



Clinical value, cost-effectiveness, and safety of myocardial perfusion scintigraphy: a position statement

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Mortality rates due to coronary artery disease (CAD) have declined in recent years as result of improved prevention, diagnosis, and management. Nonetheless, CAD remains the leading cause of death worldwide with most casualties expected to occur in developing nations. Myocardial perfusion scintigraphy (MPS) provides a highly cost-effective tool for the early detection of obstructive CAD in symptomatic individuals and contributes substantially to stratification of patients according to their risk of cardiac death or nonfatal myocardial infarction. MPS also provides valuable information that assists clinical decision-making with regard to medical treatment and intervention. A large body of evidence supports the current applications of MPS, which has become integral to several guidelines for clinical practice.

Keywords

Coronary artery disease • Cost-effectiveness • Myocardial perfusion scintigraphy • Radionuclide • Scintigraphy

Introduction

Referral of patients for myocardial perfusion scintigraphy (MPS) has increased in all European countries over the last 20 years, but with variations both between and within countries. Substantial evidence supports the accuracy and cost-effectiveness of MPS for the diagnosis of coronary artery disease (CAD). This position statement aims to summarize the current state-of-the-art of MPS and its clinical value alongside other diagnostic modalities for the evaluation of patients with suspected or known CAD. Instead of creating another set of guidelines, the leading European Nuclear Cardiology bodies [European Council of Nuclear Cardiology (ECNC), ESC Working Group 5 (Nuclear Cardiology and Cardiac CT), and European Association of Nuclear Medicine Cardiovascular Committee] have decided to provide a review with special emphasis on existing current clinical and procedural

guidelines and recommendations (Table 1), to assist in the appropriate clinical use of MPS.^{1,2}

Diagnostic value of myocardial perfusion scintigraphy in stable coronary artery disease

There is consensus across national and international guidelines in favour of MPS as a non-invasive diagnostic tool for the detection of obstructive CAD in patients with intermediate pre-test probability of disease.^{3–5} A recent meta-analysis of large studies, including thallium-201 and the technetium-99m-labelled tracers sestamibi and tetrofosmin and either exercise or pharmacological stress tests, reported an average sensitivity of 87% and a specificity of 73% for the detection of angiographically significant CAD.⁶

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Table 1 Recommendations for myocardial perfusion scintigraphy in patients with suspected or known coronary artery disease according to current clinical guidelines

Clinical scenario	Recommendation	Issuing body	Class	Level of evidence	Reference
Chronic chest pain	Diagnosis of CAD in patients with intermediate pre-test likelihood of CAD: Unable to exercise Abnormal resting ECG	ESC ACC/AHA	I	B	3,4
Chronic chest pain	Diagnosis of CAD in patients with intermediate pre-test likelihood of CAD: - Unable to exercise - Abnormal resting ECG	ESC ACC/AHA	I	B	3,4
	Identification of target coronary lesions	ESC ACC/AHA	I	B	
	Assessment of haemodynamic significance of coronary stenosis	ESC ACC/AHA	I	B	3,12,13
	Evaluation post-PCI or CABG	ESC ACC/AHA	I	B	
Acute chest pain	Detection of resting ischaemia	ESC ACC/AHA	IIb IIa	B	19–21 24,25
	Detection of ischaemia in low to intermediate risk patients after UA/NSTEMI	ESC ACC/AHA	I	B	
	Detection of ischaemia in patients with uncertain diagnosis	ESC ACC/AHA	I	A	
	Assessment of infarct size and myocardium at risk after STEMI	ESC ACC/AHA	I	B	
Pre-operative risk assessment	Risk stratification before elective non-cardiac surgery	ACC/AHA	I	C	26
Heart failure	Detection of ischaemia and viability assessment	ACC/AHA ESC study group report	IIa	B	27–29
	Diagnosis of CAD	ACC/AHA	IIb	C	27,28

ACC, American College of Cardiology; AHA, American Heart Association; CABG, coronary artery bypass grafting; CAD, coronary artery disease; ESC, European Society of Cardiology; NSTEMI, non-ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction; UA, unstable angina.

These values are consistent and independent of sub-populations selected (i.e. women, obese, and diabetic patients). However, in the last 10 years, a decline in the apparent specificity of MPS has been observed because of a post-test referral bias. The normalcy rate (the percentage of patients with below 5% likelihood of disease with a normal MPS) corrects for referral bias, and it is estimated at 91% (weighted mean).⁶

ECG-gated acquisition of MPS is now routine practice. In addition to information on left ventricular (LV) function, ECG-gating assists with the discrimination of true perfusion abnormality from artefact, particularly in case of inferior wall defects in men or anterior wall attenuation in women, with a significant reduction in the false positive rate.^{7,8} Moreover, the availability of ECG-gated images reduces the number of borderline 'normal' or 'abnormal' interpretations, thus increasing the accuracy up to 90%.⁹ Attenuation and scatter compensation also assists the detection of artefacts, further increasing the accuracy of MPS.¹⁰

