

ASNC INFORMATION STATEMENT

The role of radionuclide myocardial perfusion imaging for asymptomatic individuals

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INTRODUCTION

Radionuclide myocardial perfusion imaging (RMPI) has served as a clinical mainstay in the management of patients with known or suspected coronary artery disease (CAD) for more than two decades. RMPI provides information beyond the mere detection of disease, delineating the extent, severity, and location of perfusion abnormalities. These data also have important prognostic implications and assist in providing reassurance to the clinician and patient or suggest the need for additional therapies. However, the role of RMPI among asymptomatic patients is less defined than among those with active symptoms. Furthermore, in keeping with the recent emphasis on improved resource utilization, cost-containment, and reduction of radiation exposure, the American Society of Nuclear Cardiology (ASNC) has commissioned a review of evidence for the use of RMPI specifically for asymptomatic individuals in an attempt to provide guidance for clinicians.

The notation of symptomatic status remains a challenge since this designation is largely given to patient exhibiting chest pain suggestive of myocardial ischemia. Other symptoms such as dyspnea or syncope are often assigned to those without symptoms (i.e., no chest pain). For these patients with atypical

presentations, the symptom burden places them at an elevated risk and may require additional assessment even though they may not have chest pain. Additionally, ischemic-type abnormalities on a resting electrocardiogram (ECG) connote an increased risk of cardiac events. The most recent *Appropriate Use Criteria for Cardiac Radionuclide Imaging*¹ document discriminates between asymptomatic patients and those with an ischemic equivalent, the latter including chest pain, anginal equivalents, or an abnormal ECG.

The goal of this Information Statement is to define instances when the additional evaluation of asymptomatic patients may offer useful clinical information. In contrast, the elimination of the use of RMPI in patient groups where no benefit may be garnered serves as an important means to reduce radiation exposure.²

CLINICAL RISK ASSESSMENT

Clinical risk assessment forms the basis for risk stratification and the intensity of medical management for asymptomatic patients.^{3,4} A number of global risk scores are available for use⁵⁻⁸ with an aggregation of an array of traditional and novel risk factors into a composite score estimating major adverse cardiovascular events. In the United States, the Framingham risk score (FRS) is the most commonly applied index and renders an estimation of 10-year risk of cardiovascular death or non-fatal myocardial infarction.⁹ However, the FRS was designed as a tool to estimate population risk, and was not intended for use in individual patients. As such, there will be discordance between the absolute FRS estimate with the degree of co-morbidity and prevalence of novel biomarkers, such as obesity and the metabolic syndrome. Despite this, an individual with a low FRS has an estimated 10-year risk of cardiovascular disease (CVD) death or myocardial infarction (MI) of <6%, while higher-risk estimates are projected for those with an intermediate (6% to 20% over 10 years) or high (>20% over 10 years) FRS. For asymptomatic patients, the FRS forms the basis, but is not the sole means of an integrated risk assessment. Clinicians should integrate

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other prevalent markers of risk including obesity, the metabolic syndrome, and family history of premature coronary heart disease (CHD). Another prevalent factor that is also not included in the FRS is the occurrence of significant functional disability, when a given patient is incapable of performing routine activities of daily living.

Potential Use of RMPI Based on Risk Assessment

There are two schools of thought regarding imaging risk assessment following the use of a clinical risk score, such as the FRS. Many have advocated the use of imaging in those with a high FRS to assess ischemic risk, and there have been numerous examples of the utility of this application in the assessment of diabetic patients.^{10,11} There have also been alterations to this type of testing approach by initially performing a lower-cost scan, such as the coronary artery calcium (CAC) score, followed by selective RMPI with evidence of significant CAC (i.e., ≥ 100).¹² Patients with an intermediate FRS may be candidates for initial testing with CAC imaging, and the subsequent selective use of RMPI if the CAC findings are determined to be high-risk.^{13,14} This type of tiered testing has also been advocated for patients with the metabolic syndrome and for those with a family history of premature CHD.^{15,16} Another approach is that imaging should not be performed because all of the high FRS patients should be treated to secondary prevention goals and that imaging will not alter this management course. There are no comparative trials on this subject but concern over the added contribution of ischemia to patient management in patients without cardiac symptoms remains an important consideration for high-risk patient subsets. That is, there is no evidence that follow-up angiography and revascularization improved outcomes for the asymptomatic patient with ischemia, although it did result in improved angina stability and frequency when compared to optimal medical therapy alone.¹⁷

