Prognostic value of gated myocardial perfusion SPECT

Leslee J. Shaw, PhD,[a] and Ami E. Iskandrian, MD[b]

Risk assessment has become increasingly important in this era of evidence-based medicine in which new and existing technology requires a well-defined body of evidence on its societal benefit in order to support resource utilization. Historically, test accuracy has been defined by using sensitivity and specificity for the detection of obstructive coronary disease. However, this measurement is fraught with bias and poorly reflects test performance. The focus on risk assessment in cardiovascular medicine is consistent with a shift toward integrative patient management approaches whereby the extent and severity of inducible ischemia are used to guide therapeutic decision making. This change in focus allows nuclear cardiology to play a central role in patient management decisions. The estimation of prognosis with any given imaging modality allows a more precise linkage with patient risk and therapeutic risk reduction efforts. In addition, a nuclear-based focus for decision making concentrates on the physiologic significance of the disease state and its relationship to event risk.

This concept of medically guided care (including optimized anti-ischemic therapy and selective cardiac catheterization) is further promoted in our current era of cost-conscious health care. From nuclear-based strategies that provide information about patient risk, the ensuing posttest resource needs of any given patient group may also be estimated. The ensuing costs for tests that have established value in identifying prognostically significant disease states may be offset by the downstream savings in decreased morbidity and mortality. In the United States, annual expenditures for diagnosing and treating cardiovascular disease exceed $329 billion.[1] Health care costs have risen dramatically and exceed the rate of inflation. Although rising costs reflect an increase in the prevalence of coronary heart disease and an aging population, new technology for cardiovascular disease is also a major contributor to high rates of resource utilization. In the area of single photon emission computed tomography (SPECT) imaging, annualized growth rates for cardiologists have increased by more than 20%.[2] When one examines all of cardiovascular testing, there are an estimated 40 million noninvasive cardiac tests performed each year.[3] For echocardiography and SPECT imaging, reimbursement from Medicare encompasses approximately 30% of all payments, totaling over $1 billion in the year 2000.[4] Thus the use of testing that importantly guides lifesaving care is a critical step toward cost-effective testing for society.

From the Atlanta Cardiovascular Research Institute, Atlanta, Ga,[a] and the University of Alabama at Birmingham, Birmingham, Ala.[b]
Reprint requests: Leslee J. Shaw, PhD, Director, Outcomes Research, 5665 Peachtree Dunwoody Rd NE, Suite 225, Atlanta Cardiovascular Research Institute, Atlanta, GA 30342; *lshaw@acrionline.org.*
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ESTIMATING RISK VERSUS DISEASE

Although the focus of the current review is the estimation of prognosis with gated myocardial perfusion SPECT, recent evidence has been synthesized to reveal that gated myocardial perfusion SPECT is a highly sensitive test for the detection of a critical stenosis.[5] In a recent meta-analysis organized by the United Kingdom's National Institute of Clinical Excellence, diagnostic sensitivity for myocardial perfusion imaging was 87% (n = 2,971/3,425).[5] Specificity was lower (73%; n = 772/1,055) but was influenced by the low number of patients with negative test results who underwent the gold standard, angiography.

Specificity, as a measure of test performance, is suboptimal because it fails to consider whether a flow-limiting lesion is prognostically significant, as is supported by myocardial infarction literature in which subcritical lesions often progress to the acute event.[6] A frequently cited major limitation on the usefulness of diagnostic sensitivity and specificity is verification or workup bias. Workup bias occurs when the vast majority of patients with abnormal test results undergo the gold standard, coronary angiography, thus resulting in an overestimation in diagnostic sensitivity. Specificity is diminished (as these two measures operate as diametrically opposed calculations) because few patients with negative test results are referred to cardiac catheterization. The ensuing calculation of a high sensitivity and lower specificity, as noted in the review by Underwood et al,[5] supports the notion of verification bias in the nuclear literature, and as such, these diagnostic measures are not useful in guiding patient referral decisions.

In addition to the problems of workup bias, there are other advantages to using prognostication as a measure of test performance. The use of estimated risk versus diagnostic accuracy is advantageous in higher-risk populations including the elderly, those with peripheral arterial disease, diabetic patients, or patients with known coronary disease. It has also been shown to be helpful in populations in whom diagnosis is challenging, including the large proportion of women referred to SPECT laboratories.

SPECT RISK MARKERS SERVE AS INTERMEDIATE OUTCOME MEASURES

Thus a shift in publications from diagnostic to prognostic accuracy should be considered a tremendous advance to the field and has the benefit of coordinating outcome estimation with therapeutic randomized controlled trial data. For example, one of our greatest prognosticators in cardiovascular medicine is left ventricular ejection fraction, which is commonly estimated by gated SPECT and is inversely related to cardiac survival. Integrative management decisions can be effectively initiated based on left ventricular dysfunction measures (eg, angiotensin-converting enzyme inhibitors). In addition, these measures can provide insight into the therapeutic benefit that may result from intervention. With this example, the expected increase in life expectancy with coronary artery bypass surgery is approximately 10 years in patients with abnormal systolic function as compared with 2 years for those with normal ventricular function.[7,8] According to this logic, measures of ventricular function and myocardial perfusion imaging may be viewed as intermediate or surrogate outcomes, in that they are indicators of future adverse sequelae. This recent paradigm has fostered further research in the area of nuclear cardiology where treatment is focused on the intermediate outcome of inducible ischemia or other high-risk SPECT markers, thereby altering the expected worsening outcome in at-risk patients.[9-31] We await further research in this area of nuclear cardiology where treatment is wholly integrated and focused based on SPECT imaging results, such as with the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) and Adenosine Sestamibi Post-Infarction Evaluation (INSPIRE) trial results.

