Evidence-based Nuclear Cardiology: Imaging of CAD

The NICE document
Myocardial Perfusion Scintigraphy (MPS)
for the Diagnosis and Management of
Angina and Myocardial Infarction

Technology Appraisal Guidance 73
Issue date: November 2003
Review date: November 2006

www.nice.org.uk/TA073guidance
About NICE

**Who they are**
The National Institute for Health and Clinical Excellence (NICE) is an independent organization responsible for *providing national guidance* on the promotion of good health and the prevention and treatment of diseases.

**What they do**
NICE produces guidance in three areas of health:

- **Public health** - guidance on the promotion of good health and the prevention of diseases.
- **Health technologies** - guidance on the use of new and existing medicines, treatments and procedures.
- **Clinical practice** - guidance on the appropriate treatment and care of people with specific diseases and conditions.

**How they work**
NICE guidance is developed using the expertise of the NHS and the wider healthcare community including NHS staff, healthcare professionals, patients and carers, industry and the academic world.
The National Health Service (NHS) is the publicly funded healthcare system in the UK. The NHS provides the majority of healthcare in England, and came into effect in 1948.

The UK government department responsible for the NHS is the Department of Health, headed by the Health Secretary.

The NHS is largely funded from general taxation. Most of the expenditure of the Department of Health (USD 200 billion in 2008-9) is spent on the NHS, equivalent to about 9% of GDP.

The NHS is the world's largest health service and the world's fourth-largest employer.
Health expenses in Europe

Share of total expenses in GDP in 2005
Health expenses in Europe

Average expense per inhabitant 2005 (Euro)

Source: CEA Statistics No. 30, May 2007
Health expenses in Europe

Source: CEA Statistics No. 30, May 2007

Total expenditure and growth

Expenditure (Euro million) vs. Growth rate (inflation-adjusted)
Health expenses in Europe

Source: CEA Statistics No. 30, May 2007

Growth 2005/2004 (inflation-adjusted)
Where is Nuclear Cardiology performed?

Source: European Council of Nuclear Cardiology, June 2006
By whom is Nuclear Cardiology performed?

Source: European Council of Nuclear Cardiology, June 2006
Standing advisory committee of the NICE.

Composed by clinical professors, academics, general practitioners, scientists, biostatisticians, health economists, etc.

The total number of members is > 20.

Each Committee member is asked to disclose any conflict of interests regarding the technology to be appraised, and is excluded if necessary.

Each appraisal of a technology is assigned to a Health Technology Analyst and a Project Manager within the Institute.
Sources of evidence considered by the Committee

- Assessment Report by the Health Services Research Unit in collaboration with:
  - Health Economics Research Unit, Dpt. of Public Health
  - University of Aberdeen
  - Grampian University Hospitals NHS Trust

- Manufacturers / commercial companies:
  - Amersham, Ashby, Bartec, Bristol-Myers, GE, Philips, Siemens, Tyco.

- Institutions / professional associations / carer groups:
  - Dept. of Health, British Cardiac Society, British Nuclear Cardiology Society, British Nuclear Medicine Society, Royal College of Physicians, Royal College of Radiologists, etc.

- Commentator organizations:
  - Cochrane Heart Group, Institute of Nuclear Medicine, Inst. of Physics and Engineering in Medicine, NHS Information Authority, etc.

- Expert individuals
1. Guidance

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2. Clinical need and practice

- CAD is the commonest cause of death in the UK.
- Angina, MI and sudden cardiac death are the most common manifestations of CAD.
- About 2.65 million people in the UK have CAD (335,000 new cases/year).
- Total cost to the NHS about USD 3.4 billion/year.
- Coronary angiography (CA) is the gold standard but findings are not always a reliable indicator of the functional significance of a coronary stenosis.
- Routine use of CA without prior non-invasive testing is not advisable because of high cost and associated morbidity and mortality (0.1-0.2%).
- Non-invasive techniques include sECG, echocardiography, MPS, MRI and PET.
3. The technology

- IV injection of tracer ($^{201}$TI, $^{99m}$Tc-MIBI, $^{99m}$Tc-TETRO) during stress (exercise, pharmacologic) and rest.

- SPECT is the clinical standard – planar not acceptable.

