateness criteria, prognosis, outcome, appropriate use criteria (AUC), SPECT
Introduction

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 multi-fold 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 utilization 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 utilization prompted professional societies to develop appropriate use criteria (AUC) to guide physicians on optimal use of SPECT-MPI in patient care.\(^11\)\(^-\)\(^12\) With intensifying debate regarding healthcare costs, 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.

Design and 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 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 prior to 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 (CHD) risk estimates were calculated.\textsuperscript{16} Chest pain syndromes were classified as typical angina, atypical angina, and non-anginal chest pain on the basis of location, exacerbation with exercise, and resolution with rest or nitroglycerin.\textsuperscript{17} If clinical notes did not describe the chest pain, it was considered non-anginal. Dyspnea was classified as “non-anginal chest pain”. Consequently, the pre-test probability of obstructive CAD was determined based on age, gender, and chest pain classification according to Diamond and Forrester tables.\textsuperscript{17}

Appropriate Use Criteria
Computer-based logic was applied to assign each patient a specific indication and subsequently categorize the studies as appropriate, uncertain, or inappropriate on the basis of the 2009 AUC, in a fashion similar to prior reports.\textsuperscript{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,\textsuperscript{12} patients with appropriate and uncertain appropriateness scans were combined, thus stratifying the study cohort into Appropriate/Uncertain group and Inappropriate group.

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

Using QPS/QGS software (Cedars-Sinai Cardiac Suite; Los Angeles, CA), MPI scans were semiquantitatively interpreted by a single expert nuclear cardiologist (RD) 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).\textsuperscript{21} The segmental scores within the rest and stress scans were summed to generate summed stress and rest scores (SRS, SSS), respectively. The summed difference score (SDS) was calculated from the sum of the difference scores derived from subtracting the segmental resting scores from the segmental stress scores. Quantitative post-stress gated-SPECT left ventricular ejection fraction (LVEF) <50\% was considered abnormal. Normal MPI was defined on the basis of perfusion as SSS=0-3.\textsuperscript{22} Perfusion abnormalities were further categorized, on the basis of SSS, into mild (4-8), moderate (9-13), and severe (>13).\textsuperscript{22} Reversible perfusion abnormalities, signifying stress-induced myocardial ischemia, were defined as SDS\geq2, and further categorized on the basis of SDS, as mild (2-4), moderate (5-7), and severe (>7).\textsuperscript{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 defining abnormal MPI.\textsuperscript{24}

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

**Outcome Determination**

Subjects were prospectively followed for events of death from any cause, cardiac death, nonfatal MI, coronary angiography, percutaneous coronary intervention (PCI), and coronary artery bypass-graft surgery (CABG). 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) two 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 return was used to discern the date of death and determine follow-up time for pure mortality endpoints (death and cardiac death). The follow-up time for the composite endpoints (death or MI and cardiac death or MI) and coronary interventions was determined based on the last clinical encounter date as determined by surveys, phone interviews, or medical records. Revascularization procedures performed within 60 days following 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 endpoint was all-cause mortality. Secondary endpoints were: 1) composite endpoint of death or MI; 2) composite endpoint of cardiac death or MI.

**Statistical Analysis**

Based on published preliminary data, we predicted an abnormal MPI rate of 12%. Assuming a
baseline annual mortality of 0.5% among subjects with normal MPI, we determined that 1558 subjects would be needed to attain 80% power to detect a four-fold increase in mortality associated with abnormal MPI after 2-year follow-up using the unadjusted chi-square test (2-tailed $\alpha=0.05$). 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 (OR) of 2.0 (2-tailed $\alpha=0.05$). The nQuery Advisor 7.0 software (Statistical Solutions, Ltd – Cork, Ireland) was used for sample size estimations.