Although MPS is effective in stratifying patients with intermediate likelihood of CAD according to their risk of cardiac events, its role as a primary diagnostic tool remains undefined, in particular with regard to women. The European Society of Cardiology (ESC) recognizes the superior diagnostic accuracy of MPS in women, and recommend its use as an alternative to exercise ECG provided that adequate resources and expertise are available.³ In contrast, the American College of Cardiology (ACC) and the American Heart

Association (AHA) support the exercise ECG as the initial test but recommends stress imaging in subgroups including women with diabetes and those in whom a poor exercise performance is anticipated.^{4,11} As a secondary test, MPS is indicated in patients with non-diagnostic or unexpected exercise ECG results, i.e. patients with a low or high pre-test likelihood of CAD and an abnormal or normal exercise ECG, respectively.⁴ Because MPS adds prognostic information to exercise ECG results, both European and American guidelines recommend its use in patients with an intermediate risk Duke treadmill score.^{3,4}

In patients with known CAD and prior coronary revascularization, all guidelines give MPS a class I indication as the initial test in patients presenting with continuing or recurrent chest pain.^{3–5} The usefulness of MPS in this population relies on its ability to define the site and severity of ischaemia, an important consideration for further management that cannot be assessed accurately by the exercise ECG. MPS also provides information on the probability of subsequent cardiac events and hence the need for intervention. The site and extent of inducible perfusion abnormalities on MPS reflects the anatomical distribution of a haemodynamically significant coronary stenosis. Therefore, the ESC and the ACC/AHA favour the use of MPS before coronary revascularization to estimate the severity of disease and identify the target lesion(s).^{3,4} This application is particularly relevant to the management of patients with angiographically moderate coronary stenoses

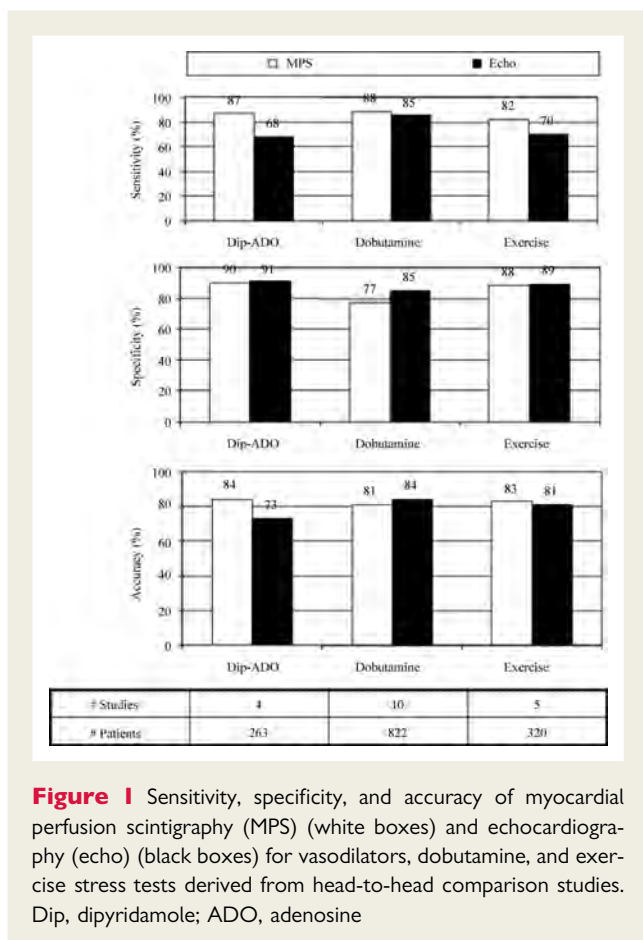


Figure 1 Sensitivity, specificity, and accuracy of myocardial perfusion scintigraphy (MPS) (white boxes) and echocardiography (echo) (black boxes) for vasodilators, dobutamine, and exercise stress tests derived from head-to-head comparison studies. Dip, dipyridamole; ADO, adenosine

and in those with lesions of uncertain functional significance. In addition, the ACC/AHA recognizes the effectiveness of selective MPS for risk stratification after percutaneous coronary intervention or coronary artery bypass grafting, particularly in patients with incomplete revascularization, proximal left anterior descending disease, diabetes, or other high-risk factors.^{12,13}

The accuracy of MPS has been compared with that of stress echocardiography, generally showing MPS to have higher sensitivity and equivalent specificity (Figure 1).

Prognostic value of myocardial perfusion scintigraphy in stable coronary artery disease

The value of MPS in assessing prognosis in patients with stable CAD has been established in large cohorts of patients with a variety of underlying risk profiles and pathologies. The following conclusions can be made.