Clinical Risk and Guidelines/Appropriate Use Criteria

The American College of Cardiology (ACC), American Heart Association (AHA), and ASNC published *Guidelines for the Clinical Use of Cardiac Radionuclide Imaging* in 2003,¹⁸ which stated that “it is not clear that detecting asymptomatic preclinical CAD with therapeutic intervention will reduce risk beyond that indicated by risk factor profiling and currently recommended strategies to reduce risk.” However these guidelines do suggest that “in some asymptomatic patients, testing may be appropriate when there is a high-risk

clinical situation.” Recently, the *2010 ACC/AHA Guideline for Assessment of Cardiovascular Risk in Asymptomatic Adults* suggests a severe restriction of the use of stress imaging, potentially limiting its application to diabetics. These latter guidelines are more focused on population trends rather than the evaluation of individual patients.¹⁹

According to the most recent *ACC/AHA/ASNC Appropriate Use Criteria for Cardiac Radionuclide Imaging*,¹ the use of RMPI imaging should be based on CHD risk in patients without an antecedent diagnosis of ischemic heart disease (Table 1). Among patients at low risk, single photon-emission computed tomography (SPECT) imaging is inappropriate, while testing would be appropriate for those at high risk. Patients with an intermediate CHD risk with an uninterpretable ECG are deemed to be uncertain, whereas an interpretable ECG would be inappropriate. Furthermore, RMPI would be appropriate when the calcium score is >400 , or when 100-400 if the patient is at high CHD risk. If a prior RMPI study was performed <2 years beforehand, repeat testing in an asymptomatic patient is inappropriate.

CHD EQUIVALENTS

Patients with medical conditions that portend a similar cardiovascular risk to those with established CHD represent an ideal asymptomatic population to discuss the role of RMPI. Conditions including diabetes mellitus, other atherosclerotic disease (e.g., peripheral arterial disease [PAD], abdominal aortic aneurysm, carotid artery disease), and a $>20\%$, 10-year risk of CHD by Framingham projections have long been identified as CHD risk equivalents and accepted as indications to justify and intensify risk modification therapies.²⁰ More recently, other conditions (e.g., erectile dysfunction [ED]) have been recognized to associate with a high CHD risk and have been proposed as additional CHD risk equivalents.^{21,22} Patients with CHD risk equivalents have both a high risk of future cardiovascular events and a high prevalence of current existing CHD. Over the last few years, there has been increasing interest in the use of RMPI in asymptomatic patients with CHD risk equivalents, and a number of new studies have addressed the utility of RMPI in these populations.

Diabetes Mellitus

The incidence of diabetes mellitus has increased at an alarming rate over the past two decades. In the year 2000, it was estimated that diabetes mellitus afflicted 17.7 million people in the U.S. and 171 million people worldwide, with projected doubling of these numbers by the year 2030.²³ It is well established that there is an association between diabetes and cardiovascular disease.²⁴ Furthermore,

Table 1. Appropriate use criteria for asymptomatic patients¹

Indication	Appropriate use score (1-9)
Detection of CAD/risk assessment	
High CHD risk (ATP III risk criteria)	A (7)
Intermediate CHD risk (ATP III risk criteria)	U (5)
ECG uninterpretable	
Intermediate CHD risk (ATP III risk criteria)	I (3)
ECG interpretable	
Low CHD risk (ATP III risk criteria)	I (1)
Risk assessment with prior coronary calcium Agatston Score	
Agatston score less than 100	I (2)
Agatston score between 100 and 400	U (5)
Low to intermediate CHD risk	
Agatston score between 100 and 400	A (7)
High CHD risk	
Agatston score greater than 400	A (7)
Risk assessment: postrevascularization (PCI or CABG)*	
Incomplete revascularization	A (7)
Additional revascularization feasible	
Greater than or equal to 5 years after CABG	A (7)
Less than 5 years after CABG	U (5)
Greater than or equal to 2 years after PCI	U (6)
Less than 2 years after PCI	I (3)
Risk assessment with normal prior stress imaging study	
Last stress imaging study done more than or equal to 2 years ago	U (6)
Intermediate to high CHD risk (ATP III risk criteria)	
Last stress imaging study done less than 2 years ago	I (1)
Low CHD risk (ATP III risk criteria)	
Last stress imaging study done less than 2 years ago	I (3)
Intermediate to high CHD risk (ATP III risk criteria)	
Last stress imaging study done more than or equal to 2 years ago	I (3)
Low CHD risk (ATP III risk criteria)	
Risk assessment with abnormal prior stress imaging study, no prior revascularization	
Poor exercise tolerance (less than or equal to 4 METs)	U (5)
Intermediate clinical risk predictors	
Known CAD on coronary angiography OR prior abnormal stress imaging study	I (3)
Last stress imaging study done less than 2 years ago	
Risk assessment: within 3 months of an ACS— asymptomatic postrevascularization (PCI or CABG)	
Evaluation prior to hospital discharge	I (1)

Inappropriate (I): scores 1-3, uncertain (U): scores 4-6, appropriate (A): scores 7-9.

CAD, coronary artery disease; CHD, coronary heart disease; ATP III, adult treatment panel III; ECG, electrocardiogram; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; METs, metabolic equivalents; ACS, acute coronary syndrome.