The chi-square test was used to compare dichotomous variables, which were expressed as frequency (percentage). The Fisher’s exact test was used for dichotomous comparisons when the number of events was $\leq 5$. The 2-tailed Student’s $t$-test was used to compare normally-distributed continuous variables which were expressed as mean ± standard deviation (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 using Spearman’s method. Cox proportional-hazards models were used to compare hazards adjusted for covariates. The clinical covariates adjusted for were: age, gender, diabetes mellitus, hypertension, dyslipidemia, tobacco use, known CAD (prior MI, CABG, or PCI), 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 chi-square value and, hence, the predictive value of clinical and imaging predictors. Two-tailed $P$ values $<0.05$ were considered significant. The 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, one-day, rest/stress, Tc-99m sestamibi SPECT-MPI study. Among those, 182 subjects met one or more exclusion criteria: 84 lacked a valid SSN; 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 Social Security Death Index. Fourteen (0.9%) subjects were lost to follow-up, none of whom were identified as deceased by 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 (51.6%), inappropriate in 688 (45.5%) and uncertain in 44 (2.9%) studies. All subjects were classifiable according to the 2009 AUC. Inappropriate use rates for individual practitioners ranged from 10% to 77% (P<0.001), and was higher among primary care physicians than cardiologists (47% vs. 28%, P<0.001). The study cohort was then stratified into 2 groups: Appropriate/Uncertain group [823 subjects (54.5%)] and 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 CHD risk (**Table-1**). Notably, women comprised 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 slightly lower Duke Treadmill Score (mean 7.4±4.0 vs. 7.9±4.1, \( P=0.04 \)), but no statically significant difference in incidence of stress-induced ischemic ST-segment deviation (10.5% vs. 7.9%; \( P=0.13 \)).

One-hundred sixty-seven (11%) subjects 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); while the breakdown of perfusion abnormality type (fixed, reversible, or mixed) was not significantly different from those in the Inappropriate group (Table 1).

Compared to subjects with complete follow-up, the patients excluded (\( n=182 \)) or lost to follow-up (\( n=14 \)) were younger (mean age 55±15 vs. 59±13 years, \( P=0.001 \)) and had lower likelihood of obstructive CAD (15±13% vs. 18±13%, \( P=0.007 \)), but similar mean 10-year Framingham CHD risk (12.7±10.8% vs. 12.8±10%, \( P=0.88 \)) and CAD prevalence (19% vs. 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 (7.0%) subjects underwent one or more coronary angiography, with subsequent 61 (4.0%) PCI and 14 (0.9%) CABG (Table 2). Thirty-six (2.3%) coronary revascularizations (30 PCI and 6 CABG) occurred within 60 days post-MPI, thus 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 (the gain in global chi-square
values: 237.8 vs. 140.8 for angiography and 241.2 vs. 118.3 for revascularization, \( P \) values<0.001).

Multivariable logistic regression analysis demonstrated that SDS was a predictor for early post-MPI revascularization [OR=1.22 per one point SDS increment (CI=1.2–1.3), \( P<0.001 \)]; adjusting 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, irrespective of appropriateness group (Table-2) and the rates of coronary angiography and revascularization were commensurate with the myocardial ischemia burden (SDS) after adjusting for clinical covariates (Figure-1A and 1B). Notably, mild degree of myocardial ischemia (SDS=2–4) was associated with significant increase in the rates of coronary angiography and revascularization (Figure-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 adjusting for clinical covariates [angiography: \( \text{HR}=1.3 \) (CI=0.8–2.1), \( P=0.24 \); revascularization: \( \text{HR} 1.2 \) (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 vs. Appropriate/Uncertain group, adjusting for clinical covariates [angiography: \( \text{HR}=1.2 \) (CI=0.6–2.4), \( P=0.66 \); revascularization: \( \text{HR}=1.1 \) (CI=0.5–2.5), \( P=0.87 \)] (Figure-1C and 1D). Once performed, coronary angiography was followed by similar rates of non-intervention, PCI, or CABG; respectively implying similar rates.
of no significant CAD, single- or two-vessel disease, and multi-vessel or left main disease (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 vs. 1.7 months and 0.6 vs. 1.3 months), but these differences were not statistically significant ($P=0.16$ and 0.34, respectively). However, in the immediate period following identifying myocardial ischemia by MPI, the time-to-coronary angiography and time-to-revascularization  were shorter in the Inappropriate group, after adjusting for SDS (Figures-2B and 2C). This difference dissipated during the remainder of the follow-up (Figure-1C and 1D).

