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THE VALUE OF MYOCARDIAL PERFUSION SCINTIGRAPHY IN THE DIAGNOSIS AND MANAGEMENT OF ANGINA AND MYOCARDIAL INFARCTION: A PROBABILISTIC ECONOMIC ANALYSIS

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ABSTRACT

Background and Aim

Coronary heart disease (CHD) is the commonest cause of death in the UK, causing over 120,000 deaths in 2001, amongst the highest rates in the world. This study reports an economic evaluation of Single Photon Emission Computed Tomography myocardial perfusion scintigraphy (SPECT) for the diagnosis and management of coronary artery Disease (CAD).

Methods

Strategies involving SPECT with and without Stress Electrocardiography (EGC), and Coronary Angiography, were compared to diagnostic strategies not involving SPECT. The diagnosis decision was modelled with a Decision Tree Model and long-term costs and consequences using a Markov Model. Data to populate the models were obtained from a series of systematic reviews. Unlike earlier evaluations, a probabilistic analysis was included to assess the statistical imprecision of the results. The results were presented in terms of incremental cost per quality adjusted life year (QALY).

Results

At prevalence levels of CAD of 10.5%, SPECT-based strategies are cost effective; ECG-CA is highly unlikely to be optimal. At a ceiling ratio of £20,000 per QALY, SPECT-CA has a 90% likelihood of being optimal. Beyond this threshold this strategy becomes less likely to be cost-effective. At over £75,000 per QALY, coronary angiography is most likely to be optimal. For higher levels of prevalence (around 50%) and more than a £10,000 per QALY threshold, coronary angiography is the optimal decision.

Conclusion

SPECT-based strategies are likely to be cost-effective when risk of CAD is modest (10.5%). Sensitivity analyses show these strategies dominated non-SPECT based strategies when risk of CAD for up to 4%. At higher levels of prevalence invasive strategies may become worthwhile. Finally, sensitivity analyses show stress ECHO as a potentially cost effective option and further research to assess the relative cost-effectiveness of ECHO should also be performed.

KEYWORDS

Coronary heart disease, coronary artery disease, cost-utility analyses, probabilistic sensitivity analysis.

INTRODUCTION

Coronary heart disease (CHD) is the commonest cause of death in the UK, causing over 120,000 deaths in 2001. Death rates have been falling in the UK since the late 1970s. However, despite this improvement, death rates are still amongst the highest in the world. Morbidity, in contrast to mortality, is rising with over 378,000 inpatient cases treated for CHD in UK NHS hospitals in 2000/2001, representing 5% of all inpatient cases in men and 2% in women.(1) The cost of CHD to the UK health care system in 1999 was estimated as £1.73 billion rising to £7.06 billion when informal care and productivity losses were included.(2)

Coronary artery disease (CAD) is the most common cause of CHD, with most CAD caused by the narrowing of the large and medium sized arteries serving the heart. Methods of detecting and assessing the presence and extent of CAD have become increasingly important in applying therapies to reduce morbidity and mortality. Coronary angiography is considered the "gold standard" for defining the site and severity of coronary artery lesions but it is costly and associated with significant risk of mortality and morbidity and not recommended without prior non-invasive testing.

Of the non-invasive tests available the most widely used, due its relatively low cost and availability, is stress (induced by either exercise or pharmacological agents) electrocardiography (ECG). However, a normal stress ECG does not exclude CAD. Furthermore, it performs poorly in low-risk populations.(3) Imaging techniques such as myocardial perfusion scintigraphy (MPS) can also be used to improve detection and/or localisation of CAD. MPS uses an intravenously administered radiopharmaceutical to evaluate regional coronary flow after stress and at rest. In single photon emission computed tomography (SPECT), the raw data are then processed to obtain tomographic images.

These non-invasive tests can be used either alone or in combination but it is not clear which of the possible diagnostic strategies that could be devised would be most efficient. This is an issue that has been addressed by a number of earlier economic evaluations that have recently been systematically reviewed.(4) This systematic review found that strategies involving SPECT were likely to be either dominant or produced more quality adjusted life years at an acceptable cost, relative to those that did not contain SPECT but that there was little consistency in the literature about which of the various strategies that involved SPECT was optimal. The available economic evaluations were almost all conducted in a single country (the US) and their results may have limited transferability to other settings. More importantly the results of all these evaluations were subject to considerable uncertainty which was addressed in only a limited fashion (if at all) by sensitivity analysis. Two particular shortcomings can be identified. First, the available economic evaluations relied on the results of either a single primary study, which may not be reliable and or generalisable, or a review of studies in which comparisons between the diagnostic performance of tests were based on indirect comparisons which may be prone to selection bias. Second, where sensitivity analysis was conducted the methods used were not well suited to addressing the statistical uncertainty surrounding the data used in the study.(5)

In this study an attempt has been made to overcome these limitations in an evaluation of which strategy for the diagnosis of CAD is most likely to be cost-effective. In particular, the evaluation compares alternative strategies involving

SPECT alone or in combination with other non-invasive tests with strategies that do not involve SPECT.

METHODS

Overview of the Model

Economic Modelling techniques were used to compare diagnostic strategies including SPECT to strategies that did not. A two-stage model was developed. In the first stage, a decision tree model (DTM), constructed in Excel(6), was used for the diagnosis decision (Figure 1) and in the second stage a Markov Model, developed in Data 4.0(7), was created to model longer term cost and consequences (Figure 2). Specifically, it considered the management of patients with suspected CAD. The model structure was developed following consultation with clinicians and consideration of the existing economic evaluation literature.(4)

Decision Tree Model

The DTM is a way of displaying the proper temporal and logical sequence of a clinical decision problem.(8) In practical terms, it may take weeks or even months for a patient to go from the first decision node to the final diagnosis.

