Myocardial perfusion scintigraphy: the evidence

A consensus conference organised by the British Cardiac Society, the British Nuclear Cardiology Society and the British Nuclear Medicine Society, endorsed by the Royal College of Physicians of London and the Royal College of Radiologists

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Abstract. This review summarises the evidence for the role of myocardial perfusion scintigraphy (MPS) in patients with known or suspected coronary artery disease. It is the product of a consensus conference organised by the British Cardiac Society, the British Nuclear Cardiology Society and the British Nuclear Medicine Society and is endorsed by the Royal College of Physicians of London and the Royal College of Radiologists. It was used to inform the UK National Institute of Clinical Excellence in their appraisal of MPS in patients with chest pain and myocardial infarction. MPS is a well-established, non-invasive imaging technique with a large body of evidence to support its effectiveness in the diagnosis and management of angina and myocardial infarction. It is more accurate than the exercise ECG in detecting myocardial ischaemia and it is the single most powerful technique for predicting future coronary events. The high diagnostic accuracy of MPS allows reliable risk stratification and guides the selection of patients for further interventions, such as revascularisation. This in turn allows more appropriate utilisation of resources, with the potential for both improved clinical outcomes and greater cost-effectiveness. Evidence from modelling and observational studies supports the enhanced cost-effectiveness associated with MPS use. In patients presenting with stable or acute chest pain, strategies of investigation involving MPS are more cost-effective than those not using the technique. MPS also has particular advantages over alternative techniques in the management of a number of patient subgroups, including women, the elderly and those with diabetes, and its use will have a favourable impact on cost-effectiveness in these groups. MPS is already an integral part of many clinical guidelines for the investigation and management of angina and myocardial infarction. However, the technique is underutilised in the UK, as judged by the inappropriately long waiting times and by comparison with the numbers of revascularisations and coronary angiograms performed. Furthermore, MPS activity levels in this country fall far short of those in comparable European countries, with about half as many scans being undertaken per year. Currently, the number of MPS studies performed annually in the UK is 1,200/million population/year. We estimate the real need to be 4,000/million/year. The current average waiting time is 20 weeks and we recommend that clinically appropriate upper limits of waiting time are 6 weeks for routine studies and 1 week for urgent studies.

Abbreviations. Acc Diagnostic accuracy · ACS Acute coronary syndromes · BCS British Cardiac Society · BNCS British Nuclear Cardiology Society · BNMS British Nuclear Medicine Society ·
is Nuclear Medicine Society · CABG Coronary artery bypass grafting · CHD Coronary heart disease · CT Computed X-ray tomography · LBBB Left bundle branch block · MI Myocardial infarction · MIBI Technetium-99m 2-methoxy-isobutyl-isonitrile · MPS Myocardial perfusion scintigraphy · NSF National Service Framework for Cardiovascular Disease · NSTEMI Non-ST segment elevation myocardial infarction · PCI Percutaneous coronary intervention · Q Quantity-adjusted life-year · RCP Royal College of Physicians of London · RCR Royal College of Radiologists · Sens Sensitivity · Spec Specificity · SPET Single-photon emission tomography · STEMI ST segment elevation myocardial infarction · Tetro or tetrofosmin Technetium-99m 1,2-bis[2-ethoxyethyl]phosphino]ethane · UA Unstable angina · V Visual analysis

**Introduction**

**Background**

Coronary heart disease (CHD) is a major cause of mortality and morbidity in Europe and its management consumes a large proportion of national healthcare budgets. New imaging technologies have added to the immediate costs of investigation but they also have the potential to reduce overall costs, by virtue of their greater diagnostic and prognostic accuracy. This allows a more informed selection of therapy, which in turn can lead to a better clinical outcome.

Myocardial perfusion scintigraphy (MPS) is an established imaging technique that is already an integral part of the management of CHD and is included in a number of professional guidelines. Its most important applications are in the diagnosis of CHD, prognostication, selection for revascularisation and assessment of acute coronary syndromes, and it is of special value in some patient subgroups.

In this consensus document we review the evidence supporting the clinical effectiveness and cost-effectiveness of MPS and we assess its potential to improve patient care in the UK. The current utilisation of MPS is reviewed and targets for service improvements are proposed.

**Description of process for consensus meeting**

Representatives of the British Cardiac Society (BCS), the British Nuclear Cardiology Society (BNCS) and the British Nuclear Medicine Society (BNMS) met at a consensus conference in January 2003 to review the evidence for the clinical and cost-effectiveness of MPS and to draft a document for submission to the National Institute for Clinical Excellence (NICE). The document was a submission for the NICE appraisal of MPS in the diagnosis and management of angina and myocardial infarction. The final document was endorsed by the three societies and also by the Royal College of Physicians of London (RCP) and the Royal College of Radiologists (RCR).

**What is MPS?**

MPS was developed in the 1970s and has been used increasingly in clinical cardiology since the 1980s. Technical developments that have fuelled this recent increase are single-photon emission tomographic imaging (SPET), pharmacological stress and ECG-gated imaging.

The technique involves intravenous injection of small amounts of a radioactive tracer, usually during some form of cardiovascular stress. The three commercially available tracers are thallium-201 thallous chloride (thallium), technetium-99m 2-methoxy-isobutyl-isonitrile (MIBI) and technetium-99m 1,2-bis[2-ethoxyethyl]phosphino]ethane (tetrofosmin). These are avidly extracted by cardiac myocytes and hence their initial myocardial distribution reflects a combination of the distribution of myocytes and perfusion. Comparison of images following stress and rest injections of tracer (or following redistribution for thallium) allows myocardial viability and perfusion to be assessed independently.

Pharmacological stress, using a vasodilator such as adenosine or a beta sympathetic agonist such as dobutamine, allows patients who cannot achieve maximal cardiovascular stress on a treadmill to be studied, and this is a particularly valuable aspect of the technique that is relevant to between one-third and one-half of patients.

SPET is the preferred imaging technique, whereby the camera rotates around the patient over 10–20 min and the resulting set of planar projection images are reconstructed into a three-dimensional stack of tomographic slices through the myocardium. The tomograms are displayed using a colour scale to provide a semi-quantitative assessment of regional tracer uptake, and comparison with databases of normal appearances allows objective assessment of the presence, depth and extent of abnormalities. The stress and rest images are normally separated by 3–4 h but the total patient contact time for stress, injection and image acquisition is approximately 45 min.

Homogeneous myocardial uptake of tracer indicates normal myocardium and perfusion and hence the absence of clinically significant infarction or coronary stenosis. A defect in the stress images that normalises in the rest images (a reversible defect) indicates an inducible perfusion abnormality and normally corresponds to a
significant coronary stenosis. A defect in both stress and rest images (a fixed defect) indicates an area with loss of viable myocardium such as after myocardial infarction. The site, extent and depth of these abnormalities are readily assessed and hence the technique is valuable for the diagnosis of CHD, for assessing its severity, which in turn is related to prognosis, and for assessing global and regional myocardial function from ECG-gated moving images.

Safety

MPS is non-invasive and safe, particularly in comparison with invasive investigation, which it can sometimes replace. The complication rate of dynamic exercise is well established from treadmill exercise electrocardiography as at most 0.01% deaths and 0.02% morbidity [1] and similar rates have been observed with pharmacological stress [2, 3, 4]. These low rates are at least two orders of magnitude less than the risk of underlying CHD and so, except in patients with unstable CHD or other contraindications to stress, the risk is not normally considered significant.

The radiation exposure to the patient is 10 mSv for a 1,000 MBq tetrofosmin study, 12 mSv for a 1,000 MBq MIBI study and 18 mSv for an 80 MBq thallium study [5]. A 10 mSv exposure is equivalent to 5 years of natural background radiation; it is similar to the exposure from computed X-ray tomography (CT) and coronary angiography [6] and it produces a 1 in 1,800 risk of cancer 10–20 years after the exposure [7]. Although this is higher than the risk of the stress test, it is small alongside the lifetime risk of cancer in the general population (1 in 3), and it is of even lesser importance in the elderly and those with known CHD, the population that is most commonly referred for MPS.

Coronary angiography is complicated by death in 0.1% of cases and by non-fatal events such as myocardial infarction, stroke and emergency bypass grafting in 2% [8]. Lesser complications such as bleeding, dissection and thrombosis of the vascular access site occur in 0.5% [8].

Diagnosis

Coronary angiography and myocardial perfusion

MPS is the only widely available method of assessing myocardial perfusion directly. It therefore has a clear role in the diagnosis of CHD in patients presenting with chest pain. An inducible perfusion abnormality indicates impaired perfusion reserve, which in turn usually corresponds to epicardial coronary obstruction. The site, depth and extent of the abnormality provide diagnostic and management information that cannot be determined reliably from other tests such as the ECG. Conversely, normal stress MPS indicates the absence of coronary obstruction and hence of clinically significant disease. It is important to note that normal perfusion does not exclude non-obstructive coronary disease, but such disease is unlikely to be related to symptoms and is not prognostically important (see section “Prognosis”).

Coronary angiography is the standard technique for assessing epicardial coronary anatomy and MPS is the standard technique for assessing myocardial perfusion. Although the anatomical extent of disease is best demonstrated by coronary angiography, MPS provides a complementary assessment of its physiological significance and hence information on important features such as endothelial function, small vessel function and collateralisation, in addition to the haemodynamic significance of epicardial stenoses. Discrepancies between coronary anatomy and myocardial perfusion do not necessarily indicate a failure in the assessment of either; instead they indicate the complexity of the relationship. Complete accuracy of MPS to predict the findings at coronary angiography is neither expected nor necessary for clinical management, and when MPS is used for the diagnosis of CHD it is not being used purely to predict the presence of epicardial coronary disease. Nevertheless, the coronary angiogram is an accepted standard for imaging the coronary arteries and functional tests such as MPS are commonly compared with angiography.