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 \[ (r = -0.40 \ (P = 0.001)) \text{ and } r = -0.36 \ (P = 0.01), \] 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 (2.3%) deaths, 12 (0.8%) cardiac deaths, and 11 (0.7%) nonfatal MIs. When added to the clinical covariates in Cox-regression models, the SSS provided a greater incremental value than SDS in predicting MACE (the gain in global chi-square values: 20.1 vs. 3.25 for death, 41.6 vs.1.7 for death or MI, and 42.4 vs. 2.3 for cardiac death or MI; $P$ values<0.001).

Patients with abnormal MPI had higher rates of all-cause mortality, and cardiac death, as well as secondary composite endpoints of death or MI and cardiac death or MI (Table-2). Rates of primary and secondary endpoints correlated with severity of perfusion abnormality (SSS) after
adjusting for clinical covariates (Figure-3).

Patients in the Appropriate/Uncertain group experienced significantly higher overall rates of death [HR=2.9 (CI=1.05-8.0), \( P=0.04 \)], the composite of death or MI [HR=1.04 (1.01-1.07), \( P=0.03 \)], and the composite of cardiac death or MI [HR=5.7 (CI=1.3-25.6), \( P=0.02 \)] after adjusting for clinical covariates. Among patients in the Appropriate/Uncertain group, abnormal MPI continued to predict a multi-fold increase in the risk of death, cardiac death, composite of death or MI, and the 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 vs. 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 (\( P \) values 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 (CI=0.10–0.67); \( P=0.005 \)], adjusting for myocardial perfusion finding (normal vs. abnormal) [HR=2.5 (CI=1.1–5.9); \( P=0.04 \)] and depressed LVEF (<50%) [HR=3.7 (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 endpoints of death or MI [HR=0.31 (CI=0.14-0.70); \( P=0.005 \)] and cardiac death or MI [HR=0.16 (CI=0.04-0.71); \( P=0.02 \)], after adjusting for depressed LVEF, myocardial perfusion findings, and early revascularization. In these models, MPI and depressed LVEF independently predicted the composite endpoints of death or MI and cardiac death or MI, whereas undergoing early coronary revascularization following MPI was not predictive of these endpoints (\( P \) values \( \geq 0.97 \)). Finally,
in forward stepwise Cox-regression models, appropriate use was shown to have incremental
prognostic value to perfusion imaging and depressed LVEF in predicting 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
regarding 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 to 24%), particularly among primary care
physicians (47%).\textsuperscript{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 due to 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 to investigate 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.\textsuperscript{4} We demonstrated that SDS is better than SSS in predicting coronary
angiography and revascularization decisions, while SSS is the better predictor for MACE events. 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, irrespective of appropriateness. This is not surprising, as the decision-making process for coronary angiography and revascularization following abnormal MPI often does not take into account the initial appropriateness for MPI. However, when the study population was stratified based on 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 following 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 irrespective of appropriateness group. Furthermore, the time-to-coronary intervention analyses (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 following an abnormal MPI, suggesting a non-discriminative 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 COURAGE trial which demonstrated that an initial revascularization strategy does not
improve the outcome of patients with stable CAD.\textsuperscript{30}

This investigation was not intended to be powered to detect differences in MACE rates on the basis of MPI finding 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 due to an interaction between appropriateness and MPI finding, as formal statistical interaction analyses were clearly negative. Nonetheless, the incremental prognostic value of appropriate use is not surprising since robust clinical predictors such as Framingham CHD risk, likelihood of CAD, and ability to exercise are major determinants of appropriateness.\textsuperscript{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 following inappropriate testing would increase cost without clear benefit. Therefore, the economic consequences of inappropriate use of SPECT-MPI are significant; considering that an approximate 5.8 million MPI studies are performed annually in the United States, nearly 85\% of which are performed in the outpatient setting,\textsuperscript{31, 32} at a cost ranging from $800 to $1000 per study according to 2013 Medicare reimbursement schedule.\textsuperscript{33} Thus, although MPI is considered cost-effective overall,\textsuperscript{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. Furthermore, it stresses the need for national organizations of primary care and cardiology to educate their members about the AUC.