The tests considered in the DTM were SPECT, stress ECG and coronary angiography. These diagnostic tests were combined to produce the following strategies (thought, on the basis of the literature and clinical opinion, representative of current practice):

a) Stress ECG; followed by SPECT if stress ECG positive or indeterminate; followed by coronary angiography if SPECT positive –high risk– result or indeterminate
b) Stress ECG; followed by coronary angiography if stress ECG positive or indeterminate

c) SPECT; followed by coronary angiography if SPECT positive –high risk– result or indeterminate

d) Coronary Angiography (invasive test as first option).

Within the model (Figure 1) a patient may, for example, arrive in the hospital with typical chest pain. This is central chest discomfort often described as tightness, a weight on the chest or a constricting band around the chest; usually not sharp in nature and builds up and down slowly, varied in severity but lasts only a few minutes, frequently radiates down the left arm, up into the neck or through to the back. It can often be associated with cold sweat, breathlessness and tingling in the hands and/or fingers and pain would be relieved by resting. (Malcolm Metcalfe, personal communication, September 2006)

Taking the patient's history and symptoms into account the physician must decide between an invasive test (coronary angiography) and a non-invasive test as the first option (stress ECG or SPECT). If the physician decides on an invasive test, then the patient has a small risk of dying during the test. If the patient survives, then this will result in a final classification of their condition into one of three categories: High Risk (i.e. three vessel disease and poor left ventricular function or left main disease); Medium Risk (single or double vessel disease); or Low Risk, (no significant heart disease present).

If the physician opts for the non-invasive stress ECG test as the first option, and if the result of this test is positive, another non-invasive test, SPECT, could be requested. If the SPECT test result is positive this might result in a diagnosis of the patient as High Risk or result in a request for a coronary angiography to help determine appropriate management. A final outcome of this strategy for this particular patient would be if they receive a left main disease diagnosis following angiography and would be classified as High Risk. Similarly, if the SPECT results are negative then the physician classifies the patient as Low Risk.

There are three possible diagnoses and three possible disease states. However, as all individuals that have a positive result would eventually go to a further test, all those diagnosed as high risk must have gone through coronary angiography as their last test (if coronary angiography is not their first and only test). As the model assumed perfect information from coronary angiography (i.e it is defined as a gold standard), there is no possibility of misclassifying patients identifies as being as high risk by a non-invasive test. Thus, at the end of the Decision Tree a patient who has survived the diagnostic process will be in one of the following diagnostic situations: a) Low Risk; b) Medium Risk; c) High Risk; d) classified as low risk but actually high risk (false negative); e) classified as low risk but in fact medium risk (false negative); f) classified as medium risk but actually low risk (false positive); g) classified as medium risk but actually high risk. These outcomes represent the states in which the patient will start in the Markov model described below.

Markov Model

The Markov Model provides estimated costs and outcomes over a selected period of time (e.g. the expected lifetime) for cohort of patients for each of the different management strategies that could be adopted following diagnosis. A Markov Model of the type presented here has states in which patients stay for a period of time called a 'cycle'. The cycle must be a period of time relevant to the condition considered (in this case one year). At the end of the cycle, the individuals can remain in the state they started the cycle in, or they can move to a different state. The probabilities of moving from one state to another are called transition probabilities and these are defined below. Finally, in these models there must be at least one absorbing state from which the patient will not be able to leave. In this model the absorbing state is 'death' which can be reached from any of the other states.

These Markov model states can be thought of as comprising a number of events that influence cost and outcome. For instance, patients entering a Medium Risk state (Figure 2) will receive medical management and will enjoy a particular quality of life during the period of time they remain in that state. If a patient has a revascularisation the model will adjust costs and quality of life. Patients who receive and survive a revascularisation move to a revascularisation state in which they enjoy the benefits of the revascularisation (lower risk of death and MI) until the patient dies or it is felt the benefits of the revascularisation will no longer be obtained. A similar process can be described for the other states (Figure 2).

Interventions and events considered within the model are: for all states medical management and myocardial infarction. In addition, revascularisation (PTCA or CABG) is included for Low, Medium or High Risk states. For 'revascularisation' states, further revascularisation is possible. Finally, within the 'false' states part of the cohort may be re-diagnosed by coronary angiography. The assumption within the model is that all survivors are correctly diagnosed after a maximum of 10 years period either as a result of additional diagnostic tests or a non-fatal MI. This assumption reflects the belief that 'at risk' individuals would over time face other opportunities, such as regular health checks, in which they may receive a correct diagnosis.

Probabilities

Decision Tree Model Probabilities

Decision tree probabilities were derived from the literature or calculated in the model. Medline (1966-October 2002), EMBASE (1980- October 2002) and also PRE-MEDLINE and NHS-EED were searched with terms like 'coronary disease' or 'myocardial ischemia' or 'angina pectoris' amongst others. Further details of the search strategy adopted are described in Mowatt and colleagues, Appendix 1.(4)

The prevalence of coronary heart disease (Table 1) was obtained from British Heart Foundation Statistics.(1) Sensitivity and specificity data were obtained from Mowatt and colleagues.(4) Mowatt and colleagues conducted a systematic review of diagnosis accuracy of SPECT, stress ECG and coronary angiography. This review only included studies that reported direct comparisons between the three tests as opposed to other reviews that relied on indirect comparisons between studies.(9-17) In the review by Mowatt and colleagues angiography was taken as the reference standard. Sensitivity and specificity figures were determined by the interpretation by the research team of the results of the review of effectiveness.

In previous work it has been typically assumed that coronary angiography is the gold standard (sensitivity and specificity equal to 1).(4, 12, 15) Although it is known that coronary angiography is not a reliable indicator of the functional significance of coronary stenosis (3, 18) this study has assumed perfect information from coronary angiography but explored the issue in sensitivity analysis.