RISK THRESHOLDS

One of the clear benefits of using risk estimation is that it can be coordinated within population-based risk thresholds. We do know that the underlying risk in the population varies with a patient's pretest risk, such that patients without coronary disease have lower rates of coronary disease events than those with disease (ie, approximately 1% vs 2%, on average). Population risk in those without disease may be estimated by use of one of many global risk scores (eg, Framingham risk[32]). In a diagnostic population, risk is substantially lower than in a population with existing cardiovascular disease or for those disease-equivalent patients (eg, diabetic patients).[32] Thus stratification of risk must initially consider the pretest risk in the population. Beginning with a diagnostic population, optimal candidates for imaging include those intermediate-risk patients. Intermediate-risk patients may be defined as those for whom the rate of cardiac death or nonfatal myocardial infarction ranges from approximately 1% to 2% per year. In general, in symptomatic cohorts, intermediate-risk patients are those with 1 or more risk factors (excluding diabetes). Women with typical angina are also considered to be at intermediate risk. Risk compounds with the clustering of risk factors and symptom burden, such that multiple risk factors increase the risk in the population and patients with more frequent and unstable symptoms are at increasing risk.

Intermediate-risk patients are then allocated to lower- or higher-risk subsets based on posttest imaging results. Low-risk candidates are those whose estimated rate of death or myocardial infarction is lower than 1% or, in patients with known coronary disease, is lower than 2%.[33] Patients with high-risk SPECT results in a diagnostic cohort are defined as those with an estimated rate of death or nonfatal myocardial infarction of approximately 2% or greater per year. Evidence supports that an even higher-risk subset of patients with (frequently severe and extensive) known coronary disease have an annual mortality rate estimation of 3% to 5% or more. All high-risk cohorts are then targeted for aggressive posttest management. Of those with suspected or known coronary disease, high-risk SPECT results are associated with a high prevalence of obstructive and/or progressive disease, and thus these patients benefit from referral to coronary angiography.

BAYESIAN THEORY

As evidenced by the prior discussion, optimal candidate selection depends on an understanding of the underlying risk in any given patient group. Extending this reasoning one additional step, appropriate patient selection for nuclear imaging will guide the added or incremental value of imaging in any pretest risk cohort. That is, by integrating risk factor, age, and symptom data into a global risk score (eg, Framingham risk score, European risk score), a patient's pretest risk may be estimated as low, intermediate, or high. Several models have been developed in large, symptomatic cohorts to predict rates of mortality as well as significant and extensive coronary disease[8,34-36]; these prediction algorithms are based on age, sex, symptom (presence, frequency, instability), and traditional cardiac risk factors, as well as measures of systolic blood pressure and resting electrocardiographic abnormalities.

This estimation of pretest risk is the cornerstone of achieving optimal incremental value in posttest information. Thus optimal selection of candidates for SPECT is based on Bayesian theory, in which the posttest likelihood becomes a function of a patient's pretest risk. Bayesian theory may then provide us with insight as to which patient subsets will garner the greatest amount of added information from referral to nuclear imaging. In low-risk patients, the shift from pretest to posttest risk estimation is minimal. Thus this decision is ineffective and costly. A large majority of intermediate-risk patients may be shifted to lower-risk cohorts (given negative test results) or higher-risk cohorts (in the setting of moderately to severely abnormal perfusion scans). For example, published reports note that, on average, 53% of patients have normal or low-risk myocardial perfusion imaging results. Accordingly, it is expected that approximately half of intermediate-risk patients would be at low risk after testing, with an expected annual mortality rate of approximately 0.6%.[33] As one can see, a posttest shift is greatest in those patients with an intermediate pretest risk of coronary disease.

DEFINING THE EFFECTIVENESS OF CARDIAC IMAGING PRINCIPLES OF RISK STRATIFICATION

A critical step in evaluating the utility of an imaging test is its impact on patient outcome and alterations in patient management.[37] The evaluation of a test's ability to risk-stratify individuals has been proposed as an alternative to the challenges of assessing diagnostic accuracy.[38] For any given test, risk stratification may be used as a method for defining high- and low-risk cohorts where treatment is allocated to those in greatest need.[8] Furthermore, the intensity of management is directly proportional to the estimated risk of events, such that high-cost care is allocated to high-risk patients.[8] Of course, the economic benefit of risk stratification is that, left untreated, many of the high-risk individuals would have a cardiac event resulting in more costly care. Furthermore, identifying high-risk patients before the onset of clinical cardiovascular disease may offset the significant morbidity and mortality rates associated with more advanced disease. Conversely, low risk should equate to low cost to the health care system.

OUTCOME MEASURES

The broad range of outcome measures that are applicable to the use of risk stratification include (1) intermediate clinical outcomes (eg, disease detected, cardiac event predicted), (2) major adverse cardiovascular events (eg, survival rates), (3) cumulative effects of test-driven strategy (eg, life years saved), (4) patient assessment of a test's value (eg, quality of life, patient preferences), and (5) combined quantity- and quality-of-life years (eg, quality-adjusted life years, healthy-year equivalent[37]).

DEFINING THE INTERACTIVE NATURE OF RISK WITH PREDICTIVE MODELS

Risk stratification may be defined statistically as the relative risk ratio (often with 95% CIs), in which a high-risk cohort is calculated as the ratio of increased risk of events. Relative risk ratios indicate the x-fold increase in event risk in high- versus low-risk patients where a statistical increase is noted when the CIs do not include 1.0. As cardiovascular risk is often interactive, additive, or multiplicative, multivariable regression models help to define the independent contribution of any given set of variables in estimating adverse cardiac events. Thus multivariable predictive models can be used to describe the interactive nature of both historical and measured risk factors to those associated with an imaging abnormality and provide an improved method to assess the prognostic value of testing.[39-49]

A key to interpreting relative risk ratios with SPECT imaging parameters is to understand that risk increases with myocardial perfusion abnormalities (ie, directly proportional relationship) but is inversely related to measures of left ventricular function. That is, as ejection fraction measures decrease, a patient's risk increases. These opposite relationships can help to explain varying relative risk ratios where a lower risk ratio with systolic dysfunction (eg, ejection fraction = 45%) can be indicated by a relative risk ratio of 0.68, denoting a 32% increase in cardiac event risk (ie, $1 - 0.68 = 32\%$).