* In patients who have had multiple coronary revascularization procedures, consider the most recent procedure.

CAD is the leading cause of death in diabetic patients, accounting for 75% of deaths.²⁵ CAD is also more often silent in patients with diabetes,²⁶ and is silent in up to 75% of asymptomatic subjects aged 65 years or older.²⁷ Therefore, given the well-established cardiovascular risk among diabetics, the evaluation for CAD in asymptomatic diabetic patients is gaining increasing clinical importance.

Abnormal RMPI has been found in 21% to 59% of asymptomatic diabetic patients,^{28,29} with 15% to 20% of asymptomatic diabetics having high-risk findings.^{29,30} Furthermore, traditional and emerging cardiac risk factors were not associated with abnormal RMPI.^{29,30} Cardiac events among asymptomatic diabetic patients are similar to those with angina. However, it has been

suggested that this worse prognosis among asymptomatic diabetics may be mitigated by surgical revascularization as shown in a subset of patients with severe CAD detected by RMPI.^{30,31} However, the recent Detection of Ischemia in Asymptomatic Diabetics (DIAD) study results indicated that the routine screening of asymptomatic patients with diabetes is not justified because of the relatively low yield of significant abnormalities, the low overall cardiac event rate with contemporary medical therapy, and the lack of impact of screening on events.^{10,29} It is noteworthy that stress RMPI did effectively stratify patients into higher-risk (moderate to large defects and ischemic ECG) and low-risk (small defects or normal MPI) subsets, even in the DIAD study.²⁹

The DIAD trial subjects clearly were a low-risk cohort; as such, there are no data to exclude the possibility that strategies to better identify asymptomatic diabetic patients at higher risk, coupled with more effective treatment strategies, might prove to be effective for screening in the future.¹⁰ The CAC score has been shown to be the single best predictor of all-cause mortality in both diabetic and non-diabetic patients³² and an independent predictor of CHD and stroke events among type-2 diabetics.³³ The potential complementary roles of CAC scoring and RMPI for risk stratification of asymptomatic diabetic patients were found to be synergistic.³⁴ A strategy of selecting an “enriched” population of asymptomatic diabetics at risk by performing RMPI on patients with a calcium score in excess of 100 has been suggested.³⁵

Therefore, the issue of screening asymptomatic diabetic subjects for coronary disease has been controversial. In 2006,³⁶ the American Diabetes Association (ADA) suggested that stress testing should be considered in asymptomatic diabetic patients if there is evidence of PAD, while cautioning that there was insufficient evidence to guide clinicians regarding the recommendation of revascularization. The ADA currently endorses “cardiac testing” for asymptomatic diabetics in the presence of an abnormal resting ECG.³⁷

Based on the limited available data, RMPI could be recommended in asymptomatic diabetics if autonomic neuropathy or other evidence of vascular disease, such as PAD (carotid, renal, femoral, and so forth), is present. The application of a stepwise approach, with the assessment of atherosclerosis by CAC followed by RMPI when moderate coronary calcification is present, may allow for the optimal risk stratification of asymptomatic diabetic patients.

Erectile Dysfunction

Over the last decade, the relationship between erectile dysfunction (ED) and CHD has received considerable

attention. A number of large prospective investigations have demonstrated that the presence of ED is associated with an increased risk of future myocardial infarction and cardiovascular mortality.^{22,38-44} Despite the strong association with underlying CHD and the demonstrated high cardiovascular risk in men with ED, the most appropriate way to assess for existing CHD and to stratify CHD risk in men with ED has not been clearly established. A number of recent studies have addressed the use of stress testing, including RMPI, in men with ED.⁴⁵ Among men referred for RMPI testing, ED has been shown to be a strong predictor of severe CHD and high-risk RMPI findings, even after adjusting for traditional risk factors.^{45,46} Based on this available evidence, a recent expert panel has concluded that stress testing, including RMPI, should be considered in men with ED who are deemed to be at higher risk based on the presence of additional cardiovascular risk factors.²² While large outcome studies will be required to fully determine the role for RMPI in men with ED and without cardiac symptoms, evolving evidence suggests this high-risk population may benefit from risk stratification with RMPI.

Atherosclerotic Vascular Disease

Extra-cardiac atherosclerotic vascular disease, including PAD, atherosclerotic abdominal aortic aneurysms (AAA), and carotid and carotid artery disease have been established and accepted as CHD risk equivalents.²⁰ PAD, for example, is associated with a 20% to 60% increased risk of MI and a 2- to 6-fold increased risk of CHD mortality.^{47,48} Despite the high CHD risk and high co-prevalence of significant CHD, the appropriate testing strategy to stratify risk and identify existing CHD in patients with extra-cardiac disease has not been established. The prevalence of CHD, as determined by RMPI, in patients with PAD and AAA has been recently assessed. Myocardial ischemia on SPECT MPI was found in 55% of patients with PAD, in 37% of patients with AAA, and in 73% of patients with both AAA and PAD; notably only 17% reported a history of angina.⁴⁹ While it is unknown whether screening RMPI in patients with extra-cardiac disease will lead to changes in treatment or improved outcomes, this high-risk population with established atherosclerotic vascular disease represents an ideal population to pursue further study to fully determine the role of RMPI.