Using the prevalence data and data on sensitivity and specificity, positive and negative result rates were calculated for each diagnostic strategy. An assumption was made that sensitivity and specificity rates were independent of the underlying prevalence of CAD. Incorporation of these data into the DTM allowed positive and negative result rates to be calculated for diagnostic strategy at different pre-test risks of CAD.

Markov Model Probabilities

The time horizon for the Markov Model was 25 years and the transition probabilities and their sources used in this model are presented in Table 1. The risk of dying from any of the states was calculated as the mortality rate for the corresponding age group with adjustments for the relative risk caused by the level of risk and beneficial effects of medical or surgical treatment. The mortality rate for men and women for England and Wales was based on general population estimates produced by the UK Government's Actuary Department.(19)

Within the Markov model states were defined for both false negatives and false positives. The model allows for an increasing proportion of misclassified patients to be allocated properly in each cycle. As described above, for the base case the complete cohort of misclassified patients would be correctly allocated within 10 years.

The risk of MI is considered for each state. The risk for the general population, used for the Low Risk state, was obtained from Lampe and colleagues 2000.(20) This is a UK based prospective study to describe the long-term outcomes of ischemic heart disease that involved a sample of 7735 men aged 40 to 59. The relative risks for the other states were derived from the prospective USA based study by Shaw and colleagues 1999 (N=11,372).(21) These proportions were split into fatal and non-fatal MI using data from Lampe and colleagues(20) and Volmink and colleagues (population wide surveillance study based in Oxfordshire, UK) in order to correctly re-diagnose those who had a non-fatal MI.(22)

Annual revascularisation risk in Medium and High risk states as well as risk of second revascularisation when having PTCA or CABG were derived from Kuntz and colleagues.(12)

Costs

Decision Tree Model Costs

Table 1 shows the interventions considered for the Decision and Markov model, the cost in 2001/02 pounds sterling, and the sources from where the figures were obtained.

The total costs for stress ECG and coronary angiography were £105(23) and £1310.(24) The cost of stress ECG was calculated from HRG V05 category.(25) It is Admission and Emergency direct cost plus a share of support services (pathology and radiology) and has been calculated in a top-down approach.

The cost of SPECT came from Underwood and colleagues.(24) Their figures were derived by averaging 1996 data for UK centres and Royal Brompton Hospital, London, which was judged to be the most meaningful by the authors. These costs were estimated using a very detailed bottom-up costing exercise where all resources were itemised and costed (personal communication, Professor Underwood, February

2003). The cost estimate was checked with an estimate derived using a top-down approach with data from different sources, which confirm the figures from the EMPIRE study.(24) The costs reported by Underwood and colleagues were inflated using the Hospital and Community Health Services (HCHS) Pay and Prices Index.(26)

Markov Model Costs

For the different Risk states three interventions were considered: medical management, MI event management and revascularisation. Medical management cost for the different states was obtained from experts' opinion and checked with the literature. It was found that the final figure did not differ much from the one presented by Sculpher and colleagues.(27) Prices for this calculation were obtained from the British National Formulary.(28) MI event management cost data came from Boland and colleagues(29), who used NHS Reference Costs(25); figures for 2001/02 from the same source were used in this model.

The cost for PTCA was £1994(23); the calculation assumed 60 minutes of theatre time, and an angiography performed immediately prior to the PTCA. The calculation allowed for the staff cost of five healthcare professionals as well as relevant consumables plus capital items. The cost for CABG was obtained from NHS Reference Costs.(25) Where appropriate estimates were adjusted for inflation using HCHS Pay and Prices Index.(26)

Quality of life measures

One of the products of the economic evaluation is quality adjusted life years (QALYs). QALYs combine estimates of survival time and the quality of that survival time. Survival is provided by the cumulative number of cycles spent in each state of the model other than Death. Taking the time spent in each state and weighting it by a quality of life score provided an estimate of QALYs.

Estimates of QALYs were required for each of the states in the Markov model. The best data for estimation of this, given the perspective of the evaluation, would be UK studies with generic health status measures such as those provided by tools such as the EQ 5D.(30) In the absence of such data information was sought from a review of related economic evaluations(4) and from the Cost Effectiveness Analyses Registry.(31) While relatively comprehensive, the data presented in the registry were methodologically no better (and more often of lower quality) than the results of the standard gamble exercise used by Kuntz and colleagues(12) identified by a review of economic evaluations. The utility scores used in the model are described in Table 1.

It was assumed in the Markov Model that patients who have an MI or are revascularised will lose part of their QALYs as a result of the event and will recover their previous level of quality of life in three months (Table 1).(32) The gain from revascularisation is the subsequent lower risk of death but not a higher quality of life than before revascularisation.

Data analysis

The parameters for costs of interventions, risks of events and quality of life for the base case analysis were entered in decision tree and Markov models. Payoffs for the decision tree model were obtained from the Markov models run for up to 25 cycles (i.e., 25 years follow-up period). The starting age for the hypothetical cohort of patients was 60 years. Annual discount rates of 6% and 1.5% were used for costs and outcomes, respectively.(33) The costs and effects were re-estimated for different values of prevalence of disease: 10.5% (baseline), 30%, 50% and 85%. The baseline rate was calculated using data from the British Heart Foundation Statistics and is an estimation of the mean population CHD prevalence. Lower levels of prevalence were explored in sensitivity analyses.

Sensitivity Analysis

Manning and colleagues (5) developed a taxonomy of uncertainty in economic evaluations. They distinguished between 'Modelling uncertainty' from 'parameter uncertainty': the first could be further differentiated into uncertainty due to model structure and uncertainty due to the overall process of the cost-effectiveness analysis. Parameter uncertainty refers to those cases where the parameters could not be observed, for which there are disagreement about their appropriate values, or how they could change in the future (epidemiology of the disease), sampling variability, or values of parameters to feed the model for alternative settings.