However, it is important to consider the difference between absolute and relative risks. In two populations of varying underlying risk (eg, suspected and chronic coronary disease), relative risk ratios may be elevated similarly; however, the overall event rate in the population may be divergent (as previously discussed).[50] An example of this could be two patients, one at intermediate risk and one with known disease, with normal perfusion findings, in whom the relative risk may be diminished but the absolute risk of death (<1% vs 1%-2% per year) is quite different. Thus critical components of risk must include an understanding of both relative and absolute risk of events.

DEFINING THE ADDED VALUE OF SPECT

The supportive rationale for the use of imaging is that symptoms, established risk factors, physical examination, and functional status measures are often insensitive to disease states.[51] SPECT's incremental value may be calculated by quantifying the amount of added information, often called the test's incremental value. In general, tests that provide more added information would be favored over those that have less prognostic content. Diagnosis costs can be high when tests add little value (ie, in low-risk individuals[52]). As noted, SPECT imaging has a greater incremental value in intermediate-risk individuals.[53]

CONCEPTS IN LINKING RISK ASSESSMENT TO TAILORED MEDICAL INTERVENTION

SPECT imaging provides not only information about the physiologic significance of flow-limiting disease and left ventricular function but also a global estimation of risk for major adverse cardiac events. As this is the threshold for evidence-based practice, gated SPECT is the tool optimally suited to provide information to guide patient management decisions. This concept, in terms of evidence-based medicine, is called empiric risk stratification, in which optimal improvement in outcome is achieved by linking high-risk SPECT measures to risk-reducing therapies. The optimal link is the specific event that the imaging modality identifies and the therapy applied which have also been shown to reduce outcomes. This concept of tailoring intervention based on the expected risk in the patient was initially espoused in the Bethesda Conference on secondary prevention.[8]

From gated SPECT, the optimal risk assessment tool would include markers of the amount of ischemic burden and the extent of left ventricular dysfunction. A compilation of evidence suggests that varying outcomes may be estimated when using measures of myocardial ischemia as compared with left ventricular function data. In particular, measures of the amount of myocardial ischemia have been consistently shown to predict acute ischemic events including acute myocardial infarction and worsening or unstable angina (leading to late revascularization). Measures of left ventricular function are consistently linked to end-stage cardiac events including death and heart failure. In this latter group, one would also surmise that increased lung uptake of thallium and stress-induced ventricular dilatation would also provide estimation of end-stage events in higher-risk patients (ie, with severe coronary disease).

RISK OF EVENTS IN PATIENTS WITH NORMAL OR LOW-RISK FINDINGS

By definition, principles of risk stratification would define a cohort with improved outcome (ie, low risk) and exhibit a clear separation in risk between higher-risk subsets of the population. In the case of patients with normal perfusion findings, numerous studies over the past decade have reported uniformly low rates of major adverse cardiac outcomes. Table 1 details the current evidence in 19 published series on normal or low-risk myocardial perfusion SPECT.[8,33,54-69] In the 19 reports, a total of 39,173 patients were reported to exhibit a median rate of major adverse cardiac events of 0.6% per annum (25th percentile = 0.5%, 75th percentile = 0.9%).[33,54-71] (Note: This includes duplicate series from several large observational registries.) This finding has been reported with all three of the commonly used isotopes including thallium 201, technetium 99m sestamibi, and Tc-99m tetrofosmin. Most recently, a combined series evaluating near-term prognosis in all three agents was reported in 10,408 patients noting equivalent cardiac death rates (ie, 0.6% per year over a 3-year period of follow-up).[33] Furthermore, the finding of an exceedingly low event rate over a 7-year period of follow-up has recently been reported.[54] These findings are important in symptomatic cohorts, such as is noted in the 19 published series, and reflect the value of evaluating the physiology of the disease state in addition to anatomic extent and severity of stenoses. Thus, although obstructive coronary disease may be present, normal perfusion findings reveal that the disease is not flow-limiting and that, on the basis of this evidence, it is not prognostically significant. It is also important to note that a rate of 0.6% per year is similar to an intermediate-risk, asymptomatic cohort, as has been noted in prior reports from the National Cholesterol Education Program Adult Treatment Panel III and Framingham risk score estimates.[35,36]

There are important caveats to this assessment including the notation that the event rate in patients with a normal perfusion SPECT study is dependent on the underlying risk in the population. That is, our synthesis of evidence noted an annualized event rate of 0.6% and reflects the average expected yearly occurrence of cardiac death and nonfatal myocardial infarction for intermediate-risk patients with normal perfusion findings. However, higher event rates would be expected for patients with established disease or those with higher risk equivalents (including diabetic patients, the elderly, and those with existing peripheral arterial disease or undergoing pharmacologic stress imaging). The risk in these latter cohorts is higher as a result of a greater disease and comorbidity burden. On the basis of published evidence, we can expect that normal perfusion would be defined with adverse event rates of 1% to 2% per year in patients with existing cardiovascular disease and including (symptomatic) diabetic patient populations. As noted in asymptomatic population reports, patients with existing disease have an expected rate of cardiac death or nonfatal myocardial infarction of 2% per year. In two recent

Table 1. Prognostic value of normal or low-risk myocardial perfusion SPECT in estimating cardiac death and nonfatal myocardial infarction rates per year of follow-up

Year	Author	N	Agent	Average follow-up (y)	Annualized event rate (%)
2003	Elhendy[54]	218	MIBI	7.4	0.7
2003	Hachamovitch[55]	7,376	Tl/MIBI	1.8	0.6
2003	Shaw[33]	10,408	Tl/MIBI/Tetro	3.0	0.6
2002	Gibson[56]	729	MIBI	1.8	0.3
2001	Galassi[57]	459	Tetro	3.1	0.9
2000	Groutars[58]	236	Tl-201/Tetro	2.1	0.4
1999	Soman[59]	473	MIBI	2.5	0.2
1999	Gibbons[60]	4,649	Tl-201/MIBI	7.0	0.4
1999	Vanzetto[61]	1,137	Tl-201	6.0	0.6
1998	Alkeylani[62]	1,086	MIBI	2.3	0.6
1998	Hachamovitch[63]	5,183	Tl-201/MIBI	1.8	0.8
1998	Olmos[64]	225	Tl-201	3.7	0.9
1997	Boyne[65]	229	MIBI	1.6	0.8
1997	Snader[66]	3,400	Tl-201	2.0	1
1996	Geleijnse[67]	392	MIBI	1.8	0.8
1995	Heller[68]	512	MIBI	12.8	1.3
1994	Kamal[69]	177	Tl-201	1.8	0
1994	Machecourt[70]	1,926	Tl-201	2.8	0.5
1994	Stratmann[71]	534	MIBI	1.1	1.6
SPECT experience: 10 years [median (25th–75th percentile)]		39,173*		2.3 (1.8-3.0)	0.6 (0.5-0.9)