- (i) Normal MPS in patients with intermediate to high likelihood of CAD predicts a very low event rate ($\leq 1\%$ /year), leading to a negative predictive value $\geq 99\%$.^{14,15}
- (ii) Abnormal MPS in patients with intermediate to high likelihood of CAD increases the annualized event rate by a factor of 7, and the risk of events is related to the severity of perfusion abnormalities (from 3% annual death or

myocardial infarction with mild to moderate perfusion defects up to 7% in patients with severe perfusion abnormalities).^{14–16}

- (iii) In patients with a number of risk factors (diabetes, dyslipidaemia, hypertension) low event rates extend for at least 2 years and reassessment may be warranted thereafter.¹⁷
- (iv) Functional data from ECG-gated MPS are additional prognostic indicators with LV ejection fraction after stress $\leq 45\%$ or end-systolic volume ≥ 70 mL indicating an adverse outcome even in the presence of mild inducible perfusion abnormalities.¹⁸
- (v) ECG-gated MPS provides additional prognostic information even when the clinical history, exercise ECG and coronary angiography are available. This has been shown in the general population, following an acute coronary syndrome and after revascularization.¹⁸
- (vi) Markers of LV dysfunction are more efficient in the prediction of death, whereas markers of ischaemia are better predictors of ischaemic events such as recurrent chest pain and non-fatal infarction.¹⁵

Myocardial perfusion scintigraphy after acute coronary syndromes

Because of its ability to identify low-risk individuals among those presenting with acute chest pain and non-diagnostic ECG, acute resting MPS has received a class II indication for excluding acute infarction and ischaemia in this setting.^{19–21} Current guidelines also recommend MPS after an episode of unstable angina or non-ST-segment elevation myocardial infarction (NSTEMI) for risk stratification, especially in patients with a low to intermediate likelihood of cardiac events according to traditional markers of risk. As in the stable setting, MPS should be performed selectively in patients unable to exercise adequately, in those with an inconclusive exercise ECG and in women.²¹

Before routine reperfusion therapy, MPS was more accurate than the exercise ECG for the prediction of cardiac events following an acute ST-segment elevation myocardial infarction (STEMI). Now that reperfusion is common practice, the reduced cardiac death and re-infarction rate might reduce the predictive value of MPS. However, recent studies have shown that both infarct size and the magnitude of inducible ischaemia are associated with an increased risk of adverse events after STEMI.²² Moreover, with the use of vasodilator stress agents, MPS can be performed safely 24–72 h after an uncomplicated STEMI allowing early risk assessment.²³ Therefore, MPS is currently recommended in patients after STEMI who might have received thrombolytic therapy but who have not yet undergone coronary angiography to determine the extent of ischaemic myocardium before possible revascularization.^{5,24,25} For the same purpose, MPS should be used in patients with preserved LV function who have an uninterpretable ECG.²⁴

Myocardial perfusion scintigraphy before non-cardiac surgery

MPS has received a class I indication for risk stratification of patients undergoing elective non-cardiac surgery.²⁶ Stress imaging

is particularly effective in patients with intermediate clinical predictors of cardiac risk and either a reduced exercise tolerance [<4 metabolic equivalents (METs)] or a high surgical risk (Table 1). MPS with pharmacological stress is also effective in determining risk in patients with poor exercise capacity undergoing high-risk surgery regardless of clinical predictors.²⁶ Information derived from MPS should be used not only for surgical risk stratification but also for the subsequent cardiac management of patients after the non-cardiac surgery.

Myocardial perfusion scintigraphy for the assessment of viable and hibernating myocardium

A number of studies have demonstrated the role of MPS in the assessment of patients with CAD and LV dysfunction. Extensive dysfunctional but viable myocardium is associated with poor prognosis, which can be reversed by appropriate intervention. American guidelines incorporate non-invasive imaging for the assessment of viability and hibernation in the initial evaluation of heart failure patients with known CAD without angina (class IIa).²⁷

Non-invasive imaging is also recommended for the detection of obstructive CAD in patients with symptomatic LV dysfunction. This indication is given a class IIb status by the American guidelines.²⁷ The recently published European guidelines for the diagnosis and treatment of chronic heart failure have not commented on the role of viability assessment in patients with LV dysfunction²⁸ although the subject has been reviewed by the ESC and recommendations made.²⁹

Cost-effectiveness of myocardial perfusion scintigraphy

Cost-effectiveness analysis combines the diagnostic accuracy of a particular test and the costs incurred in a test-led strategy.³⁰ MPS is cost-effective in several settings because it is an outpatient investigation of moderate cost, high diagnostic accuracy and low risk.^{31–33}