Diagnostic accuracy of MPS

Many studies have assessed the diagnostic accuracy of MPS for the detection of coronary heart disease, but they are of variable size and quality. Tables 1, 2, 3 and 4 summarise the findings according to the four main forms of stress and also grade the quality of the studies according to accepted principles [9, 10]. The highest quality score is 3, when the study involves a clearly defined population, when it avoids verification bias and when MPS is interpreted independently of angiography. A quality score of 2 fulfils two of these criteria and a score of 1 only one criterion. An additional criterion of quality is the exclusion of patients with previous infarction since the most relevant population is the diagnostic study, where MPS may be less sensitive than in patients with previous infarction and abnormal resting images.

Sensitivity and specificity

Because of the variation in study size, quality and design, we have avoided giving weighted averages of sensitivity and specificity in the above tables. Specificity in particular varies between studies depending upon patient population, nature of reporting and referral bias (see section “Factors affecting observed diagnostic perfor-
In the largest single study of 2,560 patients randomised to each of the three tracers and using mainly adenosine stress (the ROBUST study, UK based), overall sensitivity in the subset of patients undergoing angiography was 91% and specificity 87%, with no significant difference between the three tracers [55]. In general terms,

**Table 1.** Diagnostic accuracy of exercise MPS for the detection of ≥50% coronary stenosis defined angiographically

| Author, year [ref.] | No. | Tracer | Analysis | MI excluded | Quality | Sens (%) | Spec (%) | Acc (%) |
|---------------------|-----|--------|----------|-------------|---------|----------|----------|---------|
| Tamaki, 1984 [11]   | 104 | ^201^Tl | Q        | Both        | 2       | 98       | 91       | 96      |
| DePasquale, 1988 [12] | 210 | ^201^Tl | Q        | Both        | 2       | 95       | 74       | 92      |
| Fintel, 1989 [13]   | 135 | ^201^Tl | V        | No          | 2       | 83       | –        | –       |
| Iskandrian, 1989 [14] | 193 | ^201^Tl | V        | Yes         | 2       | 86       | 62       | 79      |
| Maddahi, 1989 [15]  | 110 | ^201^Tl | Q        | Both        | 3       | 95       | 56       | 88      |
| Mahmarian, 1990 [16] | 296 | ^201^Tl | Q        | Both        | 3       | 87       | 87       | 87      |
| Van Train, 1990 [17] | 242 | ^201^Tl | Q        | Both        | 2       | 94       | 43       | 85      |
| Coyne, 1991 [18]    | 100 | ^201^Tl | V        | No          | 2       | 81       | 74       | 77      |
| Quinones, 1992 [19] | 112 | ^201^Tl | V        | Yes         | 1       | 77       | 81       | 78      |
| Chae, 1993 [20]     | 243 | ^201^Tl | V        | No          | 3       | 71       | 63       | 69      |
| Grover-McKay, 1994 [21] | 18 | ^201^Tl | V        | No          | 1       | 91       | 86       | 89      |
| Tamaki, 1994 [22]   | 25  | ^201^Tl | V        | No          | 1       | 95       | 33       | 88      |
| Ho, 1997 [23]       | 51  | ^201^Tl | V        | Both        | 3       | 76       | 77       | 76      |
| Kiat, 1990 [24]     | 53  | MIBI    | Q        | Both        | 2       | 94       | 80       | 92      |
| Pozzoli, 1991 [25]  | 75  | MIBI    | V        | No          | 1       | 84       | 88       | 85      |
| Solot, 1993 [26]    | 78  | MIBI    | V        | No          | 2       | 96       | 74       | 90      |
| Marwick, 1994 [27]  | 86  | MIBI    | V        | Yes         | 2       | 73       | 70       | 72      |
| Van Train, 1994 [28] | 124 | MIBI    | Q        | Both        | 2       | 89       | 36       | 81      |
| Tamaki, 1994 [22]   | 26  | Tetro   | V        | No          | 1       | 96       | 67       | 92      |
| Ho, 1994 [29]       | 23  | Tetro   | V        | No          | 2       | 87       | –        | –       |
| Benoit, 1996 [30]   | 30  | Tetro   | V        | Yes         | 2       | 81       | 89       | 83      |
| Shapoury, 1998 [31] | 26  | Tetro   | V        | No          | 2       | 96       | –        | –       |

**Table 2.** Diagnostic accuracy of dipyridamole MPS for the detection of ≥50% (or ≥70%\(^a\)) coronary stenosis defined angiographically

| Author, year [ref.] | No. | Tracer | Analysis | MI excluded | Quality | Sens (%) | Spec (%) | Acc (%) |
|---------------------|-----|--------|----------|-------------|---------|----------|----------|---------|
| Francisco, 1982 [32] | 75  | ^201^Tl | Q        | No          | 2       | 90       | 96       | 92      |
| Huikuri, 1988 [33]  | 93  | ^201^Tl | V        | No          | 2       | 96       | 75       | 94      |
| Go, 1990 [34]       | 202 | ^201^Tl | V        | Both        | 3       | 76       | 80       | 77      |
| Mendelson, 1992 [35] | 79  | ^201^Tl | V        | Both        | 2       | 90       | –        | –       |
| Cramer, 1994 [36]   | 38  | ^201^Tl | V        | No          | 3       | 90       | 71       | 87      |
| Grover-McKay, 1994 [21] | 18 | ^201^Tl | V        | Unknown     | 1       | 91       | 100      | 94      |
| Ho, 1995 [37]       | 54  | ^201^Tl | V        | Unknown     | 3       | 98       | 73       | 93      |
| Watanabe, 1997 [38] | 53  | ^201^Tl | V        | Yes         | 2       | 80       | 72       | 77      |
| Tartagni, 1991 [39] | 30  | ^201^Tl; MIBI | V        | No          | 2       | 100      | 75       | 97      |
| Miller, 1997 [40]   | 244 | MIBI    | V        | Both        | 2       | 91       | 28       | 81      |
| Schillaci, 1997 [41] | 40  | MIBI    | V        | Yes         | 1       | 95       | 72       | 85      |
| Soman, 1997 [42]    | 27  | MIBI    | V        | No          | 3       | 90       | 66       | 89      |
| Ogilby, 1998 [43]   | 26  | MIBI    | V        | No          | 2       | 90       | 100      | 92      |
| Santoro, 1998 [44]  | 60  | MIBI    | V        | Yes         | 3       | 97       | 89       | 93      |
| He, 1997 [45]       | 64  | Tetro   | V        | No          | 2       | 85       | 54       | 80      |

Abbreviations as defined in Table 1 and list of abbreviations

\(^a\) Accuracy reported in full group and in subset without infarction; figures in table relate to whole patient group

\(\geq 70\%\) coronary stenosis

\(^b\) Accuracy reported in full group and in subset without infarction; figures in table relate to whole patient group
Table 3. Diagnostic accuracy of adenosine MPS for the detection of ≥50% coronary stenosis defined angiographically

| Author, year [ref.] | No. | Tracer | Analysis | MI excluded | Quality | Sens (%) | Spec (%) | Acc (%) |
|---------------------|-----|--------|----------|-------------|---------|----------|----------|---------|
| Nguyen, 1990 [46]   | 60  | $^{201}$Tl | V        | No          | 2       | 92       | 100      | 93      |
| Verani, 1990 [47]   | 45  | $^{201}$Tl | Q        | No          | 2       | 83       | 94       | 87      |
| Coyne, 1991 [18]    | 100 | $^{201}$Tl | V        | Both$^b$    | 2       | 83       | 76       | 79      |
| Nishimura, 1991 [48] | 101 | $^{201}$Tl | V        | Both$^b$    | 3       | 84       | 84       | 84      |
| Allman, 1992 [49]   | 76  | $^{201}$Tl | Q        | Yes         | 3       | 85       | 38       | 80      |
| Pennell, 1995 [50]  | 226 | $^{201}$Tl | V        | No          | 3       | 96       | 78       | 92      |
| Mohiuddin, 1996 [51]| 202 | $^{201}$Tl | Q        | No          | 3       | 90       | 86       | 89      |
| Amanullah, 1993 [52]| 40  | MIBI    | V        | No          | 4       | 94       | 100      | 95      |
| Marwick, 1993 [53]  | 97  | MIBI    | V        | Yes         | 2       | 86       | 71       | 80      |
| Jamil, 1999 [54]    | 32  | MIBI    | V        | No          | 2       | 75       | –        | –       |
| Kapur, 2002 [55]$^a$ | 2,560 | $^{201}$Tl | V        | Yes         | 2       | 91       | 87       | 91      |

Abbreviations as defined in Table 1 and list of abbreviations

$^a$ Accuracy reported in full group and in subset without infarction; figures in table relate to whole patient group