MIBI, Tc-99m sestamibi; *Tetro*, Tc-99m tetrofosmin.
*Total n includes duplicate series.

reports in patients with normal perfusion findings, the annual rate of cardiac death was approximately 0.9% for patients with a prior history of coronary disease as compared with 0.2% for those without a prior diagnosis.[33,55] Thus an elevated risk would warrant a closer posttest evaluation with recommended serial testing as soon as at 1 year of follow-up.[55] Thus these results are consistent with the "low end" of expected risk in this subset with an elevated risk. It is important to realize that those with chronic coronary disease (or its equivalents) have substantively higher event rates, in the setting of normal perfusion findings, but there remains a clear separation between low-risk and moderately to severely abnormal findings. Figure 1 illustrates the expected event rates with low- to high-risk SPECT findings in varying patient populations. As is noted in this figure, there is a clear separation in risk between low- to high-risk subsets of the population; however, the expected risk in the population increases proportionally.

RISK OF EVENTS IN PATIENTS WITH ABNORMAL MYOCARDIAL PERFUSION SPECT RESULTS

In the setting of moderate-severely abnormal myocardial perfusion SPECT, rates of "hard" cardiac events, notably cardiac death and nonfatal myocardial infarction, increase logarithmically over and above patients with low-risk findings. As previously noted, the relative increase (ie, x-fold) in risk is commonly calculated by use of a relative risk ratio. On average, relative risk ratios are increased 5- to 7-fold, with the results being highly dependent on the available sample size.[8] In larger populations (ie, >1,000 patients), relative risk ratios are elevated 3- to 5-fold.[8] The absolute risk of events as reported in 39 reports (N = 69,655 [including duplicate series]) is shown in Table 2.[50,53,57,61-71,72-96] Although the definition of high risk varies with the published series, it typically includes patients with moderately to severely abnormal scans, multivessel perfusion abnor-

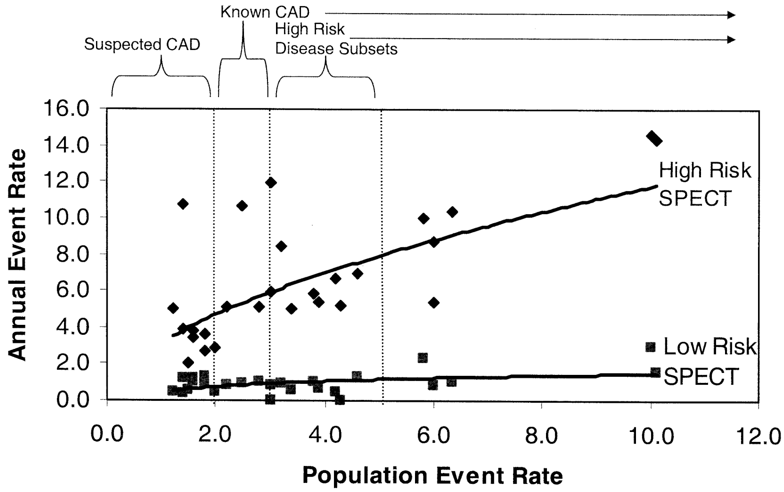

Figure 1. Scatter plot of the relationship of population event rates to annual rates of cardiac death or nonfatal myocardial infarction in patients with low-risk or normal perfusion and high-risk SPECT imaging findings (eg, summed stress score >8, moderately to severely abnormal or multivessel perfusion patterns). These results reveal that event rates are decidedly lower in populations with suspected coronary disease (*CAD*) (defined as annual event rate <2%) as compared with patients with chronic coronary disease (defined as annual event rate ≥2%). Of the latter patients, those with high-risk, severe and extensive disease exhibit the highest overall event rates (defined as annual event rates ≥5%).

malities, or a summed stress score greater than 8.[8,50,53,57,61-71,72-96]

Although we will not specifically discuss the types of defects, the literature supports the concept that the extent of fixed defects provides a better estimation of cardiac death and that reversible defects often predict acute ischemic events. Thus the combination of estimating cardiac death or nonfatal myocardial infarction would balance prognostication by using both of these defect markers. However, in populations with known coronary disease, the identification of extensive fixed perfusion abnormalities would be highly predictive of worsening cardiac survival. This latter point may be lost in a discussion using the summed stress score in which both inducible and fixed defects are noted. This same high-risk cohort with extensive fixed defects would also be commonly identified with rest and stress gated left ventricular function, where a large proportion of this group would have an impaired ejection fraction (to be discussed later in this review).