Stable angina in intermediate likelihood of coronary artery disease

Several economic models have shown that, in patients with stable angina and intermediate pre-test probability of CAD, MPS is more cost effective than the exercise ECG and X-ray coronary angiography. An MPS-led management strategy results in 23–41% cost-savings compared with direct referral to coronary angiography.^{15,34–36} Although upfront costs are higher with MPS than conventional exercise ECG, MPS is more cost effective because of its better diagnostic performance. Marwick et al.³⁷ showed that a normal exercise ECG does not prevent additional diagnostic testing and causes an unexpected increase in the use of coronary angiography, whereas a normal MPS is a strong deterrent of additional investigations.³⁸ In patients with known CAD, MPS may lead to significant savings by limiting costly therapeutic procedures to patients with high-risk scans who have the most

to gain from intervention. The greatest cost-effectiveness of MPS is in women, resulting in a significant reduction in the number of normal coronary angiograms and an increase in the detection of patients with multivessel disease (from 23 to 42%).^{32,36–39}

Acute coronary syndromes

The role of MPS as a gatekeeper to hospital admission for acute chest pain is well documented.^{40,41} MPS has a high negative predictive accuracy for ruling out acute coronary syndromes and future cardiac events (99 and 97%, respectively) in patients presenting to the emergency room with acute chest pain, non-diagnostic ECG and negative cardiac enzymes.⁴² In general, only one-third of patients with acute chest pain will have an underlying cardiac cause, and several studies have demonstrated that MPS can reduce costs by avoiding unnecessary admissions without compromising patient outcome.⁴¹ MPS results do influence triage decisions and lower the threshold for early discharge of patients with low-risk scans.⁴³ Moreover, an MPS-guided chest pain work-up decreases the rates of hospitalization and ensuing admission diagnosis of 'myocardial infarction excluded'.^{44,45} Recent studies suggest that MPS may be particularly cost-effective in special subgroups including patients with diabetes.⁴⁶

Safety

Radiation exposure

MPS exposes patients to ionizing radiation. The level of exposure varies depending upon the tracer used and the protocol employed. In general, the risk from radiation exposure must be balanced by the clinical benefit and the impact test results may have on patient outcome. The harmful effects of radiation exposure are related to the absorbed energy, with an additional lifetime risk of 0.04%/Sv of fatal cancer in young or middle-aged patients. In elderly patients, the risk is lower because of the delay between exposure and adverse event. The recently published EANM/ESC procedural guidelines for MPS recommend a total activity of 1600–2000 MBq for a 1-day MPS study with a technetium-99m-labelled tracer with corresponding effective doses in the region of 12 and 20 mSv.^{1,47} Activities between 600 and 900 MBq per scan per day are recommended for a 2-day imaging study with the same tracers, which corresponds to effective doses between 4.5 and 9 mSv. A stress-redistribution thallium-201 MPS protocol is associated with effective doses in the region of 12.9 and 19.5 mSv for 74–111 MBq of thallium-201 with an additional dose of 6.5 mSv (37 MBq) if stress-reinjection thallium-201 imaging is performed.^{1,47} Therefore, radiation exposure from a 1-day stress/rest MPS study with 1600 MBq (12 mSv) of technetium-99m-tetrofosmin is higher than that from a conventional X-ray coronary angiogram (2–6 mSv)^{48,49} but comparable to that from multi-detector CT coronary angiography (6–15 mSv).^{50,51} However, MPS is non-invasive and provides the functional effect of an atherosclerotic lesion.

Complications from stress tests

The complication rate of dynamic exercise (death, infarction, or sustained ventricular tachycardia) is 1.2 per 10 000 tests.^{52,53}

The complication rate of pharmacological stress with dipyridamole or adenosine is comparable.⁵⁴ Interestingly, the complication rate is low even shortly after an uncomplicated acute infarction (<3 days).²³ A higher complication rate is reported using dobutamine (one severe adverse reaction every 335 tests in a meta-analysis of 26 438 patients).⁵⁵

Conclusions

MPS has proven a safe and highly cost-effective strategy for the early detection of obstructive CAD in symptomatic individuals. It is powerful to stratify patients according to their risk of cardiac death or nonfatal myocardial infarction and assists clinical decision-making with regard to medical treatment and intervention. A large body of evidence supports the current application of MPS, and radionuclide imaging guidelines have been established by multiple societies. Also, MPS is successfully integrated in several guidelines for clinical practice in cardiology. Further, formal integration of this diagnostic and prognostic tool into the clinical practice and training of general cardiology is encouraged.

Conflict of interest: none declared.