- Uptake patterns: homogeneous, reversible, non-reversible, mixed.

- Technical improvements: AC, gating.

- Complication rates (=stress): morbidity ~ 0.02%, mortality ~ 0.01%.

- Radiation exposure ~ coronary angiography.

- Cost (NHS reference): ~ USD 500 vs. sECG USD 200, CA USD 2,200.
4. Evidence and interpretation

- Clinical effectiveness

  ➔ Diagnostic performance (83 studies) (*)

  - SPECT MPS vs. sECG (CA gold standard, 21 studies):
    Sensitivity 81% (63-93%) vs. 65% (42-92%)
    Specificity 65% (10-90%) vs. 67% (41-88%)

  - SPECT MPS only (CA gold standard, 62 studies):
    Sensitivity 86%
    Specificity 74%

(*) ACC/AHA Task Force Guideline:
  Specificity 89-90%
  Specificity 70-76%
4. Evidence and interpretation

- Clinical effectiveness
  - Diagnostic performance
  - Long term prognostic value (46 studies)
    - Annual cardiac event rate (*):
      - MPS abnormal: 6.7%
      - MPS normal: 0.7%

(*) Meta-analyses of 15,000 and 20,963 pts. respectively
4. Evidence and interpretation

- Clinical effectiveness
  - Diagnostic performance
  - Long term prognostic value (46 studies)
    - Proportion of normal angiograms (*)
      With previous MPS: 18 - 33%
      With no previous MPS: 33 - 43%

(*) 2 studies – not pooled – 6,800 and 4,688 pts. respectively)
4. Evidence and interpretation

- Clinical effectiveness
  - Diagnostic performance
  - Long term prognostic value (46 studies)
    - Rate of subsequent revascularization (*)
      - MPS-CA strategy: 13 - 27%
      - Direct CA strategy: 16 - 44%

(*) 3 studies – pooled data – approx. 11,000 pts.)
4. Evidence and interpretation

- Clinical effectiveness
  - Diagnostic performance
  - Long term prognostic value (46 studies)
    - Extent and size of perfusion defects predict the likelihood of future cardiac events.
    - MPS provides independent and incremental prognostic information that helps to risk-stratify patients and influence the way in which they are managed.
    - This also applies for special sub-groups:
      - women
      - diabetics
      - post-MI
      - post-revascularization
      - medically treated
      - hospitalized w/ angina.
4. Evidence and interpretation

- Cost effectiveness
  - Modelling
    - Decision tree models (for diagnostic performance)
    - Markov models (long term costs and benefits)
  Hypothetical cohort: 1,000 pts.
  Starting age: 60.
  Assumed effectiveness of therapy: 10 yrs.
  Time horizon: 25 yrs.
4. Evidence and interpretation

- **Cost effectiveness**
  - Modelling
  - Diagnostic strategies
    - sECG $\rightarrow$ MPS $\rightarrow$ CA
    - sECG $\rightarrow$ CA
    - MPS $\rightarrow$ CA
    - CA
4. Evidence and interpretation

- **Cost effectiveness**
  - Modelling
  - Diagnostic strategies
  - Presented as incremental cost:
    - per true-positive diagnosed
    - per accurate diagnosis
    - per life year gained
    - per quality-adjusted life year (QALY*) gained
    - for different levels of prevalence of CAD

(*) QALY = quality-adjusted life year (score is 0–1 per year)
4. Evidence and interpretation

- Cost effectiveness
  - Modelling
  - Diagnostic strategies
  - Presented as incremental cost
  - Results:
    - As prevalence of CAD increased, total cost increased and total # of QALYs gained decreased for each strategy.
    - \textit{MPS} \rightarrow \textit{CA strategy} has better ICERs\(^(*)\) at low levels of prevalence of CAD.
    - \textit{sECG} \rightarrow \textit{CA} and \textit{direct CA} strategies have better ICERs at higher prevalence levels.