Functional Impairment

Patients incapable of performing five metabolic equivalents (METs) of work, or those with decided restrictions in activities of daily living, form a high-risk subset that may benefit from the evaluation of cardiac

risk with imaging. Another important consideration is that patients frequently accommodate their angina burden by reducing physical activity. To that end, a reduction of exercise tolerance is felt to be an ischemic equivalent, thus potentially eliminating the patient from the asymptomatic category.¹ There are simple questionnaires, such as the Duke Activity Status Index, that may be used to estimate physical functioning in activities of daily living and provide an estimate of METs.⁵⁰ It has long been recognized that patients referred for pharmacologic RMPI testing have a higher risk of future cardiac events and more abnormal RMPI studies compared higher-functioning patients capable of exercise RMPI testing.⁵¹ While there is no clear evidence that screening RMPI in patients with reduced functional capacity leads to improved outcomes, this high-risk population deserves further study to determine the role of risk stratification with RMPI.

UNIQUE PATIENT POPULATIONS

Several unique medical conditions are associated with an elevated risk for cardiovascular events and cardiac death. The detection of asymptomatic CAD in patients with these medical conditions may improve patient outcomes by identifying patients who may benefit from aggressive medical therapy and/or coronary revascularization. This section examines the currently available evidence for the clinical application of RMPI in asymptomatic individuals with these medical conditions.

Chronic Kidney Disease

Chronic kidney disease (CKD) markedly increases the risk of cardiac events,⁵² and cardiovascular disease is the leading cause of death in patients with CKD.⁵³ In addition to a high prevalence of conventional CAD risk factors (e.g., diabetes, hypertension, dyslipidemia), the pathogenesis of CVD in patients with CKD involves multiple factors which impact on coronary atherosclerosis and plaque rupture.⁵⁴ The prognostic value of RMPI has been extensively studied in cohorts of CKD patients, including asymptomatic subjects. Inducible ischemia on RMPI has independent prognostic value for the prediction of cardiac events and all-cause mortality, even after adjusting for confounding variables such as the glomerular filtration rate, and has been shown to be useful with several pharmacologic stress agents.⁵⁵ There is also extensive literature regarding the value of RMPI in entirely asymptomatic CKD cohorts,⁵⁶⁻⁶¹ who have a moderately high prevalence of obstructive CAD and an incidence of ischemic perfusion defects between 10% and 22%.⁵⁹ More importantly, perfusion abnormalities by RMPI have been consistently found to predict

adverse cardiac events in these asymptomatic CKD patients.⁵⁶⁻⁶⁰ In summary, asymptomatic subjects with CKD have an intermediate likelihood of having occult CAD, and RMPI has been shown to have excellent diagnostic accuracy and independent prognostic value in these patients. However, the comparative effectiveness and cost-effectiveness of RMPI in asymptomatic subjects with CKD is unknown.

Human Immunodeficiency Virus

Patients infected with human immunodeficiency virus (HIV) have accelerated coronary atherosclerosis, and acute myocardial infarction is the initial presentation in 77% of patients.⁶² Little information is presently available regarding the value of RMPI in patients with HIV. A single study examined the use of RMPI in asymptomatic HIV-infected subjects and did not demonstrate an increase in the prevalence of abnormal myocardial perfusion.⁶³ Thus, no data is presently available to support the use of RMPI for detection of occult CAD in asymptomatic HIV-infected patients, although certain anti-HIV medications may increase the risk of cardiac events.

Autoimmune Diseases

There is a significant increase in the incidence of CAD in patients with certain autoimmune-inflammatory diseases,⁶⁴ such as rheumatoid arthritis^{65,66} and systemic lupus erythematosus.⁶⁷ Although RMPI has been found to be a useful method to identify subclinical CAD in patients with systemic lupus erythematosus,^{68,69} scant literature defining a role for RMPI in patients with autoimmune-inflammatory diseases is available.

Anti-Arrhythmic (Type IC) Therapy Initiation

Given the pro-arrhythmic risk of type-I anti-arrhythmic medications (i.e., flecainide), testing to exclude ischemic heart disease is commonplace. Despite a lack of literature support, this practice may be reasonable prior to initiation of type IC agents in patients at risk for ischemic heart disease.^{70,71}

PRIOR TEST RESULTS

Among asymptomatic patients with prior abnormal imaging results, RMPI may be used for both the diagnosis of ischemia and/or scar as well as to improve risk assessment (i.e., prognosis). However, serial (repeated test) and sequential or layered (additional test) testing may add substantial expense and risk, including radiation exposure.

