Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
Diagnostic tests for coronary artery disease comprising initial angiography and initial testing with one of five noninvasive tests. In particular: (1) exercise treadmill testing; (2) planar thallium imaging; (3) single-photon emission computed tomography (SPECT); (4) stress echocardiography; and (5) positron emission tomography (PET). These five tests were followed by coronary angiography if non-invasive test results were positive. Testing was followed by observation, medical treatment, or revascularisation.

Type of intervention
Diagnosis.

Economic study type
Cost-effectiveness analysis.

Study population
Men and women of 45, 55, and 65 years of age, with a history of chest pain whose age, sex, risk factors, and features of chest pain placed them at an intermediate (25-75%) pretest probability of having coronary artery disease. Coronary disease is defined as stenosis of at least 50% in the left main coronary artery or stenosis of at least 70% in any other coronary artery, as measured by angiography. The base case applied to men 55 years of age whose pretest risk for coronary disease was 50%.

Setting
The practice setting was a hospital outpatient clinic. The economic study was carried out in California, USA.

Dates to which data relate
The effectiveness data were based on a literature review of studies published between 1978 and 1994. All costs were derived from 1996 sources (Medicare payments). The price year was also 1996.

Source of effectiveness data
The evidence for effectiveness was based on a synthesis of published studies of diagnostic tests for coronary artery disease, and other estimates based on authors’ assumptions.

Modelling
A Markov model was used to estimate the effects on health outcomes of correct and incorrect classification of disease on costs of care, taking into account the greater benefits that result from detecting severe coronary disease.

Outcomes assessed in the review
The review assessed the sensitivity and specificity of each test using coronary angiography as the reference test, to
detect both severe (left main or three-vessel) disease and all forms of coronary disease. A test result was considered to
be true-positive if angiographic disease in any vascular distribution was present. Sensitivity for left main vessel or three-
vessel disease was defined as presence of at least 50% or greater obstruction of the left main coronary artery or
significant stenosis in all three major arteries.

**Study designs and other criteria for inclusion in the review**
Studies were included if they met the following criteria: a comparison between one or more of the five candidate
diagnostic tests was made; all patients underwent angiography and at least one other non-invasive test; the method of
inducing stress was exercise or a commonly used pharmaceutical agent such as dipyridamole, adenosine, or dobutamine;
for the scintigraphic tests (SPECT and planar thallium imaging), the radiotracers 201thallium or Tc-99m (sestamibi),
were used; for PET studies, a Food and Drug Administration-approved PET radiotracer (rubidium) was used; the
method for evaluating whether a test result was positive was described; readers of diagnostic test results and coronary
angiograms were blinded to the results of the other test; data were presented on all patients studied; unit of analysis was
the patient rather than the artery; the definition of coronary artery disease was based on the percentage stenosis of one
or more coronary arteries using either a 50% or 70% stenosis cutoff to define significant coronary stenosis; the numbers
of true-positive results, false-positive results, false-negative results, and true-negative results could be determined from
the paper. Meta-analyses were also included. The following were excluded: studies including patients with an
excessively broad spectrum of indications, studies recruiting more than one third of patients with a history of
myocardial infarction without stratification of findings by cases with and without myocardial infarction, evaluations
reporting fewer than 25% or more than 75% of patients with coronary artery disease on coronary angiogram, and
studies recruiting more than one third of patients without coronary artery disease as healthy controls.

**Sources searched to identify primary studies**
MEDLINE was searched for English language studies of each of the five diagnostic tests using the search strategy
'(diagnostic test) AND cardiac AND sensitivity.' Bibliographies of review articles were examined to identify further
relevant material. Some relevant published meta-analyses were used to obtain test characteristics for planar thallium
imaging and exercise testing.

**Criteria used to ensure the validity of primary studies**
Not stated.

**Methods used to judge relevance and validity, and for extracting data**
Sensitivities of the tests for both severe, and all forms of coronary disease, were estimated for each included study. The
processes used for selecting studies, assessing validity, and extracting data, were not described.

**Number of primary studies included**
Twenty-four studies were included overall (n= 2,525). There were six studies of planar thallium imaging (n=511), ten
studies of echocardiography (n=1174), eight studies of SPECT (n=862), and three studies of PET (n=206). There was
some degree of overlap between the groups of studies.