Table 4. Diagnostic accuracy of dobutamine MPS for the detection of ≥50% (or ≥70%$^a$) coronary stenosis defined angiographically

| Author, year [ref.] | No. | Tracer | Analysis | MI excluded | Quality | Sens (%) | Spec (%) | Acc (%) |
|---------------------|-----|--------|----------|-------------|---------|----------|----------|---------|
| Pennell, 1991 [56]  | 50  | $^{201}$Tl | V        | No          | 2       | 97       | 80       | 94      |
| Warner, 1993 [57]   | 16  | $^{201}$Tl | V        | No          | 2       | 93       | 100      | 94      |
| Hays, 1993 [58]     | 67  | $^{201}$Tl | Q        | No          | 2       | 86       | 90       | 87      |
| Huang, 1997 [59]    | 93  | $^{201}$Tl | Q        | No          | 3       | 90       | 81       | 87      |
| Huang, 1998 [60]    | 110 | $^{201}$Tl | V        | Yes         | 3       | 82       | 82       | 82      |
| Caner, 1997 [61]    | 29  | MIBI    | V        | Uncertain   | 3       | 89       | 70       | 83      |
| Gunalp, 1993 [62]   | 27  | MIBI    | V        | Yes         | 2       | 94       | 89       | 93      |
| Forster, 1993 [63]  | 21  | MIBI    | V        | Yes         | 3       | 85       | 89       | 86      |
| Marwick, 1993 [53]  | 97  | MIBI    | V        | Yes         | 2       | 80       | 74       | 77      |
| Marwick, 1993 [64]  | 217 | MIBI    | Q        | Yes         | 3       | 76       | 67       | 73      |
| Mairesse, 1994 [65] | 129 | MIBI    | V        | Yes         | 3       | 76       | 65       | 72      |
| Marwick, 1994 [27]  | 82  | MIBI    | V        | Yes         | 2       | 65       | 68       | 66      |
| Senior, 1994 [66]   | 61  | MIBI    | V        | No          | 3       | 95       | 71       | 88      |
| Di Bello, 1996 [67] | 45  | MIBI    | V        | Yes         | 3       | 87       | 86       | 87      |
| Ifitih, 1996 [68]   | 38  | MIBI    | V        | No          | 2       | 79       | 90       | 82      |
| Kiscak, 1996 [69]   | 69  | MIBI    | V        | No          | 3       | 96       | 64       | 86      |
| Slavich, 1996 [70]  | 46  | MIBI    | V        | Yes         | ?       | 82       | 83       | 83      |
| San Roman, 1998 [71]| 92  | MIBI    | Q        | Yes         | 3       | 87       | 70       | 82      |
| Santoro, 1998 [44]$^a$ | 60  | MIBI    | Q        | Yes         | 3       | 91       | 81       | 87      |
| Elhendy, 1998 [72]  | 70  | MIBI    | V        | No          | ?       | 64       | 72       | 67      |

Abbreviations as defined in Table 1 and list of abbreviations

$^a$ 89% of studies with adenosine and 137 patients undergoing angiography

However, the sensitivity of exercise MPS for detecting angiographically defined CHD is consistently above 70%, but in the better designed studies it is in the region of 85–90% [13, 14, 15]. Reported specificity varies from 33% to 100% but in the better quality studies it is in the region of 70–75% [26, 27], with values up to 94% when ECG-gated imaging is used [73]. For pharmacological stress studies using thallium, a number of good quality studies show that sensitivity is in the region of 90% for both dipyridamole [21, 32, 35, 36] and adenosine [46, 51] and that specificity is 75–80% [18, 33, 34, 39, 50] although some studies have reported even higher values (95-100%) [21, 32, 46]. Results obtained using MIBI are similar to those obtained using thallium [40, 41, 43, 44, 52, 53, 54]. When dobutamine is used with thallium, the sensitivity is in the region of 90% while the specificity ranges from 81% to 100% [56, 57, 58, 59, 60]. When dobutamine is used with MIBI,
most studies have shown that the sensitivity is above 80% [53, 61, 62, 63, 66, 67, 70, 71] but the specificity ranges from 64% to 90% [68, 69].

Fewer diagnostic studies have been performed using tetrofosmin because of its more recent introduction commercially. For exercise studies using tetrofosmin, sensitivity and specificity range from 81% to 96% [22, 30, 31] and from 67% to 91% [22, 30] respectively.

Factors affecting observed diagnostic performance

When the reference standard for diagnosis, in this case coronary angiography, is not used in all patients and referral to angiography is more likely when MPS is abnormal, then the findings are affected by referral bias and specificity appears falsely low [74, 75, 76, 77, 78, 79, 80, 81]. Indeed, if only patients with abnormal MPS undergo angiography then the observed sensitivity will be 100% and the specificity 0%. Normalcy is therefore a better parameter for defining the performance of a test in patients without disease. It is the percentage of studies that are normal in a population with a low likelihood of CHD, defined clinically. Normalcy has been reported in a number of studies (Table 5) and the weighted average of normalcy is 89%.

Another form of referral bias is when mainly high-likelihood patients are referred for MPS, which increases apparent sensitivity because of the higher proportion of patients with more severe disease [75, 83]. Analysis of the tables above shows that mean sensitivity reduces from 92% to 87% when studies including patients with prior infarction are excluded. Sensitivity is also higher with more extensive and severe disease and lower with single-vessel disease or in those with stenoses involving branches of the major vessels (91% versus 83%).

The intensity of stress is also a confounding factor and several studies have shown that sensitivity is related to the intensity of exercise [14, 23, 84]. Anti-angina medication reduces sensitivity using dynamic exercise [85, 86] and medication should ideally be discontinued before diagnostic studies [87]. It is less clear whether medication reduces diagnostic sensitivity using vasodilator stress but reduced sensitivity has been observed [88].

Tracer activity below the diaphragm is commonly seen with MIBI and tetrofosmin and this can reduce accuracy in some studies [40, 45]. Other causes of artefact that can reduce specificity are photon attenuation and scatter, patient motion, low count statistics, reconstruction artefact or processing errors. Experienced practitioners can normally identify these problems and they maintain sensitivity and specificity not only by recognising common abnormal appearances but also by taking account of the clinical circumstances. Thus, studies where images are interpreted in the absence of clinical information can lead to relatively poor diagnostic performance [73]. Image quantification can help inter-observer variability but its value for accuracy is less clear, with some studies showing greater accuracy with quantification [11, 32, 47] and others no difference [12, 16, 17, 28, 83]. Correction for photon attenuation and scatter, using simultaneous or sequential transmission imaging, is also now feasible but its value is not yet clearly established [89, 90, 91, 92, 93].

ECG-gating is another option that improves diagnostic accuracy and it is now used routinely in many centres. This aids the distinction between true perfusion abnormality and artefact [94, 95, 96] and it provides additional prognostic information from global and regional left ventricular function [97].

Despite their different physical and imaging characteristics, all three radiotracers have comparable diagnostic accuracies for detecting CAD. This can be seen in the above tables and it has been confirmed clinically in a large randomised study (the ROBUST study) [55]. However, the technetium-99m labelled tracers have myocardial uptake curves that plateau at lower levels of hyperaemia than thallium, and it has been suggested that they may not perform well when used with vasodilator stress [98]. However, several studies with MIBI indicate that diagnostic accuracy is not compromised with vasodilators [36, 41, 42, 43, 44, 52, 53]. Studies using tetrofosmin with vasodilator stress are less consistent, with some reporting good diagnostic accuracy [55] and others

| Author, year [ref.] | No. | Tracer | Stress | Normalcy (%) |
|---------------------|-----|--------|--------|--------------|
| Iskandrian, 1989 [14] | 131 | $^{201}$Tl | Exercise | 94           |
| Maddahi, 1989 [15]  | 52  | $^{201}$Tl | Exercise | 86           |
| Van Train, 1990 [17] | 76  | $^{201}$Tl | Exercise | 82           |
| Coyne, 1991 [18]    | 45  | $^{201}$Tl | Exercise, adenosine | 80 |
| Kiat, 1992 [22]     | 55  | $^{201}$Tl | Exercise | 89           |
| Nishimura, 1991 [48] | 39  | $^{201}$Tl | Exercise | 92           |
| Nishimura, 1991 [48] | 39  | $^{201}$Tl | Adenosine | 95 |
| Van Train, 1994 [28] | 37  | $^{201}$Tl | Exercise | 81           |
| Kiat, 1990 [24]     | 8   | MIBI    | Exercise | 88           |
| Heo, 1994 [29]      | 61  | MIBI    | Exercise | 95           |
| Weighted average    | 543 |  |  | 89 |
showing reduced sensitivity in patients with mild disease [31, 99]. Reduced sensitivity has also been reported in some but not all studies of MIBI performed with dobutamine [69, 72].

Overall accuracy of MPS

In summary, therefore, despite the availability of three different tracers, several forms of stress and the confounding factors described above, it is reasonable for the purposes of this appraisal to consider MPS as a generic test without regard for the different ways in which it can be performed. When this is done, good quality studies show a sensitivity for CHD defined angiographically as high as 90% and a normalcy of 89%.

Prognosis

MPS and prognosis

For many patients with CHD, the assessment of prognosis, or likelihood of future cardiac events, is an essential step in choosing between medical management and revascularisation. The power of MPS for predicting future coronary events has been demonstrated in a large number of high-quality studies and in many thousands of patients. It is perhaps the area of nuclear cardiology where the evidence is most strong [100, 101, 102].

The most important variables that predict the likelihood of future events are the extent and severity of inducible ischaemia [103] but other predictors are increased lung uptake of thallium [104], stress-induced ventricular dilatation[105] and left ventricular ejection fraction [106, 107]. In general, markers of left ventricular dysfunction tend to predict cardiac mortality and inducible ischaemia predicts acute coronary syndromes [108, 109]. MPS has incremental prognostic value even after clinical assessment, exercise electrocardiography and coronary angiography [97, 110]. In other words, patients who appear to be high risk after coronary angiography can be separated into higher and lower risk groups by MPS.