Thus, performing RMPI should provide incremental value to clinical information that is already available.

Asymptomatic patients without prior, known CAD may undergo screening for the presence of pre-clinical atherosclerosis with either a CAC computed tomography (CT) scan or an assessment of carotid intima-media thickness (CIMT) using ultrasound.

Pre-Clinical Atherosclerosis: Calcium Scoring

There is considerable data showing that the presence of CAC is a strong predictor of incident CHD which provides predictive information beyond traditional risk factors^{13,72} and offers an opportunity to substantially improve risk classification.⁷³ Notably, among intermediate-risk participants in the Multi-Ethnic Study of Atherosclerosis (MESA) study, the use of CAC resulted in a net reclassification improvement of 55%.⁷³ The use of CAC and RMPI are often complementary for predicting both short- and long-term events.^{74,75} Among patients with normal RMPI, the presence of CAC can be used to identify the presence of pre-clinical atherosclerosis. Specifically, among patients with an intermediate risk, a CAC score of ≥ 400 would result in reclassifying them as high risk ($>2\%$ event rate per year),¹³ thereby potentially allowing for more aggressive therapies for patients with normal MPI that have extensive coronary calcifications (i.e., a CAC score of >400).^{74,76-79} Conversely, in selected patients with extensive CAC, the use of RMPI may be used to identify the presence of ischemia.⁸⁰ Appropriate use criteria propose two indications which are considered to be appropriate following abnormal CAC: (a) patients with a high CHD risk who have an Agatston CAC score between 100 and 400, and (b) any patient with an Agatston score >400 .^{1,19}

Pre-Clinical Atherosclerosis: Carotid Intimal Medial Thickness

Increased carotid intimal medial thickness (CIMT) thickness, or the presence of carotid plaque, is a marker of atherosclerosis which can be used to identify asymptomatic individuals with an elevated risk of cardiovascular disease. Adding CIMT to traditional risk factors improves CHD risk prediction with a net-reclassification index of approximately 10% (17% applied to intermediate-risk patients).⁸¹ The *2009 Appropriate Use Criteria for Cardiac Radionuclide Imaging* document does not specifically address the use of RMPI following CIMT, although it appears reasonable to consider the use of RMPI in selected groups of intermediate-risk patients who would be reclassified as high-risk based on CIMT

(e.g., CIMT $> 75\%$, particularly if plaque is also present).¹

Left Ventricular Dysfunction Assessment

Multiple imaging modalities can be used for the evaluation of left ventricular (LV) systolic function. In asymptomatic patients who are found to have LV dysfunction (e.g., ejection fraction [EF] $< 50\%$), establishing the etiology of LV dysfunction has important therapeutic and prognostic implications. When obstructive CAD is suspected as the cause of LV dysfunction, invasive angiography or non-invasive assessment of ischemia is useful in differentiating ischemic from non-ischemic cardiomyopathy. Unfortunately, neither guidelines nor appropriate use criteria specifically address the use of RMPI among asymptomatic patients with LV dysfunction. However, the *2009 Focused Update Incorporated into the ACC/AHA 2005 Guidelines for the Diagnosis and Management of Heart Failure in Adults* states that the use of noninvasive imaging to detect myocardial ischemia and viability is reasonable in patients presenting with heart failure who have known CAD but no angina (Class IIa).⁸²

Prior RMPI

The performance of serial RMPI remains a controversial area with minimal supportive data. Yet it is not an infrequent practice to perform repeat imaging even when a formerly symptomatic patient becomes asymptomatic. Additionally, a patient at risk for CAD and cardiac events who has previously had a normal SPECT study still may have disease progression. While it is well accepted that a normal SPECT study is associated with a low annual event rate, the “warranty period” for a normal examination is controversial. As the cardiac event rate for 2 years after a normal SPECT study in an asymptomatic individual is low (i.e., 1.1%),⁸³ the current recommendation to avoid repeat testing within 2 years, irrespective of CHD risk, is rational.¹ Regarding patients with a previously abnormal SPECT study, in the absence of symptoms, repeat testing within 2 years is not justified.¹

PRE-OPERATIVE EVALUATION

The systematic use of MPI in the preoperative evaluation of noncardiac surgery patients began more than two decades ago^{84,85} and has been recently updated by several national guidelines^{86,87} and appropriate use criteria.¹ The incidence of serious cardiac events in this large population has driven the effort to appropriately risk stratify this group in an efficient and cost-effective manner.⁸⁸ Patients may be asymptomatic for CAD but

the standard clinical preoperative evaluation involves the Revised Cardiac Risk Index (RCRI), which includes five factors: history of ischemic heart disease, history of compensated or prior heart failure, history of cerebrovascular disease, diabetes mellitus, and renal insufficiency (preoperative serum creatinine > 2.0 mg/dL).⁸⁹ Therefore, the peri-operative evaluation of asymptomatic patients has two different perspectives.