**Methods of combining primary studies**
The pooled sensitivity and specificity for both severe and all forms of coronary disease were estimated, using a
weighting system (not explained)

**Investigation of differences between primary studies**
Not stated.
Results of the review
PET is the most sensitive non-invasive test and exercise testing the least sensitive. SPECT is nearly as sensitive as, and somewhat less specific than PET. Echocardiography is more specific than PET but less sensitive. Planar thallium imaging (6 studies): the pooled sensitivity for all coronary disease was 0.79 (range: 0.70-0.94), and specificity 0.73 (range: 0.43-0.97); the sensitivity for severe disease was 0.93. SPECT (8 studies): the pooled sensitivity for all coronary disease was 0.88 (range: 0.73-0.98), and specificity 0.77 (range: 0.53-0.96); the sensitivity for severe disease was 0.98. Echocardiography (10 studies): the pooled sensitivity for all coronary disease was 0.76 (range: 0.40-1.00), and specificity 0.88 (range: 0.80-0.95); the sensitivity for severe disease was 0.94. PET (3 studies): the pooled sensitivity for all coronary disease was 0.91 (range: 0.69-1.00), and specificity 0.82 (range: 0.73-0.88); the sensitivity for severe disease was unavailable. Exercise electrocardiography (132 studies): the pooled sensitivity for all coronary disease was 0.68, and specificity 0.77 (ranges not reported); the sensitivity for severe disease was 0.86.

Methods used to derive estimates of effectiveness
The authors also made their own assumptions.

Estimates of effectiveness and key assumptions
Since no identified article reported the sensitivity of PET for severe disease alone, the authors estimated this by assuming that the false-negative rate decreased by the same proportion for PET as for SPECT when the outcome in question is severe, rather than all, coronary disease. The authors also made the following assumptions relating to the management of patients: patients with positive or indeterminate test results underwent angiography and subsequent treatment depending on the anatomic distribution of obstruction; patients with no coronary disease continued the previous management course; diseased patients were subject to the risks of angiography and the long-term consequences of their underlying disease and of treatment; patients who have negative test results did not have angiography; if the test was false-negative, the patient continued with conservative management and delayed, or did not receive, appropriate treatment; if the result was true-negative, the patient avoided the costs and health risks of unnecessary angiography.

Measure of benefits used in the economic analysis
Life years gained and quality-adjusted life years (QALYs) were the measures of benefit. The authors state that the quality of life improvements result from the successful treatment of angina and prevention of myocardial infarction. The authors also mention that the specific quality weights attached to these events were derived from published utility assessments. No details were provided of the specific instruments used. However, one of the studies relates to time trade-off (Nease et al 1995 and Tsevat et al 1993) The estimated survival of patients with coronary disease treated surgically or medically, angina patterns experienced after medical or surgical interventions, and effects of treatment with angioplasty, were based on published data (Rogers et al 1990; Emond et al 1994; Sim et al 1995).

Direct costs
The reported perspective was that of society. The analysis included only costs arising from the testing strategies and treatment of coronary disease and its complications. Medicare payments based on national average relative value units for 1996 were the principal source of outpatient and diagnostic costs. Since Medicare did not reimburse for PET, the assumed cost of this test is representative of private insurance payments. Costs and quantities were reported separately. The present value of future health expenditures in 1996 US dollars was calculated using a 3% discount rate. The time horizon used was 30 years.

Statistical analysis of costs
Not applicable.

Indirect Costs
The authors stated that the perspective of the study was societal, but they did not describe or report any indirect costs.
Currency
US dollars ($).

Sensitivity analysis
In order to test the variability in the data, sensitivity analyses were carried out according to: (1) changes in the level of prevalence of coronary artery disease; (2) changes in the indeterminacy rate; and (3) changes in the assumptions made about complications of angiography. Cost-effectiveness ratios were calculated for each scenario. A one-way simple sensitivity analysis was carried out according to the variables described above. To account for uncertainty about the cost of PET scans, results were calculated for a range of costs, from 50% to 100% of the average insurer payment.

Estimated benefits used in the economic analysis
Details of estimated benefits for men and women aged 45, 55, and 65 years are provided in the paper. The following estimates relate to the base case, i.e., men 55 years of age whose pretest risk for coronary artery disease is 50%. Life expectancy varies little by testing strategy: 16.581 years for exercise testing, 16.592 years for planar thallium imaging, 16.595 years for echocardiography, 16.600 years for SPECT, and 16.601 years for both PET and angiography. In terms of QALYs, estimates were as follows: 12.234 for exercise testing, 12.243 for planar thallium imaging, 12.244 years for echocardiography, 12.253 for SPECT, 12.255 for PET, and 12.259 for angiography.