Patients with abnormal MPS have on average an annual event rate (cardiac death or myocardial infarction) of 6.7% (Table 6). In contrast, it is an almost universal finding that normal MPS indicates good clinical outcome, irrespective of other features such as the presence of non-obstructive coronary disease. Thus 16 studies performed between 1994 and 2001, which reported 20,983 patients with normal MPS and a mean follow-up of 28 months, showed a rate of cardiac death or myocardial infarction of 0.7% per year, a rate similar to that of an asymptomatic population (Table 7) [111]. Similar findings have recently been reported in a multicentre registry of 4,728 patients [112]. Thus, whether minor coronary artery disease is present or not, further investigation can be avoided.

Patients with chest pain and a normal resting ECG who are able to exercise will often undergo exercise electrocardiography as the initial test for diagnosis and risk stratification. Intermediate risk results, however, occur in approximately 30–55% cases [128, 179] and it is in these patients that perfusion imaging has its greatest role. It has incremental prognostic value within this risk category, and there is a closer association of subsequent coronary angiographic data with the results of the perfusion scan than with the exercise electrocardiogram [126].

When the resting ECG is abnormal, exercise testing can provide some prognostic information from the exer-

### Table 6. Prognostic value of MPS in definite or suspected CHD (adapted from reference [111])

| Year | Author [ref.] | No. | Agent | Abnormal MPS (%) | Mean F/U (m) | HE (%) | HE with abnormal MPS (%) | HE with normal MPS (%) | RR |
|------|---------------|-----|-------|------------------|--------------|--------|-------------------------|------------------------|----|
| 2001 | Galassi [113] | 459 | Tetro | 77               | 37           | 2.5    | 3.0                     | 0.9                    | 3.25 |
| 1999 | Vanzetto [114] | 1,137 | 201Tl | 66               | 72           | 1.5    | 2.0                     | 0.6                    | 3.53 |
| 1998 | Hachamovitch [108] | 5,183 | MIBI/201Tl | 43 | 21.4 | 3.0 | 5.9 | 0.8 | 7.50 |
| 1998 | Olmos [115] | 225 | 201Tl | 49               | 44.4         | 1.8    | 2.7                     | 0.9                    | 2.86 |
| 1998 | Alkeylani [116] | 1,086 | MIBI | 62               | 27.6         | 3.4    | 5.0                     | 0.6                    | 8.92 |
| 1997 | Snader [117] | 3,400 | MIBI | 21              | ~24          | 1.6 (ACM) | ~3.8 (ACM) | ~1.0 (ACM) | 3.75 |
| 1997 | Boyne [118] | 229 | MIBI | 32               | 19.2         | 2.2    | 8.7                     | 0.8                    | 10.67 |
| 1997 | Geleijnse [119] | 392 | MIBI | 67               | 22           | 6.0    | 5.1                     | 0.8                    | 10.67 |
| 1995 | Heller [120] | 512 | MIBI | 58               | 12.8         | 4.6    | 6.9                     | 1.3                    | 5.29 |
| 1994 | Machecourt [121] | 1,926 | 201Tl | 63               | 33           | 2.0    | 2.9                     | 0.5                    | 6.23 |
| 1994 | Kamal [122] | 177 | 201Tl | 83               | 22           | 4.3    | 5.2                     | 0       | –  |
| 1994 | Stratmann [123] | 534 | MIBI | 66               | 13           | 10.1   | 14.3                    | 1.6                    | 9.12 |
| 1994 | Stratmann [124] | 521 | MIBI | 60               | 13           | 4.2    | 6.7                     | 0.5                    | 14.60 |

ACM, All-cause mortality; HE, hard event (cardiac death or non-fatal MI); RR, relative risk; other abbreviations as defined in Table 1 and list of abbreviations.
cise duration but ECG changes are unhelpful. In contrast, MPS maintains its prognostic power [130].

Prognosis can be assessed in patients who are unable to exercise using MPS with pharmacological stress. The risk of cardiac death in these patients is higher than in patients able to exercise, most likely because of higher underlying likelihood of disease [131].

MPS as the gatekeeper to angiography

Because of its prognostic power, MPS can be used as the gatekeeper to coronary angiography. Bateman and colleagues showed that referral to coronary angiography after normal, mild to moderately abnormal and severely abnormal perfusion scans was 3.5%, 9% and 60% respectively [132]. Importantly, a policy of selective referral to coronary angiography based upon high-risk findings is defensible, patients with mild to moderate abnormalities managed medically having outcomes comparable to those undergoing invasive evaluation and subsequent angioplasty [133].

Risk assessment before non-cardiac surgery

MPS can provide useful information about cardiac risk in patients requiring non-cardiac surgery although these patients are generally at low risk and the predictive value of a normal perfusion study is greater than that of an abnormal study. In a meta-analysis of 3,718 patients undergoing vascular and other surgery, the positive predictive value of inducible ischaemia for peri-operative death or infarction was 12.9% compared with a negative predictive value of 98.6%, a risk ratio of 9.1 (Table 8).

The ACC/AHA algorithm for pre-operative risk assessment considers initially the urgency for surgery, its inherent cardiac risk, the patient’s risk factors and exercise tolerance [134]. Patients with only minor clinical predictors (advanced age, abnormal resting ECG, previous stroke or uncontrolled hypertension) who require low- to moderate-risk surgery are at low risk and do not require further investigation. Patients with intermediate clinical predictors (mild angina, prior infarction, treated heart failure or diabetes) or with minor predictors and reduced exercise tolerance need further assessment before moderate- or high-risk surgery. Patients at high clinical risk (recent infarction or unstable angina, uncontrolled heart failure or significant arrhythmias) require investigation before any sort of surgery. When further investigation is required, the choice lies primarily between the exercise ECG and MPS, the latter usually being reserved for patients with an abnormal resting ECG or who are unable to exercise. In general, patients identified as low risk can undergo surgery without further investigation. All other patients require aggressive medical management at the time of surgery, intervention usually being reserved for those in whom revascularisation is indicated regardless of the need for surgery.

Table 7. Prognostic value of normal MPS in patients presenting with stable chest pain (adapted from reference [111])

| Year | Author [ref.] | No. | Agent | Normal MPS (%) | Mean F/U (months) | HE with normal MPS (%) per yr |
|------|---------------|-----|-------|---------------|-----------------|--------------------------|
| 2001 | Galassi [113] | 459 | Tetro | 23            | 37              | 0.9                      |
| 2000 | Groutars [125]| 236 | Tetro$^{201}$Tl | 100             | 25              | 0.4                      |
| 1999 | Gibbons [126] | 4,473 | $^{201}$TI/MIBI | 100             | 36              | 0.6                      |
| 1999 | Soman [127]  | 473 | MIBI  | 100           | 30              | 0.2                      |
| 1999 | Vanzetto [114]| 1,137 | $^{201}$TI | 34             | 72              | 0.6                      |
| 1998 | Hachamovitch [108]| 5,183 | MIBI/$^{201}$TI | 57             | 21.4             | 0.8                      |
| 1998 | Olmos [115]  | 225 | $^{201}$TI | 51             | 44.4             | 0.9                      |
| 1998 | Alkeylani [116]| 1,086 | MIBI  | 38            | 27.6             | 0.6                      |
| 1997 | Snader [117] | 3,400 | $^{201}$TI | 79            | ~24             | ~1.0 (ACM)               |
| 1997 | Boyne [118]  | 229 | MIBI  | 68            | 19.2             | 0.8                      |
| 1997 | Geleijnse [119]| 392 | MIBI  | 33            | 22              | 0.8                      |
| 1995 | Heller [120] | 512 | MIBI  | 42            | 12.8             | 1.3                      |
| 1994 | Machecourt [121]| 1,926 | $^{201}$TI | 37            | 33              | 1.3                      |
| 1994 | Kamal [122]  | 177 | $^{201}$TI | 17            | 22              | 0                        |
| 1994 | Stratmann [123]| 534 | MIBI  | 34            | 13              | 1.6                      |
| 1994 | Stratmann [124]| 521 | MIBI  | 40            | 13              | 0.5                      |
| Total|               | 20,963 |       | 53           | 28.3             | 0.7                      |

ACM, All-cause mortality; HE, hard event (cardiac death or non-fatal MI); RR, relative risk; other abbreviations as defined in Table 1 and list of abbreviations
Special groups

Women

Cardiovascular disease is the commonest cause of death in women in Europe [162]. Underlying mechanisms are complex, although increasing prevalence of risk factors and greater life expectancy play an important role. The prevalence of risk factors is higher in women than in men, and triglycerides, HDL-cholesterol, cigarette smoking and diabetes are particularly important [163]. In addition to the obvious hormonal influences in women, there are gender-related structural differences in plaque composition (more cellular fibrous tissue) [164] and incidence of sub-clinical atherosclerosis [165]. These factors may explain, in part, why women present with symptoms some 10 years later than men, are less likely to complain of chest pain and are more likely to suffer upper abdominal pain, dyspnoea, nausea and fatigue.

Diagnosis

In men, the exercise ECG is the conventional gatekeeper for invasive investigation and possible intervention when assessing known or potential CHD. In women, however, the exercise ECG has at best only moderate accuracy for the detection of CHD [166]. In contrast, MPS is equally accurate for the detection of disease in women and men [167].