The median annual rate of major adverse cardiac events in the setting of high-risk perfusion abnormalities is 5.9% (25th percentile = 4.6%, 75th percentile = 8.5%).[50,53,57,61-71,72-96] The recent stable angina guidelines note high risk, in patients with chronic coronary disease, as annualized event rates in the range of 3% to 5% or higher.[97] Thus evidence of high-risk, moderately to severely abnormal myocardial perfusion findings has the associated risk to a patient with chronic coronary disease (including severely obstructive lesions and/or multivessel disease). Therefore posttest management in this high-risk cohort should be aggressive and include consideration of coronary angiography as well as optimized anti-ischemic therapy and risk factor modification. An example of this nuclear-based management strategy is currently being evaluated in the Department of Veteran's Affairs and Medical Research Council of Canada's COURAGE trial.[28]

RISK OF EVENTS BY POSTSTRESS MEASURES OF LEFT VENTRICULAR FUNCTION

Although nuclear cardiology has been capable of obtaining measures of left ventricular function by first-pass and gated techniques for a number of decades, today rest and poststress estimations of systolic function are frequently performed as gated SPECT imaging. Estimates of left ventricular dysfunction are perhaps one of our greatest known prognosticators in cardiovascular medicine. In this era of gated SPECT imaging, a number of recent reports have provided an estimate of the current predictive value of this measure (Figure 2).[98-104] This evidence is consistent with reports using angiographic and echocardiographic estimates noting an inversely proportional relationship between left ventricular ejection fraction measurements and event-free survival. That is, lower ejection fraction values are associated with higher event rates. A synthesis of this evidence using

Table 2. Prognostic value of normal (low-risk) and moderately to severely abnormal (high-risk) myocardial perfusion SPECT in estimating annual rates of cardiac death and nonfatal myocardial infarction

Year	Author	n	Agent	Average follow-up (y)	Annual event rate	High risk	Low risk
2003	Elhendy[72]	327	MIBI	7.0	3.8	6.9	—
2003	Patel[73]	174	MIBI	3.5	2.0	4.3	0.9
2003	Zellweger[74]	356	Tl-201/MIBI	4.0	4.7	17.3	4.3
2003	Berman[75]	6,173	Tl-201/MIBI	2.3	1.0	4.6	0.6
	Nondiabetic						
	Diabetic					7.4	2.2
2002	Hachamovitch[76]	10,627	Tl-201/MIBI	1.9	0.7	6.7	0.7
2003	Schinkel[77]	648	Tetro	4.0	4.3	14.9	1.0
2003	Elhendy[78]	224	MIBI	7.0	3.5	7.3	—
2003	Acampa[79]	206	MIBI	3.1	3.8	5.8	1.0
2002	Schinkel[80]	528	MIBI	8.0	1.6	3.4	1.2
2002	De Lorenzo[81]	108	MIBI	3.0	6.3	10.3	1.0
2002	Bravo[82]	150	Tl-201	4.3	20.0	14.7	3.0
2002	Schinkel[83]	721	Tetro	3.1	2.8	5.1	1.0
2002	Feola[84]	82	Tl-201	2.3	3.0	11.9	0.0
2003	Hachamovitch[85]	3,058	Tl-201/MIBI	18.0	1.4	3.9	0.4
2002	Groutars[86]	597	Tetro	2.0	3.9	5.3	0.7
2001	Calnon[87]	308	MIBI	1.8	5.8	10.0	2.3
2001	Galassi[57]	459	Tetro	3.2	2.5	10.7	0.9
2001	Cottin[88]	152	Tl-201	3.3	3.2	8.4	0.9
2001	Diaz[50]	7,163	Tl-201	6.7	1.8	3.6	1.3
2000	Shaw[53]	8,411	MIBI/Tl-201	2.5	1.2	5.0	0.5
2000	Kaminek[89]	70	Tl-201/MIBI	2.1	1.4	10.7	1.2
2000	Amanullah[90]	633	Tl-201/MIBI	1.8	6.0	5.4	0.8
1999	Vanzetto[61]	1,137	Thallium	6.0	1.5	2.0	0.6
1999	Kang[91]	1,271	Tl-201/MIBI	2.0	3.3	7.0	1.5
1998	Hachamovitch[63]	5,183	Tl-201/MIBI	1.8	3.0	5.9	0.8
1998	Olmos[64]	225	Tl-201	3.7	1.8	2.7	0.9
1998	Alkeylani[62]	1,086	MIBI	2.3	3.4	5.0	0.6
1997	Snader[66]	3,400	Thallium	2.0	1.6	3.8	1.0
1997	Boyne[65]	229	MIBI	1.6	2.2	5.1	0.8
1997	Hachamovitch[92]	1,159	Tl-201/MIBI	2.3	4.5	4.6	0.7
1996	Geleijnse[67]	392	MIBI	1.8	6.0	8.7	0.8
1996	Hachamovitch[93]	4,136	Tl-201/MIBI	1.7	1.4	6.8	0.6
1996	Hachamovitch[94]	2,200	Tl-201/MIBI	1.6	1.1	6.3	0.2
1995	Hachamovitch[95]	3,211	Tl-201/MIBI	1.6	1.9	5.2	0.6
1995	Berman[96]	1,702	Tl-201/MIBI	1.7	1.8	4.4	0.2
1995	Heller[68]	512	MIBI	12.8	4.6	6.9	1.3
1994	Machecourt[70]	1,926	Thallium	2.8	2.0	2.9	0.5
1994	Kamal[69]	177	Thallium	1.8	4.3	5.2	0.0
1994	Stratmann[71]	534	MIBI	1.1	10.1	14.3	1.6
SPECT experience: 10 years [median (25th–75th percentile)]		69,655*		2.3 (1.8-3.9)	3.0 (1.7-4.3)	5.9 (4.6-8.5)	0.85 (0.6-1.2)

MIBI, Tc-99m sestamibi; *Tetro*, Tc-99m tetrofosmin.
*Total n includes duplicate series.

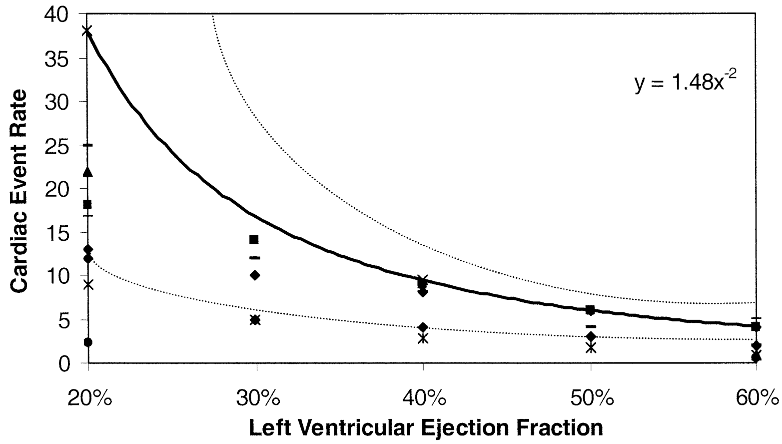

Figure 2. Cumulative evidence on prognosis associated with poststress gated SPECT measurements of left ventricular function. The line of best fit (*solid line*) is based on a power regression function (95% CI, *dotted lines*) optimizing explanatory variation.

gated SPECT imaging noted cardiac event rates ranging, on average, from 2.4% to 17.3% for measures of 60% to 20% or less.[98-104] On the basis of these six reports and a prior meta-analysis, one can estimate the expected rate of events from the ejection fraction value by using the following equation: $y = 1.48x - 2$, in which y is the cardiac event rate and x is the left ventricular ejection fraction. These data reveal a strong and log-linear relationship between ejection fraction measurements and rates of major adverse cardiac events.