\(^(*)\) ICER = incremental cost-effectiveness ratio = Ratio of the change in costs of an intervention (compared to the alternative) to the change in effects of the intervention.
4. Evidence and interpretation

- Consideration of the evidence

- Uncertainty remains on true values for Sen & Esp for MPS.
- MPS value depends on the likelihood of CAD in the target population.
- MPS is **cost-effective** across a wide range of clinical situations.
- MPS influences pts. management (i.e., enabling redirection into medical rather than surgical treatment).
- Increased availability and provision of MPS within the NHS is desirable on the basis of this evidence.
- Increased use of MPS should initially be targeted at groups for whom it provides the greatest benefit in cost-effectiveness.
5. Recommendations for further research

Further research is recommended in pts. with known CAD regarding the value of MPI relative to other procedures such as:

- Echocardiography
- Magnetic Resonance Imaging
- Computed Tomography
- PET & PET/CT
6. Implications for the NHS

- Utilization of Nuclear Cardiology in the UK (British Nuclear Cardiology Society, 2000):
  - 1200 scans / million population / year.
  - Average waiting time: 20 weeks.

- Estimated optimal level:
  - 4000 scans / million / year.
  - Average waiting time: 6 wks. routine, 1 wk. urgent.

- Needs:
  - 73 additional gamma cameras.
  - Training.
7. Final Guidance

- MPS using SPECT is recommended for the *diagnosis* of suspected CAD:
  
  - As the *initial diagnostic tool* when treadmill exercise is difficult or impossible, and when stress echo is of low sensitivity or difficult to interpret (LBBB, women, diabetics).
  
  - As *part of investigational strategy* in pts. with low to intermediate likelihood of CAD.

- MPS using SPECT is recommended as part of the investigational strategy in the *management* of established CAD:
  
  - In patients who remain *symptomatic* following *MI* or *reperfusion interventions*. 
8. Implementation and audit

- NHS hospitals and clinicians should *take account of the guidance*.
- Local guidelines or care pathways for CAD patients should *incorporate the guidance*.
- *Audits on MPS* could be carried out to ensure that the technique is used appropriately.
- *Audits on patient management* (pts. referred for investigation of suspected CAD, pts. with known CAD symptomatic following MI, CABG or PTCA).
8. Implementation and audit

- Calculation of Compliance with guidance (%):

\[
\frac{\text{No. of pts. whose care is consistent with the criterion} + \text{No. of pts. who meet any exception listed}}{\text{No. of pts. to whom the measure applies}}
\]
8. Review of guidance

- The **Review Date** for a Technology Appraisal is when the Guidance Executive will consider any new evidence in the form of an **Updated Report** and decide whether the technology should be referred to the Appraisal Committee for review.

- This guidance was reviewed in **November 2006**.
9. Upcoming guidance

- Acute coronary syndromes.
- Acute chest pain.
- Stable angina.
- CT coronary angiography.
Appendix 1  Literature search strategies

Sources searched for systematic reviews and other evidence-based reports:

   URL: http://www.hag.unimaas.nl/Internationalising/onderzoek/Cochrane/database%20Fr ank%20Buntinx/welcome_on_the_webpage_of_medion.htm
7. Trip database URL: http://www.tripdatabase.com/ 
10. American Society of Nuclear Cardiology URL: http://www.asnc.org/
14. European Society of Cardiology URL: http://www.escardio.org/
15. Royal College of Physicians URL: http://www.rcplondon.ac.uk/
## Appendix 7  Characteristics of included studies of effectiveness