Probabilistic sensitivity analysis was used to address parameter uncertainty. The importance of this has been stressed elsewhere.(5, 34, 35) Prior probability distributions to allow for uncertainty in the mean parameters values were specified following usual practice (34, 36) and are shown in Table 1. Detailed information on costs was limited, nonetheless as a mean and range were available triangular distributions for costs were used. For proportions, beta distributions were used (i.e. sensitivity or specificity of diagnosis tests).(37) Gamma distributions were used for probabilities that were very near to zero (i.e. death during an ECG test)(Alan Brennan, personal communication, April 2004)(38) and lognormal distributions were used for relative risks (i.e. relative risk of death for High Risk patients).(35)

One thousand Monte Carlo simulation iterations were obtained for the Markov Payoff Model. These results were used as probability distributions for the payoffs in the Decision Tree Model. Monte Carlo Simulation was then performed in the Decision Tree Model using the Excel added on Crystal Ball software.(6, 39)

These results were used for calculating credible intervals for the deterministic results presented in Table 2 and for constructing cost-effectiveness acceptability curves (CEACs). CEACs detail the probability that the intervention is optimal for any maximum value that the Decision Maker would be willing to pay (Ceiling Ratio) for an extra unit of effectiveness (in our case for an extra QALY).(40)

While probabilistic sensitivity analysis allow us to know how precise the results in the model are, it could potentially give us a very precise wrong answer if the data used as inputs, in this case sensitivity and specificity of the tests, for instance, were potentially biased. Therefore, probabilistic sensitivity analysis was combined with other forms of sensitivity analysis. Mowatt and colleagues(4) stated that there was heterogeneity between the studies that provided data on the specificity or sensitivity of the tests. Figures from some of these studies were used to address this potential problem. A similar problem also limited previous economic evaluations identified by the systematic review of economic evaluations(4), although it has not previously been elucidated. Furthermore, the uncertainty surrounding estimates of sensitivity and specificity used in earlier studies has been further compounded by potential biases caused by the indirect comparisons used.

Other sensitivity analysis was also conducted. First the time horizon over which costs and effects are considered was varied from 25 to 10 and 5 years, as it may be unrealistic to assume that costs and outcomes over such a long period can be reliably estimated. Second, the period in which false negatives are correctly re-diagnosed has been modified from the maximum of 10 years assumed for the base case. Third, alternative data for the likelihood that a test was indeterminate were used.(12) Kuntz and colleagues assume higher values for ECG indeterminacy (30% vs. 18% base case) and lower value for SPECT indeterminacy (2% vs. 9% base case). Fourth, the analysis was repeated with a £25 and £225 cost for stress ECG, £128 and £340 cost for SPECT, and £895 and £1724 cost for coronary angiography based on data from Mowatt and colleagues.(4) Finally, a sub-group analysis for female cohort has been performed which took data suggesting a lower prevalence of disease and slightly higher sensitivity and specificity for SPECT.(4)

Average costs were used as the basis of estimates of costs for the diagnostic tests used. Such costs include elements for the capital and overheads of providing these services. As there may be concerns that they do not adequately reflect opportunity costs, the impact of using these costs was also explored in the sensitivity analysis.

The generalisability of this analysis could be undermined due to exclusion of potentially relevant strategies for other settings. Particularly relevant seems to be the case of Echocardiography (ECHO) that appear to be a cost-effective option in previous studies.(12) Further sensitivity analysis was conducted and two strategies were added to the original model. Namely, ECHO followed by coronary angiography if ECHO positive result, and ECHO followed by SPECT if ECHO positive result, followed by coronary angiography if SPECT high-risk diagnostic result. Data needed to feed the model added strategies were obtained from Kuntz and colleagues(12) for ECHO sensitivity, specificity, and assumed the same indeterminacy and mortality rates as ECG(15), and probability distributions were attached for probabilistic analysis (Table 1).

The prevalence rates used for the base case analysis might be considered high according to some sources.(41) This also could potentially undermine the generalisability and practical use of this study results to other settings. The original model was run for lower prevalence rates (e.g. 0.1%, 0.5%, 1% and 5%) as part of the sensitivity analysis.

Finally, it is known that coronary angiography is not a reliable indicator of the functional significance of coronary stenosis(3, 18). Therefore, an additional probabilistic sensitivity analysis was performed assigning further probability distributions to the sensitivity and specificity of coronary angiography. Beta distributions were used with mean 0.99 and standard deviation of 0.005 for both parameters.

RESULTS

Base case analyses

Table 2 show the deterministic results of the base case analysis and a range of different prevalence rates. As prevalence increases, cost increases and QALYs decrease. At all prevalence levels the order of the strategies remain the same. This table also shows the incremental cost per QALY. This outcome is based upon diagnostic and treatment costs (obtained from the payoff model) and estimated QALYs. As a consequence, the incremental cost per QALY is driven, not only by diagnostic performance, but also the costs and consequences of management strategies chosen on the basis of diagnostic information.

For a prevalence of 10.5% the incremental cost per QALY gained (ICER) for the move from SPECT-coronary angiography strategy to coronary angiography strategy is £48,600. ECG-SPECT-coronary angiography and SPECT-coronary angiography strategies have extended dominance over the ECG-coronary angiography strategy (i.e. managing patients with a combination of ECG-SPECT-coronary angiography and SPECT-coronary angiography would result in a lower incremental cost per QALY than managing all patients with the ECG-coronary angiography strategy alone). This is because the ICER for movement from ECG-SPECT-coronary angiography to ECG-coronary angiography (£26,249) is higher than going from ECG-coronary angiography to SPECT-coronary angiography (£9261)). The ICER without the extended dominated strategy is £15,241.