References

- Hesse B, Tagil K, Cuocolo A, Anagnostopoulos C, Bardies M, Bax J, Bengel F, Busemann Sokole E, Davies G, Dondi M, Edenbrandt L, Franken P, Kjaer A, Knuuti J, Lassmann M, Ljungberg M, Marcassa C, Marie PY, McKiddie F, O'Connor M, Prvulovich E, Underwood R, van Eck-Smit B. EANM/ESC procedural guidelines for myocardial perfusion imaging in nuclear cardiology. *Eur J Nucl Med Mol Imaging* 2005;**32**:855–897.
- American Society of Nuclear Cardiology. Imaging Guidelines for Nuclear Cardiology Procedures. 2006; Available at http://www.asnc.org/section_73.cfm://www.asnc.org/section_73.cfm.
- Fox K, Garcia MA, Ardissino D, Buszman P, Camici PG, Crea F, Daly C, De Backer G, Hjelm Dahl P, Lopez-Sendon J, Marco J, Morais J, Pepper J, Sechtem U, Simoons M, Thygesen K, Priori SG, Blanc JJ, Budaj A, Camm J, Dean V, Deckers J, Dickstein K, Lekakis J, McGregor K, Metra M, Morais J, Osterspey A, Tamargo J, Zamorano JL. Guidelines on the management of stable angina pectoris: executive summary: the Task Force on the Management of Stable Angina Pectoris of the European Society of Cardiology. *Eur Heart J* 2006;**27**:1341–1381.
- Gibbons RJ, Abrams J, Chatterjee K, Daley J, Deedwania PC, Douglas JS, Ferguson TB Jr, Fihn SD, Fraker TD Jr, Gardin JM, O'Rourke RA, Pasternak RC, Williams SV. ACC/AHA 2002 guideline update for the management of patients with chronic stable angina—summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on the Management of Patients With Chronic Stable Angina). *Circulation* 2003;**107**:149–158.
- Klocke FJ, Baird MG, Lorell BH, Bateman TM, Messer JV, Berman DS, O'Gara PT, Carabello BA, Russell RO Jr, Cerqueira MD, St John Sutton MG, DeMaria AN, Udelson JE, Kennedy JW, Verani MS, Williams KA, Antman EM, Smith SC Jr, Alpert JS, Gregoratos G, Anderson JL, Hiratzka LF, Faxon DP, Hunt SA, Fuster V, Jacobs AK, Gibbons RJ, Russell RO. ACC/AHA/ASNC guidelines for the clinical use of cardiac radionuclide imaging—executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/ASNC Committee to Revise the 1995 Guidelines for the Clinical Use of Cardiac Radionuclide Imaging). *J Am Coll Cardiol* 2003;**42**:1318–1333.
- Underwood SR, Anagnostopoulos C, Cerqueira M, Ell PJ, Flint EJ, Harbinson M, Kelion AD, Al-Mohammad A, Prvulovich EM, Shaw LJ, Tweddell AC. Myocardial perfusion scintigraphy: the evidence. *Eur J Nucl Med Mol Imaging* 2004;**31**:261–291.
- DePuey EG, Rozanski A. Using gated technetium-99m-sestamibi SPECT to characterize fixed myocardial defects as infarct or artifact. *J Nucl Med* 1995;**36**:952–955.
- Taillefer R, DePuey EG, Udelson JE, Beller GA, Latour Y, Reeves F. Comparative diagnostic accuracy of Tl-201 and Tc-99m sestamibi SPECT imaging (perfusion and ECG-gated SPECT) in detecting coronary artery disease in women. *J Am Coll Cardiol* 1997;**29**:69–77.
- Smanio PE, Watson DD, Segalla DL, Vinson EL, Smith WH, Beller GA. Value of gating of technetium-99m sestamibi single-photon emission computed tomographic imaging. *J Am Coll Cardiol* 1997;**30**:1687–1692.
- Kjaer A, Cortsen A, Rahbek B, Hasseldam H, Hesse B. Attenuation and scatter correction in myocardial SPET: improved diagnostic accuracy in patients with suspected coronary artery disease. *Eur J Nucl Med Mol Imaging* 2002;**29**:1438–1442.
- Mieres JH, Shaw LJ, Arai A, Budoff MJ, Flamm SD, Hundley WG, Marwick TH, Mosca L, Patel AR, Quinones MA, Redberg RF, Taubert KA, Taylor AJ, Thomas GS, Wenger NK. Role of noninvasive testing in the clinical evaluation of women with suspected coronary artery disease: Consensus statement from the Cardiac Imaging Committee, Council on Clinical Cardiology, and the Cardiovascular Imaging and Intervention Committee, Council on Cardiovascular Radiology and Intervention, American Heart Association. *Circulation* 2005;**111**:682–696.
- Eagle KA, Guyton RA, Davidoff R, Edwards FH, Ewy GA, Gardner TJ, Hart JC, Herrmann HC, Hillis LD, Hutter AM Jr, Lytle BW, Marlow RA, Nugent WC, Orszulak TA. ACC/AHA 2004 guideline update for coronary artery bypass graft surgery: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1999 Guidelines for Coronary Artery Bypass Graft Surgery). *Circulation* 2004;**110**:e340–e437.
- Smith SC Jr, Dove JT, Jacobs AK, Kennedy JW, Kereiakes D, Kern MJ, Kuntz RE, Popma JJ, Schaff HV, Williams DO, Gibbons RJ, Alpert JP, Eagle KA, Faxon DP, Fuster V, Gardner TJ, Gregoratos G, Russell RO, Smith SC Jr. ACC/AHA guidelines for percutaneous coronary intervention (revision of the 1993 PTCA guidelines)—executive summary: a report of the American College of Cardiology/American Heart Association task force on practice guidelines (Committee to revise the 1993 guidelines for percutaneous transluminal coronary angioplasty) endorsed by the Society for Cardiac Angiography and Interventions. *Circulation* 2001;**103**:3019–3041.
- Iskandrian AS, Chae SC, Heo J, Stanberry CD, Wasserleben V, Cave V. Independent and incremental prognostic value of exercise single-photon emission computed tomographic (SPECT) thallium imaging in coronary artery disease. *J Am Coll Cardiol* 1993;**22**:665–670.
- Hachamovitch R, Berman DS, Shaw LJ, Kiat H, Cohen I, Cabico JA, Friedman J, Diamond GA. Incremental prognostic value of myocardial perfusion single photon emission computed tomography for the prediction of cardiac death: differential risk stratification for risk of cardiac death and myocardial infarction. *Circulation* 1998;**97**:535–543.