Although we did not specifically discuss the data on left ventricular volumes, recent evidence suggests that end-diastolic and end-systolic volume data would further help to refine prognostication by measures of left ventricular function. In fact, in one recent report, end-systolic volume provided independent predictive value over and above left ventricular ejection fraction.[103] In particular, an end-systolic volume greater than 70 mL was associated with worsening 2-year survival.[103] Left ventricular remodeling (ie, end-diastolic volume measures) has also been an important guide to therapeutic decision making in patients with systolic dysfunction and evidence of myocardial viability. Other measures of ventricular impairment including transient ischemic dilation are also of prognostic significance.[105] In this case high risk is defined by transient ischemic dilation greater than 1.21.[105] This latter study was performed in patients with normal perfusion findings and suggests that it is important to consider other findings including ventricular size, function, and evidence of dilation after stress.

INTEGRATIVE MANAGEMENT APPROACHES

One of the benefits of the wealth of evidence on prognosis with SPECT imaging is that the data can be easily integrated into risk-based patient management algorithms. There are several examples of risk-based algorithms that have been developed in certain patient cohorts. For example, a recent taskforce of the American Society of Nuclear Cardiology has published an evidence-based guideline for at-risk women focusing on selecting candidates who receive the greatest incremental value from referral to SPECT imaging.[106] Another example of a risk-based patient management algorithm is currently being tested in the COURAGE trial.[28] This trial will enroll approximately 3,000 patients with coronary disease who are then randomized to optimal anti-ischemic and risk factor modification therapies as compared with percutaneous coronary interventions plus medical management. After enrollment, it is recommended that patients who have recurrent or worsening (but not unstable) chest pain undergo gated SPECT imaging with initial risk stratification based on left ventricular ejection fraction measures followed by the extent and severity of inducible ischemia. On the basis of the expected risk in each patient subset, high-risk subsets undergo re-angiography for the assessment of progressive coronary disease.

HIGH-RISK FINDINGS AND HIGH-RISK PATIENT SUBSETS

A review of evidence suggests that high-risk findings on SPECT imaging include patients whose expected rate of major adverse cardiac events is 3% to 5% or more and patients with moderately to severely abnormal perfusion abnormalities, multivessel perfusion abnormalities, or a summed stress score greater than 8. Patients with a high-risk poststress left ventricular ejection fraction lower than 45% are at an elevated risk of major adverse cardiac events. Other high-risk markers include

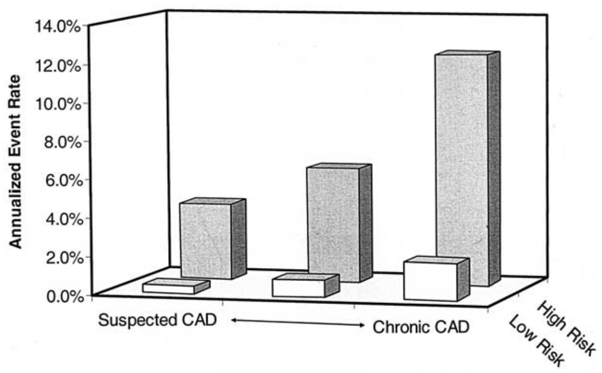

Figure 3. Expected risk of major adverse cardiac events in patients with suspected to chronic coronary disease (*CAD*) based on SPECT findings of low-risk (ie, normal perfusion) or high-risk myocardial perfusion results (eg, summed stress score >8, moderately to severely abnormal or multivessel perfusion patterns). *Chronic CAD*, Known coronary disease and risk equivalents (ie, pharmacologic stress, peripheral arterial disease, diabetic patients).

transient ischemic dilation, larger ventricular volumes, and increased lung uptake by Tl-201 imaging.[6]

A review of evidence suggests that optimal use of risk data is dependent on understanding the underlying risk in the population. Figure 3 notes the varying cardiac event rates in patients with suspected to chronic coronary disease. As expected, lower event rates are noted for patients without a prior coronary disease diagnosis. We also have extended our evaluation of the chronic coronary disease patient series to include those patient cohorts whose cardiac event risk is equivalent to a diseased population. This risk-equivalent population should also include patients with diabetes, those with evidence of peripheral arterial disease, and those referred to pharmacologic stress imaging.

OPTIMAL REFERRAL CANDIDATES BASED ON ADDED RISK EFFECTIVENESS

Although this review has focused on risk assessment in suspected or known coronary disease, there are specific subsets of patients for whom risk assessment is particularly valuable, with abundant evidence, including diabetics,[75,81,91,107,108] women,[109-110] and patients referred to pharmacologic stress imaging.[53,55,63,67-69,71-72,75,78,80,82-83,85,92] Figure 4 depicts a synthesis of evidence on the prognostic value of myocardial perfusion SPECT by sex and diabetes mellitus. These results reveal that expected event rates are higher in women and diabetic patients.[75,81,91,107-110] However, diabetic women are the highest-risk cohort, with expected event rates approximately 10% to 40% higher than those of their male counterparts (Figure 4).