Prognosis

Although initial prognostic data were acquired for largely male populations aged less than 70 years, recent studies have established that the prognostic power of normal and abnormal myocardial perfusion images is equally strong in men and women. In fact women with severe abnormalities may have a worse outcome than men with

| Year | Author [ref.] | No. | Inducible ischaemia (%) | MI/death (%) | PPV | NPV |
|------|---------------|-----|-------------------------|--------------|-----|-----|
| Vascular surgery | | | | | | |
| 1985 | Boucher [135] | 48 | 16 (33) | 3 (6%) | 19% (3/16) | 100% (32/32) |
| 1987 | Cutler [136] | 116 | 54 (47) | 11 (10%) | 20% (11/54) | 100% (60/60) |
| 1988 | Fletcher [137] | 67 | 15 (22) | 3 (4%) | 20% (3/15) | 100% (56/56) |
| 1988 | Sachs [138] | 46 | 14 (31) | 2 (4%) | 14% (2/14) | 100% (24/24) |
| 1989 | Eagle [139] | 200 | 82 (41) | 15 (8%) | 16% (13/82) | 98% (61/62) |
| 1990 | McEnroe [140] | 95 | 34 (36) | 7 (7%) | 9% (3/34) | 96% (44/46) |
| 1990 | Younis [141] | 111 | 40 (36) | 8 (7%) | 15% (6/40) | 100% (51/51) |
| 1991 | Mangano [142] | 60 | 22 (37) | 3 (5%) | 5% (1/22) | 95% (19/20) |
| 1991 | Straw [143] | 68 | n/a | 4 (6%) | n/a | 100% (21/21) |
| 1991 | Watters [144] | 26 | 15 (58) | 3 (12%) | 20% (3/15) | 100% (11/11) |
| 1992 | Hendel [145] | 327 | 167 (51) | 28 (9%) | 14% (23/167) | 99% (97/98) |
| 1992 | Leite [146] | 355 | 161 (45) | 30 (8%) | 17% (28/161) | 99% (160/162) |
| 1992 | Madsen [147] | 65 | 45 (69) | 5 (8%) | 11% (5/45) | 100% (20/20) |
| 1993 | Brown [148] | 231 | 77 (33) | 12 (5%) | 13% (10/77) | 99% (120/121) |
| 1993 | Kresowik [149] | 170 | 67 (39) | 5 (3%) | 4% (3/67) | 98% (64/65) |
| 1994 | Baron [150] | 457 | 160 (35) | 22 (5%) | 4% (7/160) | 96% (195/203) |
| 1994 | Pry [151] | 237 | 110 (46) | 17 (7%) | 11% (12/110) | 100% (97/97) |
| 1995 | Koutelou [152] | 106 | 47 (44%) | 3 (3%) | 6% (3/47) | 100% (49/49) |
| 1995 | Marshall [153] | 117 | 55 (47%) | 12 (10%) | 16% (9/55) | 97% (33/34) |
| 1997 | Van Damme [154] | 142 | 48 (34%) | 3 (2%) | n/a | n/a |
| Non-vascular surgery | | | | | | |
| 1990 | Camp [155] | 40 | 9 (23) | 6 (15%) | 67% (6/9) | 100% (23/23) |
| 1991 | Iqbal [156] | 31 | 11 (41) | 3 (11%) | 27% (3/11) | 100% (20/20) |
| 1992 | Coley [157] | 100 | 36 (36) | 4 (4%) | 8% (3/36) | 98% (63/64) |
| 1992 | Shaw [158] | 60 | 28 (47) | 6 (10%) | 21% (6/28) | 100% (19/19) |
| 1993 | Takase [159] | 53 | 15 (28) | 6 (11%) | 27% (4/15) | 100% (32/32) |
| 1994 | Younis [160] | 161 | 50 (31) | 15 (9%) | 18% (9/50) | 98% (87/89) |
| 1996 | Stratmann [161] | 229 | 67 (29%) | 10 (4%) | 6% (4/67) | 99% (91/92) |
| Weighted average | | 3,718 | 246 (7%) | 12.1% (186/1,397) | 98.6% (1,549/1,571) |

MI, Myocardial infarction; NPV, negative predictive value; PPV, positive predictive value; n/a, not available
severe abnormalities. In a study of 1,394 women followed for a mean of 20 months, MPS was able to stratify women according to risk irrespective of presenting likelihood of CHD [168]. In a further study of 3,402 women, normal MPS predicted a favourable outcome and the extent of inducible ischaemia was strongly associated with mortality [169]. Three-year survival reduces from 99% to 85% as the number of vascular territories with perfusion abnormality increases from zero to three [170]. This prognostic power is additional to clinical information and information from the exercise ECG [20, 168, 171, 172].

Acute myocardial infarction

Women with acute myocardial infarction have an increased probability of surviving to reach hospital but they have a higher mortality at 30 days than men [173]. MPS is helpful for triage in the general population presenting with acute chest pain but there are few data on MPS in this setting in women [174].

The elderly

An ageing population leads to increasing use of NHS resources. Because the elderly have reduced capacity for exercise and frequently have abnormal resting ECGs, the exercise ECG is of limited use [175] but MPS using pharmacological stress is effective and it retains its diagnostic and prognostic power [176, 177, 178, 179].

Diabetes

Diabetes is a vascular disease. Type 2 diabetes is associated with the same cluster of risk factors as cardiovascular disease and life expectancy is reduced by 8–10 years in the 40- to 70-year age group. Type 1 diabetes carries the same mortality even though it is not associated with the same risk factors [180].

Several studies have demonstrated the prognostic power of MPS in diabetic patients [181, 182, 183]. In a study of 1,371 patients, normal MPS was associated with an incidence of cardiovascular events of 1–2% per year, while the incidence was greater than 7% per year in those with severe perfusion abnormalities [184]. Multivariate analysis has shown that MPS abnormalities, retinopathy and duration of diabetes are independent predictors of cardiac events [185]. It has been suggested that MPS might be used to screen for CHD in high-risk asymptomatic diabetics, and a multicentre clinical trial to evaluate the effectiveness of this approach is in progress [186].

Ethnicity

South Asians resident in the UK have a 40–50% higher mortality from CHD than the population average, the reason for which is not clearly defined. MPS is equally effective in South Asians and Afro-Caribbeans for the diagnosis of CHD and assessment of prognosis, although account should be taken of the different CHD profiles [187, 188, 189].

Revascularisation

Before revascularisation

MPS is superior to the exercise ECG for the detection of myocardial ischaemia and it provides independent and incremental information in predicting future cardiac events [190, 191]. This applies in almost all clinical circumstances, including suspected CHD, stable angina, after stabilisation of acute coronary syndromes and before non-cardiac surgery. It also applies before and after myocardial revascularisation and hence the technique is valuable in assessing the need for and the outcome of intervention [192].

In patients with ischaemic left ventricular dysfunction, MPS can define the need for revascularisation by determining the presence and extent of ischaemia and of viable but hibernating myocardium [193, 194, 195, 196] (Table 9). This is particularly the case with severe left ventricular dysfunction, when MPS can predict the improvement in left ventricular function and the overall prognosis [181, 197, 198]. MPS is most helpful when left ventricular ejection fraction is severely reduced, and in these high-risk patients rest imaging alone can detect viable myocardium [199, 200, 201, 202, 203, 204].

After revascularisation

MPS is more sensitive than the exercise ECG in detecting inducible ischaemia if angina recurs after revascularisation, and it can be used to evaluate the success of revascularisation [205]. It is an accurate technique for detecting bypass graft occlusion or stenosis, with sensitivity and specificity of 81% and 79%, respectively [206, 207, 208] (Table 10).

Table 9. Indications for MPS before revascularisation

| Detection, localisation and quantification of ischaemia as a cause of symptoms |
| Detection of silent ischaemia |
| Risk stratification and prognostication |
| Detection and quantification of viable/hibernating myocardium |
Chest pain and exercise electrocardiography are largely unhelpful in identifying patients at risk after revascularisation [209] but MPS is of proven value [197, 208, 210, 211, 212]. In the NIH-sponsored Emory Angioplasty versus Surgery Trial (EAST), inducible perfusion abnormalities 1 year after revascularisation separated the patients into low- and high-risk groups [213]. This prognostic power lasts for a considerable time and the technique is valuable for long-term follow-up [209, 211, 214, 215, 216, 217].

Following percutaneous intervention the situation is more complex. Normal perfusion excludes restenosis and indicates a good prognosis [212] but inducible perfusion abnormalities can be seen in the first 6 weeks after angioplasty in the absence of restenosis and these are thought to correspond to abnormal small vessel or endothelial function [218]. Thereafter an abnormal perfusion study is predictive of adverse cardiac events [219].

### Acute coronary syndromes

Cardiological management of patients with acute coronary syndromes (ACS) was an important implication of the National Service Framework for CHD [220]. The joint BCS and RCP guidelines for the management of ACS without persistent ST segment elevation [221] have recommended that dedicated units for the assessment of low-risk patients with acute chest pain should be evaluated based upon evidence from the USA [222] and the UK [223]. High-risk patients, including those with raised troponin, persistent symptoms and/or ST segment changes or adverse exercise ECG results, should have urgent coronary angiography, with the intention of revascularisation to improve outcome. However, if symptoms settle on medical therapy and there are no clinical markers of high risk, MPS can be used for risk stratification [224, 225]. This concept applies across the spectrum of ACS, from patients without diagnostic ECG changes, to unstable angina (UA), to non-ST segment elevation myocardial infarction (NSTEMI) and to ST segment elevation myocardial infarction (STEMI). Risk assessment, together with appropriate aggressive secondary prevention, is particularly helpful in the UK situation of uneven access to revascularisation, and allows for appropriate prioritisation of patients.