At a 30% prevalence level the order of the strategies is the same but the ICERs associated with movement between the strategies fall. The situation of extended dominance described above persists.

At a prevalence level of 50% the ICER for moving from ECG-SPECT-coronary angiography to ECG-coronary angiography was £2473; from ECG-coronary angiography to SPECT-coronary angiography was £4032 and from SPECT-coronary angiography to coronary angiography strategy £3372. In this case the ECG-coronary angiography and coronary angiography strategies have extended dominance over the SPECT-coronary angiography strategy (ICER: £5,200). Finally, for an 85% prevalence level the ICERs for the movement between strategies are further reduced and ECG-coronary angiography and coronary angiography strategies continue to have extended dominance over the SPECT-coronary angiography strategy.

[Table 2 Estimated costs and outcomes for each diagnostic strategy] [HERE]

Sensitivity Analysis

From the probabilistic sensitivity analysis credible limits for costs and QALYs for each strategy were obtained (Table 2). From these data, it was not immediately obvious if one strategy could dominate any of the others. Therefore, the probabilistic results were presented in a series of CEACs (Figure 3).

In the base case analysis ECG-coronary angiography strategy is highly unlikely to be optimal (Figure 3a). Moreover, if the decision maker is willing to pay less than £8000 for a QALY the strategy with higher probability of being optimal is ECG-SPECT-coronary angiography. At approximately £9000 per QALY, ECG-SPECT-coronary angiography and SPECT-coronary angiography strategies have a similar probability of being optimal. At ceiling ratio of £20,000 SPECT-coronary angiography has a 90% likelihood of being considered the more cost effective option, but beyond this value, the likelihood falls such that at willingness to pay values over £75,000 coronary angiography is the strategy most likely to be optimal.

At a 30% prevalence of disease (Figure 3b), strategies that involve SPECT seem to be optimal for decision makers willingness to pay for a QALY of up to £20,000; coronary angiography being the optimal strategy decision for higher values of willingness to pay for a QALY. For higher levels of prevalence of disease and for a threshold of more than a £10,000 per QALY, coronary angiography is the optimal decision (Figure 3c and 3d).

On the basis of sensitivity analysis on the model parameters (not reported) the model results were found to be more sensitive to the prevalence of disease (Figure 3) and tests performance. The values used in the model for sensitivity and specificity of tests were similar to those used in previous studies.(12) If other central values than those used in the base case were chosen the model might produce very different results. As there was known to be heterogeneity in the data other sources of specificity and sensitivity data were used for ECG and SPECT. These data were based on De and colleagues(42) as an example of a scenario where SPECT performs poorly and from Michaelides and colleagues(43) for a well performing SPECT scenario. As expected, in the worst SPECT performance scenario, SPECT-coronary angiography strategy did not appear in the frontier of optimal solutions for any level of prevalence of disease, while ECG-SPECT-coronary angiography strategy appears optimal for 10.5% prevalence of disease and when the threshold is less than £5,000. Using data from

Michaelides and colleagues gave similar results to those presented in the base case (Figure 3). It should be noted that even for this most optimistic scenario, at a level of prevalence higher than 60% and a threshold over £16,000 per QALY, the coronary angiography strategy appears to be the optimal diagnostic strategy.

With respect to changes in the time horizon adopted for the analysis, it was found that as the time horizon reduces the incremental cost per QALY increases. This is because the costs of initial diagnosis and treatment are not offset by survival and quality of life gains. Increasing the likelihood that misdiagnoses will be rectified reduces the penalty associated with making a false negative diagnosis (i.e. it improves the cost-effectiveness of non-invasive strategies compared with coronary angiography). With respect to use of the higher values for ECG indeterminacy and lower value for SPECT indeterminacy it was found that SPECT strategies were more likely to be considered cost-effective. The results of the analysis were relatively insensitive to the alternative cost data used and to the changes considered in the probability distributions for the sensitivity and specificity of coronary angiography sensitivity and specificity. Furthermore, for the sub-group analysis restricted to women it was found that the results were slightly more favourable to SPECT based strategies.

When strategies involving ECHO were added to the model using data from Kuntz(12), they were shown to be potentially cost-effective options. Furthermore, at a 10.5% prevalence of CAD, ECHO-SPECT-coronary angiography strategy dominated both ECG-SPECT-coronary angiography and ECG-SPECT strategies, while ECHO-coronary angiography dominated both ECG-coronary angiography and SPECT-coronary angiography strategies.

At low levels of prevalence of CAD up to 1%, the strategy ECG-SPECT-coronary angiography dominated all others, for prevalences between 1% and 4% SPECT based strategies dominated non-SPECT based strategies while at 5% only SPECT-coronary angiography strategy dominated coronary angiography strategy.

DISCUSSION

This analysis indicates that it is possible that the incremental cost per unit of QALY for the move from stress ECG-SPECT-coronary angiography to SPECT-coronary angiography might be considered worthwhile when the prevalence of CAD is below 30%. A combination of ECG-SPECT-coronary angiography and SPECT-coronary angiography strategies would be more efficient than a reliance on a strategy of ECG-coronary angiography only at these levels of prevalence of disease. Probabilistic sensitivity analysis suggests that the ECG-coronary angiography strategy is highly unlikely to be the most cost effective and does not form part of the cost-effectiveness efficiency frontier described by the CEACs. The coronary angiography option is more likely to be considered optimal at high levels of prevalence of disease (>30%), but at lower levels of prevalence of disease, SPECT-coronary angiography strategy is more likely to be considered optimal. This result should be compared with the deterministic studies, which frequently concluded that strategies including SPECT were the most cost-effective. However, there is no consensus in the literature on which strategy was more cost-effective. For example, three studies compared SPECT-coronary angiography and stress ECG-SPECT-coronary angiography and two concluded that stress ECG-SPECT-coronary angiography was cost-effective(13, 24) and one reported that the extra benefits provided by SPECT-coronary angiography might be worth its additional cost.(44)