Synthesizing from published reports, the expected annual risk of cardiac death or nonfatal myocardial infarction is decidedly higher in patients referred to pharmacologic stress imaging including intravenous adenosine, dipyridamole, or dobutamine imaging (Figure 5), as compared with higher-functioning patients capable of performing exercise testing. Low-risk and high-risk patients undergoing pharmacologic stress imaging have an annual cardiac event risk of 1.2% and 8.3%, respectively, as compared with 0.7% and 5.6%, respectively, for exercising patients.

FUTURE APPLICATIONS OF OUTCOMES ASSESSMENT IN NUCLEAR CARDIOLOGY

Although the paradigm of estimating risk has added tremendous value to the use of nuclear imaging in guiding patient management decisions, its concept is largely based on the principle of defining the natural history of myocardial perfusion and ventricular function abnormalities. That is, we have defined SPECT risk markers as being associated with major adverse event rates of 4.8% to 8.5% (25th to 75th percentile) per year.[50,53,57,61-96] However, in our current era of aggressive management, the hope for patients is that optimal intervention, including anti-ischemic therapy, risk factor modification, and revascularization (if necessary), would improve the expected adverse outcome of at-risk patients. By use of our existing Cox proportional hazards models, patients who undergo coronary revascularization are censored during the analytical process. Therefore the true benefit of nuclear imaging is that risk is identified and the ensuing natural history is changed by important risk-reducing therapies.

Future applications in SPECT imaging are unfolding, in which SPECT risk markers serve as surrogate or intermediate outcomes. With this reasoning, SPECT is performed serially to examine changes in perfusion and function after the initiation of a given treatment strategy. The key to using SPECT risk markers as surrogate outcomes is that a given threshold of change in perfusion or function should signify a worsening of or improvement in patient outcome. This is optimally what clinicians and patients expect from any given test referral; they hope to garner information on disease presence and severity so that changes in management can return patients to full functioning and a healthy quality of life.

Recently, an increasing number of reports have used serial SPECT imaging to define the effectiveness of therapies to diminish inducible ischemia concomitant with control of anginal symptoms.[9-31] The pathophysiologic basis for the use of SPECT is that the onset of an acute coronary syndrome is initiated by impaired vasomotion along with plaque rupture of a subcritical stenosis. SPECT imaging plays a critical role in identifying

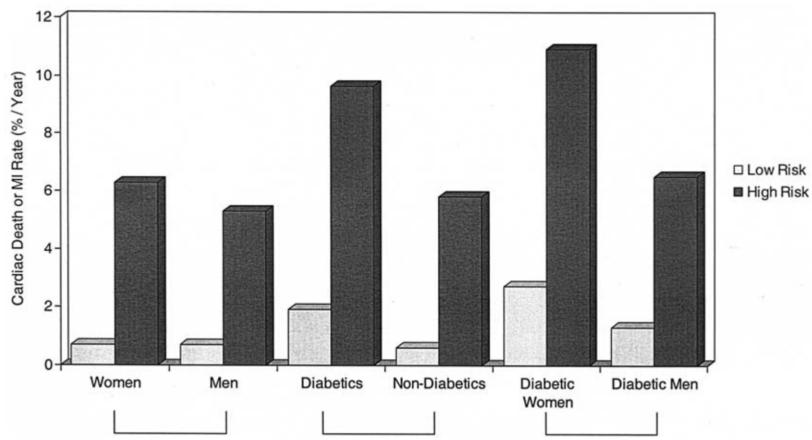

Figure 4. Annual risk of cardiac death or nonfatal myocardial infarction (*MI*) in important patient subsets referred to gated SPECT imaging including diabetic and nondiabetic women and men. This series includes prognostic data on symptomatic women and men as well as asymptomatic and symptomatic diabetic patients.

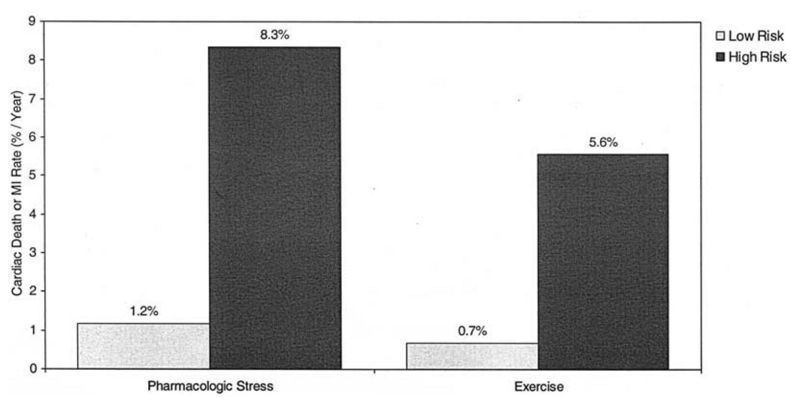

Figure 5. Annual risk of cardiac death or nonfatal myocardial infarction (*MI*) in patients referred to exercise and pharmacologic stress myocardial perfusion SPECT imaging.

risk by defining the extent and severity of reduced blood flow with an established relationship in estimating acute ischemic events. Not only will anti-ischemic therapies affect endothelial function, but statins also exhibit a beneficial effect and reduce ischemic events through a number of mechanisms (eg, improving endothelial function, reduced inflammation, and plaque stabilization).[9,31]

The use of SPECT as a surrogate outcome is based on numerous randomized trials and American College of Cardiology/American Heart Association guidelines noting that ischemia-guided therapy results in optimal patient selection and greater proportional risk reduction.[9-31,97] Although several prior reports have noted the use of SPECT imaging in assessing restenosis approximately 6 months after percutaneous coronary intervention,[111-122] more recently, optimal medical management has been applied in several controlled clinical trials.[9-31] In general, on the second scan, a threshold of change (ie, change in summed stress score ≥3 or ≥9% change in quantitative estimates) in ischemic defect size, extent, and severity reflects a clinical worsening or improvement, depending on the direction (eg, increase in summed stress score from 6 to 10 indicates worsening) of change. Preliminary results have revealed that 50% to 89% of patients will exhibit significant improvement in inducible ischemia after the initiation of aggressive anti-ischemic therapies and risk factor modification.[27,30,31] In a recent small series by Schwartz et al,[31] 6 months of statin therapy in patients with chronic coronary disease was associated with 61% of patients exhibiting improvements in inducible ischemia from baseline. Although there have been a number of small series using SPECT as a surrogate outcome, there are currently a number of ongoing clinical trials that are using serial monitoring with SPECT imaging including the following: Bypass Angioplasty Investigation 2-D (in diabetic