This study is limited by AUC determination using chart review. However, this method has been used in many other reports. 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 them being “scored” for AUC adherence could artificially lower inappropriate use. Additionally, this investigation was designed as an outcome study. Thus, detailed coronary angiography findings were not collected. Furthermore, significant number of patients were either excluded from the study [182 (12%)] or lost to follow-up [14 (0.9%)]. Nonetheless, we demonstrated that the clinical, AUC, and imaging characteristics of these patients were similar to those who underwent final analysis. Therefore, it is unlikely for the excluded patients to change 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.
Conclusion

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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Conflict of Interest Disclosures: Rami Doukky serves on the Advisory Board of Astellas Pharma US. Robert Hendel serves on the Advisory Board for Astellas Pharma US and Bayer (Leverkusen, Germany). Other authors have no conflicts to report.

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Table 1. Baseline Clinical and Imaging Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Overall Cohort n=1511</th>
<th>Appropriate/ Uncertain n=823 (54.5%)</th>
<th>Inappropriate n=688 (45.5%)</th>
<th>P value</th>
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<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td>59±13</td>
<td>63±11</td>
<td>53±12</td>
<td>&lt;0.001</td>
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<td><strong>Women</strong></td>
<td>657 (43.5%)</td>
<td>258 (31.3%)</td>
<td>399 (58.0%)</td>
<td>&lt;0.001</td>
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<tr>
<td><strong>Primary Indication for MPI</strong></td>
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<tr>
<td>- Chest Pain</td>
<td>688 (45.5%)</td>
<td>495 (60.1%)</td>
<td>193 (28.0%)</td>
<td></td>
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<tr>
<td>- Dyspnea</td>
<td>158 (10.5%)</td>
<td>133 (16.2%)</td>
<td>25 (3.6%)</td>
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<tr>
<td>- Abnormal ECG</td>
<td>136 (9.0%)</td>
<td>34 (4.1%)</td>
<td>102 (14.8%)</td>
<td></td>
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<tr>
<td>- Evaluation of known CAD</td>
<td>159 (10.5%)</td>
<td>49 (6.0%)</td>
<td>110 (16.0%)</td>
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<tr>
<td>- Preoperative assessment</td>
<td>37 (2.4%)</td>
<td>18 (2.2%)</td>
<td>19 (2.8%)</td>
<td></td>
</tr>
<tr>
<td>- Syncope</td>
<td>21 (1.4%)</td>
<td>5 (0.6%)</td>
<td>16 (2.3%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>- Asymptomatic</td>
<td>262 (17.3%)</td>
<td>70 (8.5%)</td>
<td>192 (27.9%)</td>
<td></td>
</tr>
<tr>
<td><strong>Hypertension</strong></td>
<td>841 (55.6%)</td>
<td>538 (65.4%)</td>
<td>303 (44.0%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Diabetes Mellitus</strong></td>
<td>333 (22.0%)</td>
<td>244 (29.6%)</td>
<td>89 (12.9%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Dyslipidemia</strong></td>