The model considered some of the strategies that are potentially relevant for managing CAD patients. The effectiveness data for the diagnostic tests came from a systematic review of diagnostic and prognostic studies conducted by Mowatt and colleagues.(4) However, little data were available from the UK. As a result data from other countries were used, much of which came from studies conducted in the USA. In these cases, relative risks and rates of utilisation were extrapolated but absolute rates of utilisation of interventions were not, as it is well known that there are differences in utilisation rates between the USA and UK and it was believed that the use of relative rates would result in less bias.

Positron emission tomography (PET) or stress Echocardiography (ECHO) interventions were not included in the original model. Other economic evaluations have shown PET as being unlikely to be cost-effective(4) and for the UK and other countries it has very limited availability. ECHO is, however, a potentially relevant alternative and its omission from the original analysis represents a limitation of the study. Evidence suggests that this approach may be a viable alternative(4) but it was excluded by NICE from their consideration of this technology (which the research presented in this paper was originally commissioned to inform). Then, ECHO based strategies were explored in sensitivity analysis and, using data from Kuntz(12) they show to be potentially cost effective options. However, these results should be treated with caution as the data on sensitivity and specificity used were based on an ad-hoc review of the literature and indirect test comparisons. The other sensitivity and specificity data for the other tests were based on systematic review that included studies with direct test comparisons, and a meta analysis. Moreover, Mowatt and colleagues(4) sensitivities and specificities for the other tests show to be lower than those observed in the article by Kuntz and colleagues.(12) This would tend to magnify the favorable results obtained for ECHO.

The 'do nothing' strategy was not considered in the model. This option might be relevant to a situation where diagnosis was made on the basis of clinical examination only. Generally, some form of diagnostic testing is performed within the UK, as well as in other settings, and as a result this option was judged to be inappropriate for this evaluation.

In the base case model it was assumed that those patients who were not correctly classified would be correctly diagnosed within 10 years. If the assumed period were shorter, then those strategies that result in incorrect diagnoses would not be as heavily penalised, and ECG-coronary angiography strategy, for instance, would perform better.

The model allows for indeterminate results in ECG and SPECT but it does not allow for a second ECG or SPECT test after indeterminacy. Moreover, complications due to any of the tests were not considered and hence there were no quality of life adjustment for these. This might be a potentially significant caveat as the complications from coronary angiography (i.e. stroke) are likely to be more important than in the other tests. This would tend to reduce the cost-effectiveness of those strategies that make the most use of coronary angiography.

As was stated above, the main results showed that key parameters in this model were prevalence of disease and tests performance. Sensitivity analyses were carried out considering prevalence rates below the base case analysis rates (10.5%) according to professional guidelines medium and low risk rate stratification.(41) The model results are in line with those professional bodies recommendations. In other words, a stepwise approach with less invasive test as first option followed by more invasive ones in comparison with a more invasive test as first option.

The values for sensitivity and specificities for SPECT and ECG in this study are lower than those presented elsewhere.(41) The data used here are based on a more robust approach as they are based on studies that made direct comparisons between the diagnostic tests.(4) This approach might lead to less data being included as a more restrictive inclusion criteria is used, but has higher internal validity. Despite our best efforts to obtain high quality data for sensitivities and specificities the results were still uncertain. In our analysis this uncertainty has been modelled in two ways. Firstly, statistical distributions have been defined for these variables and the effect of using these distributions has been estimated in the probabilistic sensitivity analysis. Secondly, we have explored the use of fundamentally different values for these parameters in best case and worst case scenarios. The results of these analyses were as expected. For the worst SPECT scenario non-SPECT strategies represented the optimal decision, but it should be noted that the accuracy of SPECT reported in De and colleagues, used in the worst case scenario for SPECT, is quite different from that shown by other studies.(4) Using data from Michaelides and colleagues(43) as an example of best SPECT performance scenario provided similar results to the base case analysis. However, for high level of prevalence of disease (>60%) the coronary angiography strategy appears to be the optimal decision.

Conclusions about the role of coronary angiography might change if the assumption is not made that coronary angiography is a gold standard. It is very difficult to assess the effect of relaxing this assumption as the sensitivity and specificity of the other tests would need adjusting as they are compared to coronary angiography. Furthermore, it is possible that SPECT might have independent prognostic value over coronary angiography.(45) The sensitivity analysis that was conducted was unable to fully address these issues but as it reduced the performance of coronary angiography compared with the other tests it can be thought of as reflecting a worst case situation for the performance of coronary angiography. Nonetheless, results were insensitive to the changes to considered.

Linking diagnostic performance to long-term outcomes required a number of assumptions to be made about both the structure of the model and its parameters. Some of these assumptions were based on a limited evidence base and it is unclear whether these data are applicable to the UK or to other settings. Furthermore, due to the absence of data, the model presented does not allow for higher quality of life after revascularisation. Therefore, the benefits of revascularisation are derived solely from higher life expectancy. If a higher quality of life were achieved after revascularisation, those strategies that accurately identify patients for revascularisation (fewer false negatives) would perform better.

A further caveat, related to the pay-off model, is the extent to which severity of disease is linked to quality of life. The model presented, and many of the previous evaluations, makes the assumption that there is a direct link. No utility data were identified with which to test this assumption and, therefore, further research is required on this area.