The type of surgery being contemplated and the functional level of the patient would determine whether or not MPI should be performed prior to going forward with the surgical procedure. Asymptomatic patients with very low functional capacity (i.e., <4 METs) have an increased risk for cardiac events because the lack of symptoms in such patients does not take into consideration the stress and strain of the surgical procedure.^{86,87} However, asymptomatic patients who are essentially bed-ridden can safely undergo low surgical risk procedures because the level of stress induced by such a procedure does not put them at increased risk above their current functional capacity. Such low-risk (i.e., <1%) procedures include: endoscopic and superficial procedures, cataract surgery, breast surgery, and ambulatory surgery. Asymptomatic patients with low functional capacity and a RCRI score of ≥ 2 who undergo intermediate risk surgery (i.e., 1% to 5%; examples include intraperitoneal and intrathoracic procedures, carotid endarterectomy, head and neck surgery, orthopedic surgery, and prostate surgery) or vascular surgery (i.e., >5%; examples include aortic and other major vascular surgery, as well as peripheral vascular surgery) could benefit from MPI preoperative assessment.^{86,87,90}

There have also been MPI studies in patients undergoing renal⁹¹⁻⁹³ and liver^{94,95} transplant surgery but firm recommendations have not been made in the clinical practice guidelines. Renal transplant and end-stage renal disease patients clearly have relatively high cardiac event rates and MPI testing has demonstrated prognostic utility.^{96,97} However, the overall diagnostic and prognostic accuracy of MPI in this subgroup is not optimal and it is still recommended that a combination of noninvasive screening with selected coronary angiography be utilized to help guide appropriate therapy.^{98,99} The relatively low cardiac event rate in liver transplant recipients and the lack of clear prognostic utility of MPI in this group have led to the conclusion that routine MPI screening in these patients is not indicated.¹⁰⁰

The 2009 *Appropriate Use Criteria for Cardiac Radionuclide Imaging*¹ recommends noninvasive testing in patients having intermediate-risk surgery, a RCRI score of ≥ 1 and poor or unknown functional capacity. In addition, vascular surgery patients with a RCRI score of ≥ 1 or poor or unknown functional capacity (i.e., <4

METs) are also appropriate for peri-operative MPI testing. Thus, current recommendations are that RMPI be reserved for selected patients as part of the preoperative evaluation. However, whether RMPI is used to help guide and maintain this improved outcome will be an ongoing challenge for future research, especially in the area of organ transplantation and bariatric surgery.

ASYMPTOMATIC PATIENTS WITH CHRONIC CAD

RMPI has been shown to effectively risk stratify patients with chronic CAD and prior revascularization. Studies of the utility of MPI in this patient population have largely included patients with symptoms suggestive of CAD progression, and some asymptomatic patients.

Prior Diagnosis of CAD

In patients with defined but asymptomatic CAD, ongoing testing is carried out to assess risk/prognosis. RMPI effectively identifies high-risk patients based on ischemic burden and has been effectively studied in the chronic CAD population and thus can be used to clinically for risk stratification,⁵¹ although the majority of studies were not performed in an entirely asymptomatic cohort (however, only 25% of patients had symptoms).

The Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) study demonstrated that percutaneous intervention (PCI) in addition to optimal medical therapy did not reduce the risk of major cardiovascular events.¹⁷ The COURAGE nuclear substudy, in which 40% of subjects were asymptomatic, revealed an increase of 5-year event-free survival if at least a 5% reduction of ischemic burden was obtained on serial imaging.¹⁰¹ The key benefit was ischemia reduction rather than just the performance of PCI. Similarly, the Meridian study of diabetics with stable CAD¹⁰² revealed an annual event rate that was proportional to the RMPI defined ischemia severity, with 59% of subjects being asymptomatic.¹⁰³ Most recently, *ESC/EACTS Guidelines on Myocardial Revascularization* stipulate that a large area (>10% of the LV) of ischemia is an indication for revascularization, irrespective of symptoms.¹⁰⁴ Thus, the extent of ischemic burden now defines the management of chronic CAD, with RMPI playing a critical role in this process.