<td>695 (46.0%)</td>
<td>451 (54.8%)</td>
<td>244 (35.5%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Prior MI</strong></td>
<td>841 (55.6%)</td>
<td>538 (65.4%)</td>
<td>303 (44.0%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Known CAD</strong></td>
<td>271 (17.9%)</td>
<td>203 (24.7%)</td>
<td>68 (9.9%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Prior CABG</strong></td>
<td>76 (5.0%)</td>
<td>76 (9.2%)</td>
<td>0 (0%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Prior PCI</strong></td>
<td>87 (5.8%)</td>
<td>73 (8.9%)</td>
<td>14 (2.0%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Exercise Stress (Bruce) Protocol</strong></td>
<td>1164 (77.0%)</td>
<td>554 (67.3%)</td>
<td>610 (88.7%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>BMI (kg/m²)</strong></td>
<td>30±5.7</td>
<td>29±5.4</td>
<td>29±&lt;0.001</td>
<td></td>
</tr>
<tr>
<td><strong>HMG-CoA reductase inhibitor</strong></td>
<td>580 (38.4%)</td>
<td>390 (47.4%)</td>
<td>190 (27.6%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Antiplatlet</strong></td>
<td>370 (24.5%)</td>
<td>273 (33.2%)</td>
<td>97 (14.1%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>β-Blocker</strong></td>
<td>307 (20.3%)</td>
<td>216 (26.2%)</td>
<td>91 (13.2%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>ACE-I or ARB</strong></td>
<td>567 (37.5%)</td>
<td>379 (46.1%)</td>
<td>188 (27.3%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Myocardial Perfusion</strong></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>- Normal (SSS=0-3)</td>
<td>1344 (88.9%)</td>
<td>704 (85.5%)</td>
<td>640 (93.0%)</td>
<td></td>
</tr>
<tr>
<td>- Mildly abnormal (SSS=4- 8)</td>
<td>79 (5.2%)</td>
<td>51 (6.2%)</td>
<td>28 (4.1%)</td>
<td></td>
</tr>
<tr>
<td>- Moderately abnormal (SSS=9-13)</td>
<td>47 (3.1%)</td>
<td>38 (4.6%)</td>
<td>9 (1.3%)</td>
<td></td>
</tr>
<tr>
<td>- Severely abnormal (SSS&gt;13)</td>
<td>41 (2.7%)</td>
<td>30 (3.6%)</td>
<td>11 (1.6%)</td>
<td></td>
</tr>
<tr>
<td><strong>Myocardial ischemia</strong></td>
<td></td>
<td></td>
<td></td>
<td>0.03</td>
</tr>
<tr>
<td>- None (SDS≤1)</td>
<td>1399 (92.6%)</td>
<td>742 (90.2%)</td>
<td>647 (94.0%)</td>
<td></td>
</tr>
<tr>
<td>- Mild (SDS=2-4)</td>
<td>38 (2.5%)</td>
<td>27 (3.2%)</td>
<td>11 (1.6%)</td>
<td></td>
</tr>
<tr>
<td>- Moderate (SDS=5-7)</td>
<td>40 (2.6%)</td>
<td>28 (3.4%)</td>
<td>12 (1.7%)</td>
<td></td>
</tr>
<tr>
<td>- Severe (SDS&gt;7)</td>
<td>43 (2.8%)</td>
<td>26 (3.2%)</td>
<td>17 (2.5%)</td>
<td></td>
</tr>
<tr>
<td><strong>Type of Perfusion Abnormality</strong></td>
<td></td>
<td></td>
<td></td>
<td>0.14</td>
</tr>
<tr>
<td>- Reversible</td>
<td>87 (5.8%)</td>
<td>58 (7.0%)</td>
<td>29 (4.2%)</td>
<td></td>
</tr>
<tr>
<td>- Fixed</td>
<td>61(4.0%)</td>
<td>49 (6.0%)</td>
<td>12 (1.7%)</td>
<td></td>
</tr>
<tr>
<td>- Reversible and fixed</td>
<td>19 (1.3%)</td>
<td>12 (1.5%)</td>
<td>7 (1.0%)</td>
<td></td>
</tr>
<tr>
<td><strong>Post-stress LVEF&lt;50%</strong></td>
<td>78 (5.2%)</td>
<td>53 (6.4%)</td>
<td>25 (3.6%)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