### Imaging in the emergency department

The relationship between imaging and clinical outcome

There is a substantial body of literature evaluating rest MPS in patients presenting with acute chest pain and suspected ACS. When tracer is injected during pain, MPS has 96% sensitivity for severe coronary stenosis compared with 35% sensitivity for the resting ECG [226] and as much as 20% of the myocardium can be abnormal when the ECG is normal or non-diagnostic [227]. Patients with abnormal MPS have a substantially higher likelihood of adverse cardiac events during hospitalisation and follow-up (Fig. 1) [228]. Conversely, MPS has a negative predictive value for ruling out myocardial infarction of 99% or more in all studies (Fig. 2) [228, 229, 230]. Consequent reduction in the missed infarction rate from 1.8% to 0.1% has important implications for patient outcome and the cost-effectiveness of management [231, 232].
Non-ST segment elevation myocardial infarction and unstable angina

There is general agreement that the half of the patients with UA and high-risk clinical features should undergo prompt coronary angiography, but there is less agreement on the management of the other half who are at intermediate or low clinical risk, as originally defined by the US Agency for Health Care and Policy Research Guidelines [237]. MPS is known to be able to separate these patients into a low-risk group that might be managed conservatively without angiography and a higher risk group that might benefit from intervention, and recent randomised trials support this strategy [238]. Accordingly, MPS in this setting is a class 1 indication under AHA/ACC guidelines [234].

The main benefit of intervention in ACS in RITA 3 was in reducing refractory angina, which could have been identified by a conservative strategy [239], and a recent meta-analysis has suggested no clear superiority of early intervention [240]. These data therefore suggest that a conservative strategy in which stabilised patients are risk-stratified by MPS offers similar outcomes with fewer invasive procedures. This concept is relevant for UK practice and the use of MPS as a gatekeeper to angiography in stabilised ACS might reduce the trend towards diminishing marginal returns of early invasive management.

A recent retrospective analysis of the TIMI-IIIB data has shown that a simple clinical score is able to classify over half the population as low risk [241], suggesting a substantial group of patients in whom MPS might be used for further risk stratification. In TACTICS-TIMI18, the troponin positive subgroup (60% of the total population) had a larger reduction in death or myocardial infarction with the early invasive strategy, leaving 40% who might benefit from non-invasive risk stratification using MPS [242]. The UK guidelines [221] suggest a conservative strategy even for patients with an abnormal troponin providing that symptoms have settled for 48 h and there are no other high-risk features.

Comparison with enzymatic markers of myocardial damage

Acute MPS has the potential to identify ACS much earlier in its evolution than enzyme markers, with an early sensitivity for myocardial infarction of 92% compared with only 39% for troponin I assayed at the same time [233].

Randomised trials

Two randomised controlled trials have shown that MPS can improve triage decisions in the emergency department. Stowers and colleagues randomised 46 patients with acute chest pain and non-diagnostic ECGs to an MPS-guided strategy or conventional care; the former incurred less cost, shorter hospital and intensive care stays, and fewer cardiac catheterisations but there was no difference in outcome at 30 days [234]. The ERASE trial (Emergency Room Assessment of Sestamibi for Evaluation of Chest Pain) randomised 2,127 similar patients to similar strategies and showed fewer admissions of patients shown ultimately not to have ACS (20% reduction, odds ratio 0.68, P<0.001) [235]. This benefit applied independently of age, gender, risk factors or imaging experience.

Suspected acute myocardial infarction

The impetus for chest pain assessment units in an emergency admissions area is supported by the fifth joint report of the RCP and BCS on provision of cardiothoracic services [236].

ST segment elevation myocardial infarction

The majority of patients who survive the initial acute stage of myocardial infarction will have a relatively stable course, and current guidelines recommend non-invasive risk assessment before hospital discharge [243, 244]. MPS with vasodilator stress can be performed safely as early as 3 days after infarction, before the majority of recurrent clinical events occur, and can be used to guide early discharge [245]. ECG-gated imaging also provides a measure of left ventricular function, which has additional value in predicting outcome (Fig. 3) [246]. Coronary angiography does not improve a prog-
Travin and colleagues used MPS in 134 patients within 14 days of uncomplicated infarction and showed that the extent of ischaemia was the only significant predictor of future cardiac events on Cox regression analysis (Fig. 4) [248]. Similarly, Basu and colleagues in the UK showed a hazard ratio of 8.1 (95% CI 2.7–23.8, \(P<0.001\)) for coronary events comparing patients with and without inducible perfusion abnormalities [249]. Patients with no evidence of inducible ischaemia within the infarct zone, even in the presence of residual stenosis of the infarct-related artery, were found by Ellis and colleagues to derive no benefit from angioplasty [250].

Several principles underlie why a more accurate diagnostic test with additional prognostic information, such as MPS, can be more cost-effective even if it is more expensive than an alternative test such as the exercise ECG (Table 11) [251].

For instance, Fig. 5 illustrates that when a patient with a presenting likelihood of CHD of 50% has an abnormal exercise ECG the post-test likelihood of disease is 73%, which is not sufficiently high to be confident of the diagnosis. A subsequent abnormal MPS gives a likelihood of 96% but if the same patient had gone directly to MPS the post-test likelihood would have been 90%, which should be sufficiently high to diagnose the presence of CHD, depending upon the clinical circumstances.
Costs

True costs, reflecting consumption of resources, are difficult to estimate. Some analyses of cost-effectiveness have used prices as a surrogate for cost, which may be valid from the perspective of the patient or referring clinician, but is less helpful from the perspective of the healthcare provider. Two studies have estimated cost, one using UK figures [252] and the other USA figures [253], but the findings are similar, at £220 in the UK and £179 (range £159–348) in the USA (Table 12). These costs are sensitive to throughput. A reasonable throughput per camera is 2,000 patients per year but this can be increased to as much as 4,000 in high-volume centres by running the camera 12 h per day and 6 days per week.

Cost-effectiveness analysis

Although randomised controlled and blinded trials are often used to evaluate the cost-effectiveness of therapy, this study design is difficult or impossible in the case of diagnostic testing. However, some data have been derived from decision analytical models and these have demonstrated the cost-effectiveness of MPS both in patients presenting with stable chest pain syndromes [254] and in pre-operative risk assessment [255]. Garber and Solomon showed that in 55-year-old men presenting with chest pain, a strategy of MPS proceeding to angiography compared with exercise ECG proceeding to angiography cost £25,000 per quality-adjusted life-year (QALY) [256], a figure that is generally regarded as acceptable [257]. The benefit of MPS would have been even greater if a more realistic model had been used, since it was assumed that all patients with disease proceed to angiography, whereas, as demonstrated above, it is possible to treat low-risk patients with CHD without the need for angiography. Patterson et al. also found initial testing with MPS to be more cost-effective than the exercise ECG although, again, the model assumed that all patients with disease undergo angiography [258]. Kuntz found a higher incremental cost-effectiveness of initial MPS over the exercise ECG of £34,250 in a 55-year-old man with atypical chest pain but they used an unrealistically low specificity of 64% for MPS and again assumed that all patients with disease undergo angiography [259]. It would be valuable to repeat these models assuming that patients with abnormal but low-risk non-invasive tests are treated medically in the first instance, since the prognostic power of MPS is likely to lead to even greater cost-effectiveness.

Interpretation of these numbers should be placed in the context of other generally accepted medical interventions. For example, coronary artery bypass grafting for patients with triple-vessel coronary artery disease and severely impaired left ventricular function costs £25,500 per QALY gained [260] and cholesterol-lowering therapy in a 60-year-old man with cholesterol of 7.5 mmol/l costs approximately £30,000 per QALY [261]. Thus, MPS appears to be a cost-effective use of resources compared with other generally accepted medical procedures.

Mathematical simulations have the advantage of using data from diverse sources or from expert opinion, but they are limited by a lack of real-world effectiveness data. However, two controlled clinical studies have demonstrated savings for similar outcomes using MPS in patients presenting with chest pain. The EMPERE study compared patients presenting with stable chest pain syndromes to centres that routinely use MPS and those that do not in each of four European countries [252]. Diagnostic strategies using MPS were cheaper and equally effective compared with those that did not, both for the costs of diagnosis and for overall 2-year management costs, but patient outcome was the same (Fig. 6).

Table 12. Cost of common diagnostic tests calculated using principles that estimate the true consumption of resources. Estimates are shown for the UK (EMPIRE study) [252] and the USA [253]

| Test                          | EMPIRE (£) | USA average (£) | USA range (£) |
|-------------------------------|------------|-----------------|---------------|
| Rest ECG                      | 20         | 55              | 39–207        |
| Exercise ECG                  | 70         | 172             | 55–288        |
| Rest echocardiography         | 100        | 179             | 159–348       |
| CT                            | 172        | 529             | 318–739       |
| MPS                           | 220        | 771             | 582–891       |
| Coronary angiography          | 1,100      | 1,097           | 516–2,873     |

CT, Computed X-ray tomography; MPS, myocardial perfusion scintigraphy; MRI, magnetic resonance imaging; PET, positron emission tomography.