16. Hachamovitch R, Hayes S, Friedman J, Cohen I, Berman D. Stress perfusion single-photon emission computed tomography is clinically effective and cost-effective in risk stratification of patients with a high likelihood of coronary artery disease (CAD) but not known CAD. *J Am Coll Cardiol* 2004;**43**:200–208.
17. Hachamovitch R, Hayes S, Friedman J, Cohen I, Shaw L, Germano G, Berman DS. Determinants of risk and its temporal variation in patients with normal stress myocardial perfusion scans. What is the warranty period of a normal scan? *J Am Coll Cardiol* 2003;**41**:1329–1340.
18. Sharir T, Germano G, Kavanagh PB, Lai S, Cohen I, Lewin HC, Friedman JD, Zellweger MJ, Berman DS. Incremental prognostic value of post-stress left ventricular ejection fraction and volume by gated myocardial perfusion single photon emission computed tomography. *Circulation* 1999;**100**:1035–1042.
19. Erhardt L, Herlitz J, Bossaert L, Halinen M, Keltai M, Koster R, Marcassa C, Quinn T, van Weert H. Task Force on the management of chest pain. Task force on the management of chest pain. *Eur Heart J* 2002;**23**:1153–1176.
20. Bertrand ME, Simoons ML, Fox KA, Wallentin LC, Hamm CW, McFadden E, De Feyter PJ, Specchia G, Ruzyllo W. Task Force on the Management of Acute Coronary Syndromes of the European Society of Cardiology. Management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur Heart J* 2002;**23**:1809–1840.
21. Braunwald E, Antman EM, Beasley JW, Califf RM, Cheitlin MD, Hochman JS, Jones RH, Kereiakes D, Kupersmith J, Levin TN, Pepine CJ, Schaeffer JW, Smith EE 3rd, Steward DE, Theroux P, Gibbons RJ, Alpert JS, Faxon DP, Fuster V, Gregoratos G, Hiratzka LF, Jacobs AK, Smith SC Jr. ACC/AHA guideline update for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction—2002: summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on the Management of Patients With Unstable Angina). *Circulation* 2002;**106**:1893–1900.
22. Brown KA, Heller GV, Landin RS, Shaw LJ, Beller GA, Pasquale MJ, Haber SB. Early dipyridamole (99m)Tc-sestamibi single-photon emission computed tomographic imaging 2 to 4 days after acute myocardial infarction predicts in-hospital and postdischarge cardiac events: comparison with submaximal exercise imaging. *Circulation* 1999;**100**:2060–2062–66.
23. Heller GV, Brown KA, Landin RJ, Haber RJ, Haber SB. Safety of early intravenous dipyridamole technetium-99m sestamibi SPECT myocardial perfusion imaging after uncomplicated first myocardial infarction. Early Post MI IV Dipyridamole Study (EPIDS). *Am Heart J* 1997;**134**:105–111.
24. Antman EM, Anbe DT, Armstrong PW, Bates ER, Green LA, Hand M, Hochman JS, Krumholz HM, Kushner FG, Lamas GA, Mullany CJ, Ornato JP, Pearle DL, Sloan MA, Smith SC Jr, Alpert JS, Anderson JL, Faxon DP, Fuster V, Gibbons RJ, Gregoratos G, Halperin JL, Hiratzka LF, Hunt SA, Jacobs AK, Ornato JP. ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1999 Guidelines for the Management of Patients with Acute Myocardial Infarction). *Circulation* 2004;**110**:e82–e292.