Finally, the adoption of SPECT based strategies might reduce the necessary time for diagnosis as in some countries the waiting time from a positive stress ECG result to a coronary angiography may be considerable. In the UK, for instance, this waiting time is currently about 20 weeks.(4) The increase use of SPECT in rapid access clinics could reduce the distress associated with this wait. Moreover, within the UK and other countries SPECT may possibly not be as widely available as stress ECG.

Therefore, patients who require SPECT may need to travel and to support the time and financial costs associated with this. Clearly, the expansion of SPECT-based services would require considerable investment in infrastructure. Although the cost of this expansion might be important, the lack of trained staff could be a greater obstacle. In the UK, for instance, this trained staff expansion would take between 5 and 10 years.(4)

CONCLUSIONS

Strategies that involve the use of SPECT seem to be optimal for low levels of prevalence of CHD and should they be adopted this would reduce the number of invasive tests required. Although this higher use may be efficient, the expansion of services may be slow, because of the time needed to train staff adequately. For high levels of prevalence of CHD, the result seems to be the opposite; namely, strategies that do not involve SPECT seem to be optimal. Finally, future research should acknowledge that determining the optimal diagnosis strategy requires information on longer-term outcomes, especially on rates of service utilisation and on utilities. Sensitivity analyses show strategies that involved ECHO as potentially cost-effective options. Further research to assess the relative cost-effectiveness of ECHO should also be performed.

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Table 1: Summary of variables used in the analysis

Probabilities		**Parameter value**		**Source**	**Probability Distribution and parameter values**
Prevalence of disease for patient cohorts	Males	10.5	10.5 – 90	BrHF Stats 2003(1)	
	Females	5.5	5.5 – 90	BrHF Stats 2003(1)	
Stress ECG	Sensitivity	0.66	0.42 – 0.92	Mowatt 2004(4)	Beta: α=400; β=206
	Specificity	0.60	0.43 – 0.83	Mowatt 2004(4)	Beta: α=364; β=242
	Indeterminacy	0.18		Patterson 1995(15)	Beta: α=819; β=179
	Mortality risk	0.00005		Patterson 1995(15)	Gamma: scale=0.001; shape=2
SPECT	Sensitivity	0.83	0.63 – 0.93	Mowatt 2004(4)	Beta: α=503; β=103
	Specificity	0.59	0.44 – 0.90	Mowatt 2004(4)	Beta: α=358; β=248
	Indeterminacy	0.09		Patterson 1995(15)	Beta: α=89; β=910
	Mortality risk	0.00005		Patterson 1995(12, 15)	Gamma: scale=0.001; shape=2
Coronary Angiography	Sensitivity	1		Assumption	
	Specificity	1		Assumption	
	Mortality risk	0.0015		Patterson 1995(15)	Gamma: scale=1; shape=0.05
Mortality					
Annual rate for age X				Interim Life Tables(18)	
Relative Risk Medium Risk		2.3		Yusuf 1994(44)	Lognormal: μ=0.833; σ=0.05
Relative Risk High Risk		3.6		Yusuf 1994(44)	Lognormal: μ=1.281; σ=0.05
Risk of MI:					
Low Risk (& false positives)		2.5%		Shaw 1999(21)	Beta: α=145; β=5681
Untreated Medium Risk & false negative medium risk		5.0%		Shaw 1999(21)	Beta: α=291; β=5535
High Risk & false negative high risk		9.0%		Shaw 1999(21)	Beta: α=524; β=5302
Prop non-fatal MI		55.16%		Based on Lampe 2000(20) and Volmink 1998(22)	

False Negative Results		Kuntz 1999(12)	
Prop to High Risk	59%		Beta: α=590; β=409
Revascularisation:			
Proportion revascularisation Low, Medium, High risk.	5%; 50%; 100%	Assumption	Low: Beta: α=50; β=950 Medium: Beta: α=500; β=500 High: Beta: α=900; β=100
Prop PTCA low, medium and high risk respectively	90%; 61%; 10%	BrHF Stats 2003(1) for medium risk. Assumption for low and high risk	Low: Beta: α=900; β=100 Medium: Beta: α=610; β=390 High: Beta: α=100; β=900
Prop of patients with 2nd revascularisation			
PTCA	3.6%	Kuntz 1999(12)	Gamma: α=0.036; λ=1
CABG	1.8%	Kuntz 1999(12)	Gamma: α=0.018; λ=1
Mortality Risk reduction from revasc:			
High Risk	57%	Kuntz 1999(12)	Lognormal: μ=-0.562; σ=0.14
Medium Risk	15%	Kuntz 1999(12)	Lognormal: μ=-1.95; σ=0.32
Risk reduction of MI:			
PTCA	17%	Kuntz 1999(12)	Lognormal: μ=-1.772; σ=0.10
CABG	40%	Kuntz 1999(12)	Lognormal: μ=-0.99; σ=0.02
Procedures mortality			
PTCA	0.75%	Kuntz 1999(12)	Gamma: α=0.075; λ=1
CABG	3.1%	Kuntz 1999(12)	Gamma: α=0.031; λ=1
Costs	**Total Cost (2001/02 £ sterling)**	**Source**	
Stress ECG	104.86	Hartwell 2003(23)	Tri: 25-225

SPECT	261.91	Underwood 1999(24) (1996/97 prices)	Tri: 128-340
Coronary Angiography	1,309.55	Underwood 1999(24) `(1996/97 prices)	Tri: 895-1724
Medical Management	311.00	Mowatt 2004(4)	
MI	1,122.00	NHS Cost 2001/02	Tri: 761-1627
PTCA	1,993.74	Hartwell 2003(23)	Tri: 1346-2568
CABG	4,397.00	NHS Cost 2001/02	Tri: 3005-5289
Utility	**Value**	**Source**	
Low Risk	0.87	Kuntz 1999(12)	Beta: α=184; β=27
Medium Risk	0.81	Kuntz 1999(12)	Beta: α=171; β=40
High Risk	0.67	Kuntz 1999(12)	Beta: α=141; β=70
Adjustment for revascularisation or MI	0.1	Assumption	Beta: α=21; β=190
Other parameters			
Age at start of model	60 years		
Time horizon	25 years		