Fig. 6. The 2-year costs of diagnosis (dark grey) and management (light grey) in patients without CHD but presenting with stable chest pain syndromes, according to strategy of investigation and type of hospital. The strategies of investigation are: 1, exECG-angio; 2, exECG-MPS-angio; 3, MPS-angio; 4, angio. MPS, Regular user of MPS; non-MPS, occasional user of MPS [252]
The END study was a larger (11,372 patients) registry study with very similar findings of 30–40% savings in costs over 2.5 years in patients with stable chest pain syndromes undergoing initial MPS and selective angiography (Fig. 7) [262]. An additional series of 9,521 patients showed that MPS was more cost-effective than stress echocardiography in patients with known CHD and stable chest pain at $39,347 per life-year saved [263], and a separate modelling study also found MPS to be more cost-effective than stress echocardiography [264].

Other clinical studies indirectly support the cost-effectiveness of MPS. In a US practice making routine use of MPS, the number of patients with normal MPS proceeding to angiography is 1% [265], whereas in a UK rapid access chest pain clinic that makes little use of MPS, coronary angiography rates are high and 56% of coronary angiograms in women are normal [266]. It has been estimated that routine use of MPS in this setting would reduce cost by £65,000 per year, mainly by reducing the normal coronary angiography rate [267]. Similarly, in the USA it has been estimated that about one-third of referrals to coronary angiography are inappropriate [268].

**Clinical outcomes**

Modelling studies indicate that clinical outcome is improved by MPS at a cost per QALY that is acceptable and that life expectancy is increased by between 7 days and 2 years [255]. Because of the scale and nature of the studies that would be required, it has been more difficult to confirm this finding in clinical studies, but in a re-analysis of the END data [262] Shaw and colleagues have shown that testing with initial MPS adds between 1 and 2 years of life [269] and in a separate study they showed that MPS added 0.5 years compared with stress echocardiography [263].

**Current clinical guidelines for MPS**

This section reviews some of the current guidelines for the use of MPS in CHD, which in most cases have been based upon a review of the relevant evidence (Table 13).

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**Table 13. Guideline documents and statements**

| Statement                                                                 | Source             | Reference |
|---------------------------------------------------------------------------|--------------------|-----------|
| Guideline update for exercise testing, 2002                              | ACC/AHA            | [270]     |
| Guidelines for clinical use of cardiac radionuclide imaging              | ACC/AHA/ASNC       | [271]     |
| Guideline update for the management of patients with chronic stable angina, 2002 | ACC/AHA            | [272]     |
| The role of myocardial perfusion imaging in the clinical evaluation of coronary artery disease in women | ASNC               | [273]     |
| Updated imaging guidelines for nuclear cardiology procedures: part 1     | ASNC               | [274]     |
| Management of acute myocardial infarction in patients presenting with ST segment elevation | ESC                | [243]     |
| Management of acute coronary syndromes in patients presenting without ST segment elevation | ESC                | [275]     |
| Investigation and management of stable angina: revised guidelines 1998   | BCS/RCP            | [276]     |
| National Service Framework for Coronary Heart Disease                    | DoH                | [220]     |
| Guidelines for tomographic radionuclide myocardial perfusion imaging    | BNCS/BNMS          | [277]     |
| Guideline for the management of acute coronary syndromes without persistent ECG ST segment elevation | BCS/RCP            | [278]     |

ACC, American College of Cardiology; AHA, American Heart Association; ASNC, American Society for Nuclear Cardiology; ESC, European Society of Cardiology; BCS, British Cardiac Society; RCP, Royal College of Physicians; DoH, UK Department of Health; BNCS, British Nuclear Cardiology; BNMS, British Nuclear Cardiology Society
Diagnosis and assessment of stable chest pain

The superior diagnostic accuracy of MPS compared with the exercise ECG is widely recognised in the setting of stable chest pain syndromes and chronic stable angina (Table 14). Both European and American guidelines recommend MPS in patients with an intermediate pre-test likelihood of coronary artery disease. In the UK, the National Service Framework for CHD does not give specific recommendations, although it does comment on spe-

| Body/guidelines | General | Unable to exercise | Abnormal ECG | Women |
|------------------|---------|-------------------|--------------|-------|
| ACC/AHA stable angina guidelines 2002 [272] | Patients with intermediate likelihood of CHD (2b/B) | Intermediate likelihood of CHD (1/B) | Intermediate likelihood of CHD and ECG with pre-excitation (1/B), ST depression (1/B), ventricular pacing (1/C), LBBB (1/B), digoxin or LVH with minor ST change (2b/B), these ECGs with low or high likelihood of CHD (2b/B) | Indications for MPS are similar in men and women |
| ASNC updated imaging guidelines [274] | Diagnosis or prognosis in known/possible CHD | As per general recommendations, but with pharmacological stress | LBBB specifically recommended | No comment |
| ACC/AHA/ASNC guidelines for clinical use of radionuclide imaging 2003 [271] | To identify extent, site and severity of CHD | Pharmacological stress with MPS is “appropriate option” | Vasodilator stress with MPS recognised as optimal (mainly LBBB) | MPS is “logical” test |
| ACC/AHA stress testing guidelines 2002 | Low or intermediate likelihood of CHD: exercise test with MPS | Low or intermediate likelihood of CHD: pharmacological stress with MPS | Vasodilator stress for LBBB, paced rhythm, pre-excitation, ST depression (>1 mm) | MPS if reduced exercise tolerance or false positive exercise ECG suspected |
| ASNC consensus on women with IHD | MPS if reduced exercise tolerance | MPS if abnormal resting ECG | MPS if intermediate risk exercise ECG, in diabetic women, or in those with reduced functional capacity |
| BNCS/BNMS guidelines for SPET [277] | Assess patients with suspected CHD |
| NSF for Coronary Heart Disease Standard | MPS when diagnosis is uncertain | “Alternate test”, e.g. thallium scan | Other test may be needed |
| BCS/RCP guidelines for the investigation of stable angina [276] | Submaximal exercise ECG | Pharmacological MPS | MPS may be first-line (B) | MPS as first-line investigation |

Abbreviations as defined in Table 13 and the list of abbreviations

\(^a1, 2a, 2b, 3 = \text{class of recommendation; } A, B, C = \text{level of evidence}\)
specific subgroups [220]. Current BCS guidelines suggest that MPS is helpful after the exercise ECG if there is equivocal ST segment change, a negative test with a high pre-test likelihood of disease or a positive test with a low pre-test likelihood [276]. The BNMS/BNCS guidelines suggest that MPS is a useful procedure in most patients with suspected coronary artery disease [277].

Women

All of the guidelines recognise the reduced accuracy of the exercise ECG in women, but the degree to which MPS is recommended as an alternative first-line investigation, as opposed to a second-line investigation after the exercise ECG, is variable. The American guidelines suggest selective use [270, 272]. The American Society of Nuclear Cardiology states that MPS should be considered in all symptomatic women with an intermediate likelihood of CHD after an exercise ECG or as a first test if the resting ECG is abnormal, in diabetics or if poor exercise capacity is predicted [273]. British guidelines are conflicting. The National Service Framework proposes an exercise ECG for nearly all patients and, although it recognises problems with interpretation in women, it does not specifically advise on MPS unless exercise is not possible [220]. However, the BCS proposes MPS as a first-line test in all women with suspected coronary artery disease [276].

Abnormal resting ECG

ST segment displacement with exercise is an unreliable indicator of ischaemia in patients with LBBB, ventricular pacing, resting ST segment depression greater than 1 mm or pre-excitation. Two of the American guidelines recommend MPS with pharmacological stress for patients with LBBB or ventricular pacing on ECG (class I indication) [270, 272] and MPS is recommended for patients with pre-excitation or resting ST segment change. The initial test may be coronary arteriography if clinical features suggest high risk. MPS is suggested for patients taking digoxin, although this is not common to all of the guidelines. In the UK, the NSF states that MPS is indicated in patients with a high likelihood of a false positive exercise ECG, and an abnormal resting ECG is probably included in this statement [220]. The BCS suggests that MPS should be the initial investigation in patients with resting ECG abnormalities [276].

Inability to exercise

All guidelines propose MPS with pharmacological stress as a suitable test for the diagnosis of chest pain. Class I status is given by the American guidelines when there is intermediate pre-test likelihood of disease or previous coronary revascularisation [272]. In addition, vasodilator stress with MPS is preferred to stress echocardiography in patients with left bundle branch block (LBBB) or paced rhythm. The BCS guidelines make pharmacological stress with MPS the first-line investigation for this indication [276] and the National Service Framework for Cardiovascular Disease (NSF) indicates that alternatives to the exercise ECG (such as “thallium scan”) should be available [220].

Assessment before or after revascularisation

MPS is an accurate method for assessing the haemodynamic significance of known coronary lesions, identifying the site for potential revascularisation and assessing the result of previous coronary angioplasty or bypass surgery (Table 15). The exercise ECG performs poorly in...
these areas. Two of the American guidelines recommend MPS to identify the target lesion for coronary intervention and to assess symptomatic patients following bypass surgery (class 1 indications) [270, 272]. These indications are also mentioned in the joint BCS/BNCS/BNMS practice guidelines [277] but the area is not covered by the BCS guidelines on angina or by the NSF.