MPI: SPECT myocardial perfusion imaging; CAD: coronary artery disease; CHD: coronary heart disease; CABG: coronary artery bypass grafting; PCI: percutaneous coronary intervention; MI: myocardial infarction; ACE-I: angiotensin converting enzyme inhibitor; ARB: angiotensin receptor blocker; SSS: summed stress score; SDS: summed difference score; LVEF: left ventricular ejection fraction. †Based on Diamond and Forrester tables in patients with chest pain or dyspnea.17
Table 2. Event Rates Based on Myocardial Perfusion Imaging Findings and Appropriateness

### A. Intervention decisions based on the presence of myocardial ischemia (SDS≥2)

<table>
<thead>
<tr>
<th>Group</th>
<th>Total Events n (%)</th>
<th>Ischemia n=122 (8%)</th>
<th>No ischemia n=1389 (92%)</th>
<th>HR (95% CI)†</th>
<th>P value‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Entire Cohort</td>
<td>106 (7.0%)</td>
<td>47 (38.5%)</td>
<td>59 (4.2%)</td>
<td>11.3 (7.6 – 16.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Angiography</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Appropriate/Uncertain</td>
<td>72 (8.7%)</td>
<td>32 (39.5%)</td>
<td>40 (5.4%)</td>
<td>9.9 (6.1 – 16.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>- Inappropriate</td>
<td>34 (4.9%)</td>
<td>15 (36.6%)</td>
<td>19 (2.9%)</td>
<td>14.5 (7.0 – 30.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Coronary</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Entire Cohort</td>
<td>61 (4.0%)</td>
<td>29 (23.8%)</td>
<td>32 (2.3%)</td>
<td>11.8 (7.0 – 19.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Revascularization</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Appropriate/Uncertain</td>
<td>40 (4.9%)</td>
<td>20 (24.7%)</td>
<td>20 (2.7%)</td>
<td>11.4 (6.0 – 21.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>- Inappropriate</td>
<td>21 (3.1%)</td>
<td>9 (22.0%)</td>
<td>12 (1.9%)</td>
<td>12.1 (4.8 – 30.8)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

### B. Outcomes based on MPI abnormality (SSS≥4)

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

HR: hazard-ratio; CI: confidence interval; MI: nonfatal myocardial infarction. Entire cohort: n=1511. Appropriate/Uncertain group: n=823. Inappropriate group: n=688. †HR (95% CI) and P values are derived from Cox proportional-hazards models, adjusted for clinical covariates. Each line represents a separate analysis.
Figure Legends:

Figure 1. Coronary Angiography and Revascularization Following MPI. **App/Unc:** Appropriate/Uncertain group; **Inapp:** Inappropriate group; **NS:** Not Significant \((P>0.05)\). **Pane A** and **B:** Time-to-angiography and time-to-revascularization Cox proportional-hazards curves based on severity of myocardial ischemia (SDS). The hazard-ratios are calculated relative to the “No ischemia” group and adjusted for clinical covariates. **Pane 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 and Inappropriate groups. Hazard-ratios (ischemia vs. no ischemia) were calculated separately within each appropriateness group and adjusted for clinical covariates.

Figure 2. Decision Making Following Myocardial Perfusion. **Pane A:** Interventions delivered following coronary angiography. **Pane 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 SDS).

Figure 3. Major Adverse Cardiac Events Based on MPI Findings. Time-to-MACE Cox proportional-hazards curves based on severity of perfusion abnormality (SSS). The hazard-ratios are calculated relative to the “Normal” group and adjusted for clinical covariates.

Figure 4. Adverse Cardiac Events Based on MPI and Appropriateness. **App/Unc:** Appropriate/Uncertain group; **Inapp:** Inappropriate group. Time-to-MACE Cox proportional-
hazards curves of patients with abnormal vs. normal MPI within the Appropriate/Uncertain and Inappropriate groups. Hazards-ratios (abnormal vs. normal) were calculated separately within each appropriateness group and adjusted for clinical covariates.

**Figure 5.** The Incremental Prognostic Value of Appropriate MPI Use. Outcome predictors were incrementally introduced in a stepwise fashion into Cox-regression models: myocardial perfusion (normal vs. abnormal), LVEF ($\geq 50\%$ vs. $< 50\%$), AUC group (Appropriate/Uncertain vs. Inappropriate), then coronary revascularization performed within 60 days following MPI. The gain in the global chi-square ($\chi^2$) value was used to determine whether each sequentially-introduced predictor provided an incremental prognostic value.
Figure 1
Figure 2

A. Post Angiography Interventions
- No intervention
- PCI
- CABG

B. Time to Angiography
- Ischemia (SDS ≥ 2) on MPI
- HR = 2.2 (CI = 1.03 – 4.8)
- P = 0.04

C. Time to Revascularization
- Ischemia (SDS ≥ 2) on MPI
- HR = 2.6 (CI = 1.0 – 6.8)
- P = 0.05
Figure 3
Figure 4
Figure 5
The Impact of Appropriate Use on the Prognostic Value of SPECT Myocardial Perfusion Imaging
Rami Doukky, Kathleen Hayes, Nathan Frogge, Gautam Balakrishnan, Venkata Satish Dontaraju, Maria O. Rangel, Yasmeen Golzar, Enrique Garcia-Sayan and Robert C. Hendel

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