After Acute Coronary Syndrome

Following the presentation of patients with an acute coronary syndrome (ACS), the diagnosis of CAD is not in question, although their risk for subsequent cardiac

events is often far from obvious. The presence of ischemia as demonstrated by RMPI in patients evaluated after treatment for unstable angina is associated with increased cardiovascular risk.¹⁰⁵ In a small trial of patients following uncomplicated, acute MI, suppression of ischemia as measure by serial RMPI studies was associated with superior event-free survival.¹⁰⁶

Contemporary studies have focused on the need/benefit of interventional percutaneous therapy after initial treatment for ACS. The Veterans Affairs Non-Q-Wave Infarction Strategies in Hospital (VANQWISH) study¹⁰⁷ revealed that revascularization after non-Q-wave myocardial infarction (NQWMI)¹⁰⁶ was associated with lower events when driven by symptoms or ischemia rather than a routine interventional approach; 47% of the non-routine PCI group has ischemia on RMPI. However, the findings of VANQWISH are not specific for therapy guided solely by MPI results. Evidence supports the use of RMPI to identify a low-risk population best managed with optimal medical therapy after acute myocardial infarction, as was shown in the Adenosine Sestamibi SPECT Post-Infarction Evaluation (INSPIRE) study.¹⁰⁸ This trial demonstrated that early post-infarction RMPI adenosine Tc-99m sestamibi testing could identify a large low-risk population that could be managed conservatively and considered for early hospital discharge.¹⁰⁹

Following Percutaneous Coronary Intervention

Residual ischemia after PCI may reflect restenosis, unrevascularized myocardial segments in the setting of multivessel disease, as well as progression of underlying CAD. Several studies of routine SPECT MPI in patients without symptoms after PCI have shown that SPECT provides additional risk stratification in this patient population.¹¹⁰ All these studies were performed within 6 months of PCI and were found to be predictive of cardiac events up to 8 years after revascularization. As the majority of studies including asymptomatic patients after PCI were performed prior to the more routine use of drug-eluting stents, the contemporary event rates would likely be much lower.

Accordingly, based on the review of expert consensus documents, published guidelines, and appropriate-use criteria, patients with PCI who remain asymptomatic after successful PCI should not be referred for RMPI unless high risk-features are present, such as decreased LV function, multivessel disease or proximal left anterior descending disease, a history of sudden cardiac death, diabetes mellitus, employment in a hazardous occupations, or incomplete revascularization or suboptimal PCI results.^{1,18,111} The *2009 Appropriate Use*

Criteria for Cardiac Radionuclide Imaging rated RMPI as inappropriate when performed within 2 years of PCI for asymptomatic patients, but uncertain afterwards.

After Surgical Revascularization

While studies of patients with recurrent symptoms after surgical revascularization (CABG) have shown that SPECT MPI is useful in detecting ischemia due to unrevascularized myocardial segments or early graft failure,¹¹² the utility of stress SPECT MPI in patients who remain asymptomatic after CABG is less clear. A strategy of routine testing 1 year after bypass found that the overall event rate was low, and that routine perfusion imaging this early after bypass did not add any important prognostic information.¹¹³ Several studies have demonstrated the independent and incremental predictive value of RMPI for subsequent cardiac events in asymptomatic patients more than 5 years after CABG.^{114,115}

Based on these and other studies, the *2009 Appropriate Use Criteria for Cardiac Radionuclide Imaging* support the utilization of RMPI in patients who are asymptomatic after revascularization if more than 5 years after CABG. However, it is uncertain use if more than 2 years after PCI or within 5 years of CABG.¹ Routine SPECT MPI in symptom-free patients after surgical revascularization may also be appropriate in those who may have undergone incomplete revascularization and in whom additional revascularization (PCI or CABG) may be feasible.

RADIATION EXPOSURE

The current consensus, not supported by concrete data, is that even small amounts of radiation exposure increase lifetime risk of cancer.¹¹⁶ The increased risk is estimated to be approximately 0.05% for every 10 mSv of exposure. As such, both patient selection and the imaging protocol (i.e., equipment, radionuclides, doses) need to be carefully considered to keep exposure as low as reasonably achievable (ALARA).¹¹⁷ These considerations may be especially important for asymptomatic individuals, in whom the prevalence of prognostically significant disease and the benefits of testing may be less.

As discussed above, published appropriate use criteria¹ cite several categories of asymptomatic patients where RMPI is inappropriate. In these circumstances, RMPI should be avoided. RMPI is appropriate, even in asymptomatic individuals, when the benefits of accurate diagnosis and therapeutic management outweigh the risks of radiation exposure.^{117,118} In general, this pertains to individuals with intermediate CAD risk in whom testing using alternative modalities that do not expose

Table 2. Summary of recommendations Related to RMPI in asymptomatic individuals

	Recommendation for RMPI?	Literature and Guidelines/AUC support
CHD risk: low, intermediate	No	Strong
CHD risk: high	Yes	Moderate
Strong family history of CAD	Yes	Absent
Erectile dysfunction	Maybe (selected)	Weak
Peripheral vascular disease	Maybe	Absent
Reduced functional capacity	No	Absent
Diabetes: low risk	No	Strong
Diabetes: high risk	Yes	Moderate
Chronic kidney disease	Yes	Moderate
HIV	No	Absent
Autoimmune disease	No	Absent
Anti-arrhythmic therapy	Maybe (selected)	Absent
CIMT	Maybe	Weak
LV Dysfunction	No	Absent
CAC < 400	Maybe (if > 100)	Moderate
CAC > 400	Yes	Moderate
Perioperative assessment	Maybe (selected)	Moderate
After ACS	Yes	Moderate
s/p PCI < 2 years	No	Strong
s/P CABG < 5 years	No	Strong