**Table 16. Recommendation for MPS in acute coronary syndromes**

| Body | NSTEMI | STEMI |
|------|--------|-------|
| ASNC updated imaging guidelines [274] | Risk stratification post ACS  
Exercise stress  
Pharmacological stress if unable to exercise | Risk stratification post MI  
Exercise stress  
Pharmacological stress if unable to exercise  
Early risk stratification post MI-vasodilator stress |
| ACC/AHA/ASNC guidelines for clinical use of radionuclide imaging 2003 [271] | Assess degree and site of ischaemia/  
culprit lesion (1)  
Risk stratification after medical treatment (2a) | Demonstration of stress ischaemia  
post MI (1)  
Size of infarct or risk territory (rest study) (2a) |
| ACC/AHA stress testing guidelines 2002 [270] | Risk stratification in low-risk patients | MPS after mildly abnormal standard exercise ECG test  
MPS first-line if abnormal ECG or inability to exercise, in presence of moderately low risk |
| BNCS/BNMS guidelines for SPET [277] | Pre-discharge testing suggested for risk stratification  
Pharmacological stress for poor exercise capacity  
MPS for low-risk patients with inconclusive exercise ECG | Determine prognosis after MI |
| European report on management of NSTEMI [275] | Risk stratification for low-risk  
and possibly intermediate-risk patients. MPS defines extent of ischaemia and is gatekeeper to invasive management | |
| European report on STEMI management [243] | Pharmacological MPS if unable to exercise  
Exercise ECG for others  
Angiography for high-risk patients | Risk stratification for low-risk  
and possibly intermediate-risk patients. MPS defines extent of ischaemia and is gatekeeper to invasive management |
| BCS/RCP guideline for ACS without ST segment Elevation 2001 [278] | | |

NSTEMI, Non-ST segment elevation myocardial infarction; STEMI, ST segment elevation myocardial infarction; ACS, acute coronary syndromes  

^a Numbers in parentheses refer to the class of recommendation

American guidelines recommend MPS for risk stratification in low-risk medically stabilised patients. Recent UK guidelines recommend MPS in stabilised patients who cannot exercise [278]. Otherwise the standard exercise ECG is mainly suggested, although other stress tests are alluded to.

**ST elevation myocardial infarction**

**Risk stratification after acute coronary syndromes**

**Non-ST elevation myocardial infarction**

European guidelines are that MPS should be performed for risk stratification after NSTEMI in patients who cannot exercise, in those with unhelpful exercise ECG tests and in women [275]. American guidelines also emphasise its use in low-risk medically stabilised patients. Recent UK guidelines recommend MPS in stabilised patients who cannot exercise [278]. Otherwise the standard exercise ECG is mainly suggested, although other stress tests are alluded to.
and indicate that an imaging technique is superior to the exercise ECG [243].

Assessment of ischaemic left ventricular dysfunction

MPS is a key technique in the assessment of patients with ischaemic left ventricular dysfunction. Both European and American bodies recommend the technique after STEMI in patients with poor systolic function [243, 271] (Table 17). Thallium is specifically mentioned by the American guidelines for the assessment of myocardial viability, although gated imaging using technetium-99m tracers can be particularly helpful. The joint BNCS/BNMS guidelines propose this as one of the four main indications for MPS [277].

Service provision

This section focuses mainly on service provision in the UK but the principles are relevant in other European countries.

Current UK practice

The foregoing demonstrates that the effectiveness and cost-effectiveness of MPS support its use for the diagnosis and management of patients with suspected and known CHD. Accordingly, the technique is an integral part of UK and other clinical guidelines and it has long been used routinely in many centres. However, there is a general perception among those familiar with the field that the technique is not used to its full potential and that service provision in the UK has three main problems:

1. MPS is either not available or not requested in patients where the evidence and guidelines suggest benefit. An example might be the lack of nuclear cardiology support for many rapid access chest pain clinics [266, 267].
2. MPS is available but the waiting time is too long for the test to be clinically useful.
3. MPS provision is not of a uniform high standard in all centres.

MPS activity in the UK

Since 1988 the BNCS has conducted regular surveys of nuclear cardiology practice. The 1988 [279], 1994 [280] and 1997 [281] surveys are published and data from the 2000 survey are available on request. The number of MPS studies performed per million population per year (pm) has increased over this period at a linear annual rate of 26% or at a compound rate of 12.5% (Fig. 8). Nevertheless, the figure for 2000 was still only 1,200 pm, with a median number of studies per centre of 256 per year. Comparative data from 1994 show that the UK figure at this time, 560 pm, was significantly below the European average of 2,200 pm and very small compared with a comparable US figure of 10,000 pm (Fig. 9) [280].

Table 17. Recommendations for MPS for the assessment of ischaemic left ventricular dysfunction

| Body | Recommendation |
|------|----------------|
| ACC/AHA/ASNC guidelines for clinical use of radionuclide imaging 2003 [271] | Assess myocardial viability in LV impairment, $^{201}$TI suggested |
| BNCS/BNMS guidelines for SPET [277] | Assess myocardial viability and hibernation |
| European Report on STEMI management [243] | MPS recommended to assess viability after angiography if LV impaired Assess viability/ischaemia in most patients (imaging study preferred) |
cols it is relatively straightforward to perform the technical aspects of the study, but experience is required when reporting. A BNCS/BNMS audit of quality assurance in MPS demonstrated that 81% of studies in the random sample were technically of good or adequate quality, but only 68% of reports were good or adequate. [282]. Most of the reports considered inadequate were so assessed because they over-reported artefact or were clinically irrelevant or misleading. Since this time the BNCS and BNMS have concentrated their educational efforts on reporting skills through a combination of dedicated training meetings, symposia and training materials [283]. Although the audit has not yet been repeated, the impression within the profession is that quality is improving.

The low utilisation of MPS in the UK most likely arises from a combination of low perceived demand and inadequate supply. In all but a handful of centres, MPS is performed in general nuclear medicine departments, outside the direct experience of referring cardiologists and in marked contrast to other cardiac investigations such as echocardiography and angiography. It is unsurprising that the test may not be requested even when it can be clinically helpful, or that it is not available sufficiently rapidly to assist with clinical management. This vicious circle has been broken in a small number of high-volume centres where clinically relevant studies of high quality are provided. Growth in MPS is concentrated in these high-volume centres, but the clinical effectiveness and cost-effectiveness of MPS remain largely academic in many hospitals that do not have access to a reliable nuclear cardiology service.

**Estimate of need**

If there is a perception of underutilisation of MPS in the UK, how should correct usage be judged? Comparisons with practice in other countries cannot adequately answer this question but the UK is at the lower end of the spectrum for both absolute and relative numbers of studies and it therefore behoves those concerned to justify this position as an outlier.

**Past recommendations**

The BCS considered levels of provision of a number of investigations in 1994 (Fig. 11) [284, 285]. In all cases the recommended target was lower than the actual number of studies but for MPS the discrepancy was greatest, with a recommendation of 2,200 pm compared with actual numbers of 560 pm. At this time the recommendation for revascularisations (percutaneous and surgical) was 1,000 pm and, based upon this, the recommendation for coronary angiography was 2,000 pm. The ratio of 2:1 was based upon the fact that angiography does not always proceed to revascularisation and a single interven-
tion may be associated with more than a single angiogram. The concept was that angiography acts as the “gatekeeper” to revascularisation.

Estimation of need

The same concept can be used to estimate numbers of MPS studies compared with angiograms. If intervention in patients with CHD is normally performed either to relieve symptoms or to improve prognosis and if objective evidence of inducible ischaemia is required before intervention, then angiography should normally be preceded by MPS, at least in stable coronary disease. The same ratio of 2:1 for MPS to angiography might therefore be a reasonable estimate.

The UK Department of Health has set a target of 1,500 revascularisations per million per year [220], and this is credibly related to population need although with upper estimates of need being considerably higher [286]. In the UK in 2001, 2,600 non-interventional coronary angiograms were performed per million, compared with an estimated number of revascularisations of 1,161 per million (684 pm PCIs + 477 pm CABG) [287]. Thus the ratio of MPS to angiography to revascularisation is 1,200:2,600:1,161, contrasting sharply with corresponding numbers in the USA in 1996 of 12,800:7,200:5,050 (Fig. 12) [288]. The most important contrast is not the difference in scale but the difference in ratios. If it is assumed that an optimal ratio of MPS to angiography to revascularisation is in the region of 4:2:1, this implies a target number of MPS studies of 6,000 pm compared with the target number of revascularisations, or 5,200 pm compared with the actual number of angiograms.

This analysis clearly makes a number of assumptions, not least the presumed optimal ratios, and it is therefore important to err on the side of caution. However, a target for MPI studies of 4,000 pm is reasonable and it would be consistent with practice in other large European countries.

Table 19. Second-phase NSF targets for waiting times [220]

| GP referral to cardiologist or rapid access chest pain clinic | 2 weeks       |
| Specialist investigation General | “Prompt”        |
| Rapid access chest pain clinic | 2 weeks       |
| Decision to investigate to angiography | 3 months      |
| Decision to operate to PCI | 3 months      |
| Decision to operate to surgery | 3 months      |
| High risk | Others | 6 months |

PCI, Percutaneous coronary intervention

Clinically appropriate waiting time

Table 19 shows selected second-phase waiting times targets from the NSF. These have not been achieved in all centres but waiting time initiatives have successfully reduced the waiting times to intervention. No targets were proposed for MPS except indirectly by requiring completion of diagnosis and assessment in rapid access chest pain clinics within 2 weeks. Clearly an actual waiting time for MPS of 20 weeks is inconsistent with these targets. Waiting time targets have been recommended in the South East Thames region at 2 weeks for routine studies and within 2 days for urgent studies [289]. This covers the full range of nuclear medicine procedures, including diagnostic and staging studies for malignancy. Against this background, we propose that suitable waiting time targets for MPS would be 6 weeks for routine studies and 1 week for urgent studies.
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