Cost results
Details of the estimated costs for men and women aged 45, 55, and 65 years are provided in the paper. The following estimates relate to the base case, i.e., men 55 years of age whose pretest risk for coronary artery disease is 50%. The lowest cost estimate was for exercise testing at $33,281, then echocardiography at $33,341, planar thallium imaging at $33,467, SPECT at $34,047, angiography at $34,661, and PET at $35,093. Estimates are based on the total costs of care, including revascularisation, medications, and the treatment of myocardial infarction and other conditions.

Synthesis of costs and benefits
Although the cost-effectiveness of each strategy in each gender/age group is presented graphically, individual estimates are not provided in each case. SPECT produces more QALYs at higher cost compared with echocardiography; its cost-effectiveness ratio, compared with echocardiography, ranges from $64,000 (in men 65 years of age) to nearly $150,000 (in women 45 years of age) per QALY gained. PET generally produces slightly better outcomes than SPECT, but at much greater cost, and immediate angiography dominates PET in every population group. As an initial testing strategy, immediate angiography is more expensive than SPECT. Its cost-effectiveness ranges from $80,000 (in men 65 years of age) to nearly $200,000 (in women 45 years of age) per QALY gained relative to SPECT. For every population group, the cost-effectiveness ratio for angiography compared with SPECT is somewhat higher than the cost-effectiveness ratio for SPECT compared with echocardiography. This implies that angiography would be preferred if a relatively high cost-effectiveness ratio were acceptable, that SPECT would be preferred if an intermediate cost-effectiveness ratio were acceptable, and that echocardiography would be preferred if the maximum acceptable cost-effectiveness ratio were lower. A no-test strategy is unlikely to be attractive because echocardiography generates more QALYs at relatively low cost. The cost-effectiveness of echocardiography, compared with no testing, ranges from $31,000/QALY (in mean aged 65 years) to $98,000/QALY (in women aged 45 years). Results of sensitivity analyses showed that results varied little with age, gender, pretest probability of disease, or test indeterminacy rate. Results varied most with sensitivity to severe coronary disease.

Authors’ conclusions
Echocardiography, SPECT, and immediate angiography are cost-effective alternatives to PET and other diagnostic approaches. Test selection should reflect local variation in test accuracy.

CRD COMMENTARY - Selection of comparators
NHS Economic Evaluation Database (NHS EED)
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rationale for the choice of comparators (standard diagnostic procedures) was clear and appeared to be appropriate. Angiography was selected as the reference test to assess alternative strategies used for the diagnosis of coronary artery disease in patients with an intermediate (25-75%) pretest probability of having the disease. Although the use of angiography is associated with a certain amount of risk, it is considered to be the gold standard in this field.

Validity of estimate of measure of benefit
authors performed a systematic review of relevant research literature in order to derive estimates of the effectiveness of the various diagnostic tests. Overall, this was a well conducted review, and internal validity is, therefore, likely to be relatively high. However, it is possible that further relevant material could have been identified had a more comprehensive search strategy been undertaken.

Validity of estimate of costs
cost data were obtained from a reliable source, and were analysed appropriately. Costs and quantities were reported separately, and the price year was given. However, although the authors stated that the perspective of the study was societal, they did not include indirect costs in the analysis. The study appears to be more relevant to a third party payer perspective (Medicare).

Other issues
authors noted that it is possible that the results of the systematic review were subject to publication bias, since no unpublished studies were included in the analysis. The reported accuracy of tests varied among studies and may reflect differences in patient and physician characteristics. However, the authors draw attention to these points during their discussion, and compare their own findings with those from other, similar, studies. The authors used a rigorous methodological approach for estimating costs and benefits, and utilised sensitivity analyses in order to help to resolve uncertainty associated with the reliability of data derived from modelling.

Implications of the study
The authors state that there is no consensus about how management should be modified by a study such as this, but the initial strategy of testing with echocardiography or SPECT rather than angiography should be considered in choosing among testing strategies. To prolong life, a non-invasive test must detect the most severe forms of coronary disease. Since current non-invasive tests are highly sensitive for three-vessel and left-main disease, improved test performance characteristics are unlikely to greatly affect mortality unless treatment of less severe forms of disease is also shown to prolong life substantially. That is why echocardiography and SPECT are relatively cost-effective options.

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