CHD, coronary heart disease; CAD, coronary artery disease; HIV, human immunodeficiency virus; CIMT, carotid intima-media thickness ultrasound test; LV, left ventricular; CAC, coronary artery calcium score; ACS, acute coronary syndrome; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft.

the individual to radiation are not practicable or are less accurate.

Several recent professional society criteria,¹ comments,⁷¹ and informational statements¹¹⁷ provide guidance concerning optimal protocols once an individual is determined to be an appropriate candidate for an RMPI study. In general, the best option is one that provides the needed information for diagnostic and management purposes, at the lowest possible radiation dosimetry, which again is especially important for the asymptomatic patient. Because the effects of radiation exposure are cumulative, with stochastic effects on genetic changes and cancer that may take decades to develop, there should be greater attention to either alternative diagnostic tests or to using the preferred methods described above for younger individuals¹¹⁹ and for those whose disease processes have or are likely to in the future lead to repetitive imaging studies that require X-rays or radionuclides (Table 2).

CONCLUSIONS

There is robust medical evidence supporting the use of RMPI for the diagnostic evaluation and risk

assessment of symptomatic patients with known or suspected ischemic heart disease. Yet, in general, similar literature is not available for asymptomatic individuals. However, the underlying physiologic assessment of coronary blood flow and its potential to impact on patient management should be similar.

Clinical risk assessment is key with regards to applying RMPI for the evaluation of asymptomatic individuals, although the exact method of risk determination remains unclear. In many settings, a tiered approach to clinical evaluation is warranted, with risk determination and possibly other testing such as calcium scoring preceding the performance of RMPI. High-risk patients (i.e., >20% CHD risk for MI or death within 10 years) constitute a cohort where RMPI would be appropriate.

Beyond the determination of overall clinical risk, certain subgroups of asymptomatic patients warrant special attention and consideration for RMPI, such as those with a family history of premature CHD. CAD risk equivalents, such as peripheral vascular disease, ED and impaired functional capacity may benefit from RMPI testing, but there little to no supportive data to sustain a recommendation. The data to date for the use of RMPI

in diabetics appears to discourage its use in asymptomatic patients, but it appears to be reasonable to consider RMPI for high-risk diabetics, including older individuals and those with an abnormal ECG or an elevated calcium score.

There are data, albeit inconclusive, to suggest the use of RMPI in asymptomatic CKD patients, although information about comparative or cost-effectiveness is lacking. Currently, the use of RMPI for HIV patients or those with autoimmune diseases cannot be recommended. Regarding the cohort of patients undergoing pre-operative evaluation, RMPI should be ordered primarily based on the risk of the surgical procedure (i.e., intermediate to high) and the presence of at least one risk factor.

Often, prior testing may lead to the performance of RMPI. However, there is no indication at the current time for RMPI based solely on the presence of an abnormal carotid intima-media thickness or a patient with LV dysfunction. However, an elevated calcium score may provide an appropriate reason to consider RMPI, especially in high CHD risk patients. Finally, RMPI should not be routinely repeated within 2 years of a prior study in the absence of symptoms.

For patients with known disease, there are inferential data supporting the use of RMPI, but no strong recommendation may be offered. After an acute coronary syndrome, testing has been shown to allow for optimization of therapy and may play an important role in management. However, there is no value in performing RMPI in asymptomatic patients within 2 years of PCI or within 5 years of CABG.

Future research is indicated to further delineate the optimal use of RMPI in asymptomatic individuals, especially those with a strong family history of CAD and those with other tests suggesting a high-risk cohort, such as diabetic patients with an elevated calcium score. These trials must also closely examine the potential impact of therapeutic intervention on patient outcomes, as well as cost-effectiveness.

Disclosures

Robert C. Hendel, MD serves on the advisory board for Astellas Pharma US and UnitedHealth Group, serves on the speakers' bureau for Astellas Pharma US, is a consultant for PGx Health, and receives research support from GE Healthcare and PGx Health. Brian G. Abbott, MD serves on the advisory Board for Astellas Pharma US. Dennis A. Calnon, MD is a consultant for PGx Health. Jamishid Maddahi, MD receives research support from Lantheus Medical Imaging, serves on the speakers' bureau for Astellas Pharma US, serves on the advisory board for Digirad, Lantheus Medical Imaging, and Astellas Pharma US, and receives honoraria from Digirad

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