### Diagnostic studies

<table>
<thead>
<tr>
<th>Study id and Methods</th>
<th>Participants</th>
<th>Test characteristics and Outcome measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Begg 1998**</td>
<td>Inclusion criteria: Asymptomatic patients with ExEGG, SPECT and CA 6 ≤ 2 months after PTCA. All patients were symptomatic before PTCA. Exclusion criteria: Patients unable to undergo ExEGG, or those with rest ECG abnormalities receiving pharmacologic stress, Enrolled: 179</td>
<td>SPECT: Tracer: TI-201. Stress induced by: Exercise (bicycle). Image interpretation: Qualitative. Equipment: APEX SPX-4 HR (Elscint, Haifa, Israel) gamma camera. CA methods: Judkins technique. Interval between tests: ECG/SPECT 1-7 days before CA. Definition of positive SPECT test: Qualitative analysis using a 0 to 4 scale (0 = normal, 4 = severe reduction in TI-201 uptake). Exercise perfusion defect: segment with a score of ≥ 2. Ischaemia: minimal improvement of 1 point on a visual scale. Presence of restenosis: ischaemic redistribution in the territory of individual vessels, guided by a pre-PTCA angiogram. Definition of positive stress ECG test: ≥ 0.1mV ST-segment depression with or without chest pain. Angiographic definition of significant CAD: Restenosis: &gt; 50% diameter stenosis. Outcome measures: Sensitivity, specificity, positive predictive value, negative predictive value, accuracy for restenosis.</td>
</tr>
</tbody>
</table>
|                       | Age: 61 ± 10  
|                       | Gender: M 154, W 25  
|                       | History of: MI 8, PTCA 179; CABG N/5                                        |                                                                                  |
| Chae 1993**            | Inclusion criteria: Women who underwent SPECT within 3 months of CA  
|                       | Exclusion criteria: History of previous CABG, recent MI, unstable angina pectoris, valvular heart disease and congenital heart disease, Enrolled: 243 |                                                                                  |
|                       | Age: Grp 1 65 ± 11, Grp 2 61 ± 10  
|                       | Gender: M 0, W 243  
|                       | History of: MI 103; PTCA N/5; CABG excluded                                  |                                                                                  |
## Appendix 8  
Results of included studies of effectiveness

### Diagnostic studies

<table>
<thead>
<tr>
<th>Study id</th>
<th>Def’n of CAD (% stenosis)</th>
<th>Test</th>
<th>No. of patients</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Accuracy</th>
<th>True positive</th>
<th>False positive</th>
<th>False negative</th>
<th>True negative</th>
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<tbody>
<tr>
<td>Beygui 2000&lt;sup&gt;22&lt;/sup&gt;</td>
<td>≥ 50%</td>
<td>SPECT Stress ECG</td>
<td>179 179</td>
<td>0.63 0.51</td>
<td>0.77 0.62</td>
<td>0.70 0.58</td>
<td>48 33</td>
<td>24 32</td>
<td>28 79</td>
<td></td>
</tr>
<tr>
<td>Chae 1993&lt;sup&gt;23&lt;/sup&gt;</td>
<td>≥ 50%</td>
<td>SPECT Stress ECG</td>
<td>243 243</td>
<td>0.71 0.25</td>
<td>0.65 0.38</td>
<td>0.29</td>
<td>44 42</td>
<td>131 26</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daou 2002&lt;sup&gt;24&lt;/sup&gt;</td>
<td>≥ 50%</td>
<td>SPECT Stress ECG</td>
<td>338 338</td>
<td>0.63 0.47</td>
<td>0.77 0.64</td>
<td>0.66 0.51</td>
<td>167 121</td>
<td>17 29</td>
<td>98 56</td>
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</tr>
<tr>
<td>De 2002&lt;sup&gt;25&lt;/sup&gt;</td>
<td>≥ 70%</td>
<td>SPECT Stress ECG</td>
<td>55 55</td>
<td>0.67 0.44</td>
<td>0.30 0.73</td>
<td>0.39 0.65</td>
<td>8 15</td>
<td>26 23</td>
<td>4 11</td>
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</tr>
<tr>
<td>Gentile 2001&lt;sup&gt;26&lt;/sup&gt;</td>
<td>≥ 60%</td>
<td>SPECT Stress ECG</td>
<td>132 132</td>
<td>0.85 0.85</td>
<td>0.54 0.58</td>
<td>0.86 0.80</td>
<td>101 92</td>
<td>11 10</td>
<td>7 13</td>
<td></td>
</tr>
<tr>
<td>Hamasaki 1996&lt;sup&gt;27&lt;/sup&gt;</td>
<td>≥ 60%</td>
<td>SPECT Stress ECG</td>
<td>125</td>
<td>0.78</td>
<td>0.78</td>
<td>0.78</td>
<td>37</td>
<td>17</td>
<td>10</td>
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<tr>
<td>Hambye 1996&lt;sup&gt;28&lt;/sup&gt;</td>
<td>≥ 50%</td>
<td>SPECT Stress ECG</td>
<td>128 128</td>
<td>0.62 0.74</td>
<td>0.76</td>
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<td></td>
<td>≥ 70%</td>
<td>SPECT Stress ECG</td>
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Thank you...