25. Van de Werf F, Ardissino D, Betriu A, Cokkinos DV, Falk E, Fox KA, Julian D, Lengyel M, Neumann FJ, Ruzyllo W, Thygesen C, Underwood SR, Vahanian A, Verheugt FW, Wijns W. Task Force on the Management of Acute Myocardial Infarction of the European Society of Cardiology. Management of acute myocardial infarction in patients presenting with ST-segment elevation. The Task Force on the Management of Acute Myocardial Infarction of the European Society of Cardiology. *Eur Heart J* 2003;**24**:28–66.
26. Eagle KA, Berger PB, Calkins H, Chaitman BR, Ewy GA, Fleischmann KE, Fleisher LA, Froehlich JB, Gusberg RJ, Leppo JA, Ryan T, Schlant RC, Winters WL Jr, Gibbons RJ, Antman EM, Alpert JS, Faxon DP, Fuster V, Gregoratos G, Jacobs AK, Hiratzka LF, Russell RO, Smith SC Jr. ACC/AHA guideline update for perioperative cardiovascular evaluation for noncardiac surgery—executive summary a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1996 Guidelines on Perioperative Cardiovascular Evaluation for Noncardiac Surgery). *Circulation* 2002;**105**:1257–1267.
27. Hunt SA, Abraham WT, Chin MH, Feldman AM, Francis GS, Ganiats TG, Jessup M, Konstam MA, Mancini DM, Michl K, Oates JA, Rahko PS, Silver MA, Stevenson LW, Yancy CW, Antman EM, Smith SC Jr, Adams CD, Anderson JL, Faxon DP, Fuster V, Halperin JL, Hiratzka LF, Jacobs AK, Nishimura R, Ornato JP, Page RL, Riegel B. ACC/AHA 2005 Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure): developed in collaboration with the American College of Chest Physicians and the International Society for Heart and Lung Transplantation: endorsed by the Heart Rhythm Society. *Circulation* 2005;**112**:e154–e235.
28. Swedberg K, Cleland J, Dargie H, Drexler H, Follath F, Komajda M, Tavazzi L, Smiseth OA, Gavazzi A, Haverich A, Hoes A, Jaarsma T, Korewicki J, Levy S, Linde C, Lopez-Sendon JL, Nieminen MS, Pierard L, Remme WJ. Guidelines for the diagnosis and treatment of chronic heart failure: executive summary (update 2005): The Task Force for the Diagnosis and Treatment of Chronic Heart Failure of the European Society of Cardiology. *Eur Heart J* 2005;**26**:1115–1140.
29. Underwood SR, Bax JJ, vom Dahl J, Henein MY, Knuuti J, van Rossum AC, Schwarz ER, Vanoverschelde JL, van der Wall EE, Wijns W. Imaging techniques for the assessment of myocardial hibernation. Report of a Study Group of the European Society of Cardiology. *Eur Heart J* 2004;**25**:815–836.
30. Mark DB, Hlatky MA. Medical economics and the assessment of value in cardiovascular medicine part I. *Circulation* 2002;**106**:516–520.
31. Underwood SR, Shaw LJ. Myocardial perfusion scintigraphy and cost effectiveness of diagnosis and management of coronary heart disease. *Heart* 2004;**90**(Suppl. V):v34–v36.
32. National Health Service-National Institute of Clinical Excellence. Technology Appraisal Consultation document: myocardial perfusion scintigraphy for the diagnosis and management of angina and myocardial infarction Available from: URL: <http://www.nice.org.uk/TA073> guidance. Accessed June 10, 2007.
33. Mowatt G, Vale L, Brazzelli M, Hernandez R, Murray A, Scott N, Fraser C, McKenzie L, Gemmell H, Hillis G, Metcalfe M. Systematic review of the effectiveness and cost-effectiveness, and economic evaluation of myocardial perfusion scintigraphy for the diagnosis and management of angina and myocardial infarction. *Health Technol Assess* 2004;**8**:1–207.
34. Shaw LJ, Hachamovitch R, Berman DS, Marwick TH, Lauer MS, Heller GV, Iskandrian AE, Kesler KL, Travin MI, Lewin HC,