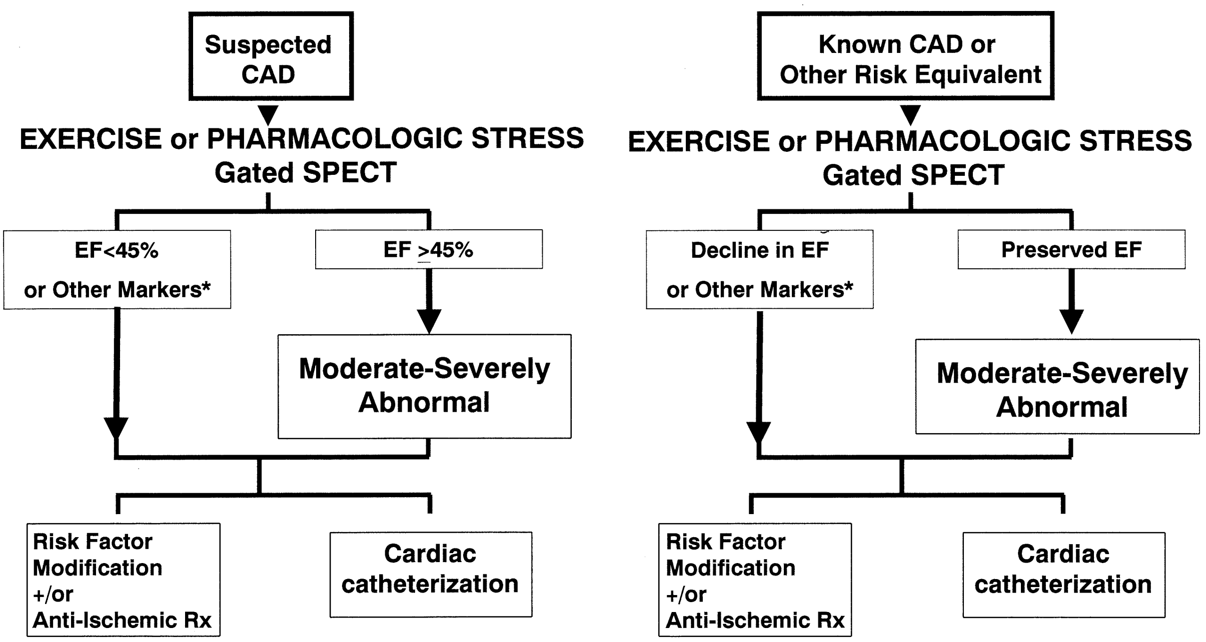

Figure 6. Risk-based patient management approach for patients with suspected or known coronary artery disease (*CAD*). An additional high-risk cohort is included and defined as patients whose cardiac event risk is equivalent to a population with existing disease. This cardiac risk-equivalent population is defined as those referred to pharmacologic stress imaging, patients with peripheral arterial disease, or diabetic patients (ie, annual risk of death or myocardial infarction ≥2.0%). *EF*, Ejection fraction.

*Other Markers include Transient Ischemic Dilation, Increased Lung Uptake, or Decreased Left Ventricular Volumes.

patients) (BARI 2-D), COURAGE, and AdenosINe Sestamibi spect Post-InfaRction Evaluation (INSPIRE).[28,30] INSPIRE is a randomized, prospective, multicenter trial designed to evaluate the role of optimal anti-ischemic and risk factor–reducing therapy with the use of adenosine Tc-99m sestamibi SPECT in low-risk, post–myocardial infarction patients.[30] The COURAGE trial is a randomized trial comparing optimal medical therapy (anti-ischemic and risk factor modification) as compared with percutaneous coronary interventions (including medical management) and enrolling more than 3,000 patients with chronic coronary disease.[28] An example of serial monitoring with SPECT has recently been published by O'Rourke et al.[11] Preliminary results from these larger trials reveal that aggressive management can ameliorate patient symptoms as well as SPECT-induced ischemia in a large proportion of patients (ie, >50% and <90%).[27,30,31]

CONCLUSION

This review provides a synopsis of available evidence on the prognostic value of gated myocardial perfusion SPECT. The magnitude of this evidence provides substantial documentation as to the maturity of this modality. As reported in 39 peer-reviewed articles, there is a clear separation in risk of major adverse cardiac events between patients with low- and high-risk perfusion imaging results over the ensuing 2 to 4 years of follow-up. From a total of 69,655 patients (including duplicates), the median annual rate of cardiac death or nonfatal myocardial infarction was 5.9% for those with high-risk SPECT results. For patients with normal perfusion results (n = 39,173), the median rate of cardiac death or nonfatal myocardial infarction was 0.6% per year. On the basis of this evidence, the intensity of posttest management may be guided by expected rates of cardiac events based on the results of SPECT imaging; intensive management (considering coronary angiography in conjunction with aggressive risk factor modification and anti-ischemic therapy) should be applied to those high-risk patients (Figure 6). Although this evidence on prognostication is substantial, future applications in the area of outcomes evaluation will focus on altering these expected adverse sequelae in high-risk patients (ie, natural history) by applying serial SPECT monitoring for observation of therapeutic effectiveness.

To date, the wealth of prognostic evidence with SPECT imaging has been developed and guided by many pioneers (and their collaborators) in the field, without whose contribution this review would not be possible. There clearly is no other noninvasive modality whose body of evidence has unfolded over the past few decades and whose depth of evidence in the area of prognostication may be used to guide management of many important patient subsets (only a few of the major indications have been highlighted herein). Thus, as we look to the future, our hope is that gated SPECT imaging research will continue to reveal evidence and guide future applications by using this well-established template of defining an imaging modality's value by the depth and accumulation of high-quality prognostic evidence.

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