- Hendel RC, Borges-Neto S, Miller DD. The economic consequences of available diagnostic and prognostic strategies for the evaluation of stable angina patients: an observational assessment of the value of precatheterization ischemia. Economics of Noninvasive Diagnosis (END) Multicenter Study Group. *J Am Coll Cardiol* 1999;**33**:661–669.
35. Mishra JP, Acio E, Heo J, Narula J, Iskandrian AE. Impact of stress single-photon emission computed tomography perfusion imaging on downstream resource utilization. *Am J Cardiol* 1999;**83**:1401–1403, A8.
36. Underwood SR, Godman B, Salvani S, Ogle JR, Ell PJ. Economics of myocardial perfusion imaging in Europe—the EMPIRE study. *Eur Heart J* 1999;**20**:157–166.
37. Marwick TH, Shaw L, Case C, Vasey C, Thomas JD. Clinical and economic impact of exercise electrocardiography and exercise echocardiography in clinical practice. *Eur Heart J* 2003;**24**:1153–1163.
38. Thomas GS, Miyamoto MI, Morello AP, Majmundar H, Thomas JJ, Sampson CH, Hachamovitch R, Shaw LJ. Technetium-99m sestamibi myocardial perfusion imaging predicts clinical outcome in the community outpatient setting: The Nuclear Utility in the Community (NUC) Study. *J Am Coll Cardiol* 2004;**43**:213–223.
39. Shaw LJ, Heller GV, Travin MI, Lauer M, Marwick T, Hachamovitch R, Berman DS, Miller DD. Cost analysis of diagnostic testing for coronary artery disease in women with stable chest pain. Economics of Noninvasive Diagnosis (END) Study Group. *J Nucl Cardiol* 1999;**9**:515–522.
40. Bülow H, Schwaiger M. Nuclear cardiology in acute coronary syndromes. *Q J Nucl Med* 2005;**49**:59–71.
41. Udelson JE, Beshansky JR, Ballin DS, Feldman JA, Griffith JL, Handler J, Heller GV, Hendel RC, Pope JH, Ruthazer R, Spiegler EJ, Woolard RH, Selker HP. Myocardial perfusion imaging for evaluation and triage of patients with suspected acute cardiac ischemia: a randomized controlled trial. *JAMA* 2002;**288**:2693–2700.
42. Heller GV, Stowers SA, Hendel RC, Herman SD, Daher E, Ahlberg AW, Baron JM, Mendes de Leon CF, Rizzo JA, Wackers FJ. Clinical value of acute rest technetium-99m tetrofosmin tomographic myocardial perfusion imaging in patients with acute chest pain and nondiagnostic electrocardiograms. *J Am Coll Cardiol* 1998;**31**:1011–1017.
43. Weissman IA, Dickinson CZ, Dworkin HJ, O'Neill WW, Juni JE. Cost-effectiveness of myocardial perfusion imaging with SPECT in the emergency department evaluation of patients with unexplained chest pain. *Radiology* 1996;**199**:353–357.
44. Abbott BG, Abdel-Aziz I, Nagula S, Monico EP, Schriver JA, Wackers FJ. Selective use of single-photon emission computed tomography myocardial perfusion imaging in a chest pain center. *Am J Cardiol* 2001;**87**:1351–1355.
45. Knott JC, Baldey AC, Grigg LE, Cameron PA, Lichtenstein M, Better N. Impact of acute chest pain Tc-99m sestamibi myocardial perfusion imaging on clinical management. *J Nucl Cardiol* 2002;**9**:257–262.
46. Kapetanopoulos A, Heller GV, Selker HP, Ruthazer R, Beshansky JR, Feldman JA, Griffith JL, Hendel RC, Pope JH, Spiegler EJ, Udelson JE. Acute resting myocardial perfusion imaging in patients with diabetes mellitus: results from the Emergency Room Assessment of Sestamibi for Evaluation of Chest Pain (ERASE Chest Pain) trial. *J Nucl Cardiol* 2004;**11**:570–577.
47. Administration of Radioactive Substances Advisory Committee ARSAC. Notes for guidance on the clinical administration of radiopharmaceuticals and use of sealed radioactive sources, March 2006. Available from: URL:<http://www.arsac.org.uk>. Accessed 20 June 2007.
48. International Commission on Radiological Protection (ICRP). Publication 34: Protection of the patient in diagnostic radiology. *Ann ICRP* 1983;9/2.
49. Betsou S, Efstathopoulos EP, Katriotis D, Faulkner K, Panayiotakis G. Patient radiation doses during cardiac catheterisation procedures. *Br J Radiol* 1998;**71**:634–639.
50. International Commission on Radiological Protection (ICRP). Publication 87: management of patient dose in computed tomography. *Ann ICRP* 2001;30/4.
51. Hunold P, Vogt FM, Schmermund A, Debatin JF, Kerckhoff G, Budde T, Erbel R, Ewen K, Barkhausen J. Radiation exposure during cardiac CT: effective doses at multi-detector row CT and electron-beam CT. *Radiology* 2003;**226**:145–152.
52. Stuart RJ Jr, Ellestad MH. National survey of exercise stress testing facilities. *Chest* 1980;**77**:94–97.
53. Myers J, Voodi L, Umann T, Froelicher VF. A survey of exercise testing: methods, utilization, interpretation, and safety in the VAHCS. *J Cardiopulm Rehabil* 2000;**20**:251–258.
54. Lette J, Tatum JL, Fraser S, Miller DD, Waters DD, Heller G, Stanton EB, Bom HS, Leppo J, Nattel S. Safety of dipyridamole testing in 73806 patients: the Multicenter Dipyridamole Safety Study. *J Nucl Cardiol* 1995;**2**:3–17.
55. Lattanzi F, Picano E, Adamo E, Varga A. Dobutamine stress echocardiography: safety in diagnosing coronary artery disease. *Drug Saf* 2000;**22**:251–262.