Table 2: Estimated costs and outcomes for each diagnostic strategy

Strategy	**Cost (95% CI)**	**QALYs (95% CI)**	**ICERs**
Prevalence 10.5% Basecase			
ECG-SPECT-Coronary Angiography	£5,192 (4,906-5,473)	12.510 (11.902-13.051)	
ECG-Coronary Angiography	£5,396 (5,081-5,722)	12.518 (11.907-13.066)	£26,249
SPECT-Coronary Angiography	£5,529 (5,183-5,821)	12.532 (11.930-13.084)	£9,261
Coronary Angiography	£5,929 (5,505-6,345)	12.541 (11.926-13.089)	£48,576
Prevalence 30%			
ECG-SPECT-Coronary Angiography	£5,787 (5,506-6,070)	11.727 (11.235-12.173)	
ECG-Coronary Angiography	£5,958 (5,647-6,297)	11.759 (11.270-12.215)	£5,454
SPECT-Coronary Angiography	£6,155 (5,793-6,471)	11.798 (11.310-12.264)	£4,997
Coronary Angiography	£6,484 (6,052-6,926)	11.840 (11.330-12.311)	£7,893

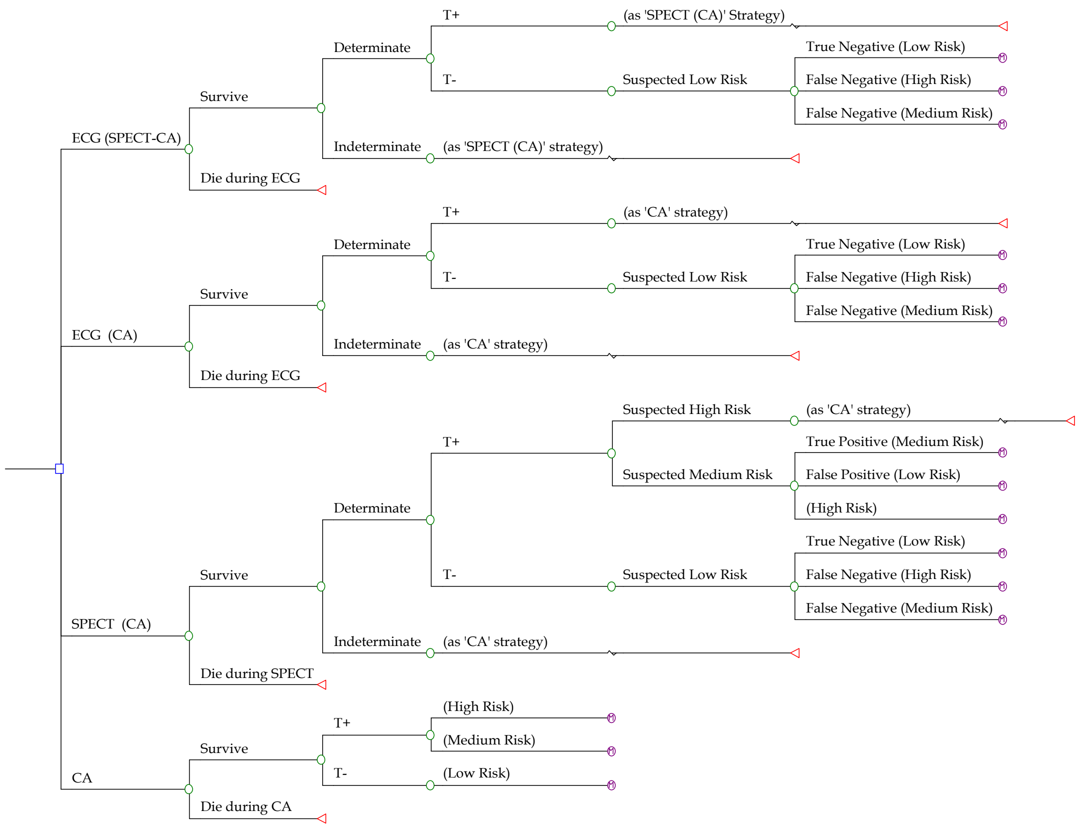
Prevalence 50%			
ECG-SPECT-Coronary Angiography	£6,397	10.924	
	(6,068-6,709)	(10.524-11.294)	
ECG-Coronary Angiography	£6,535	10.979	£2,473
	(6,167-6,906)	(10.578-11.367)	
SPECT-Coronary Angiography	£6,797	11.045	£4,032
	(6,356-7,168)	(10.631-11.455)	
Coronary Angiography	£7,053	11.121	£3,372
	(6,539-7,551)	(10.668-11.551)	
Prevalence 85%			
ECG-SPECT-Coronary Angiography	£7,464	9.518	
	(7,002-7,917)	(9.146-9.862)	
ECG-Coronary Angiography	£7,543	9.616	£803
	(7,034-8,060)	(9.219-9.994)	
SPECT-Coronary Angiography	£7,921	9.726	£3,428
	(7,306-8,469)	(9.284-10.147)	
Coronary Angiography	£8,049	9.862	£948
	(7,364-8,726)	(9.330-10.337)	

ECG = stress electrocardiography; SPECT = single photon emission computed tomography myocardial perfusion scintigraphy, CI = credible interval

* ICER against ECG-SPECT-Coronary Angiography strategy: for 10.5% prevalence rate of CAD = £15,241; for 30% prevalence rate = £5,200

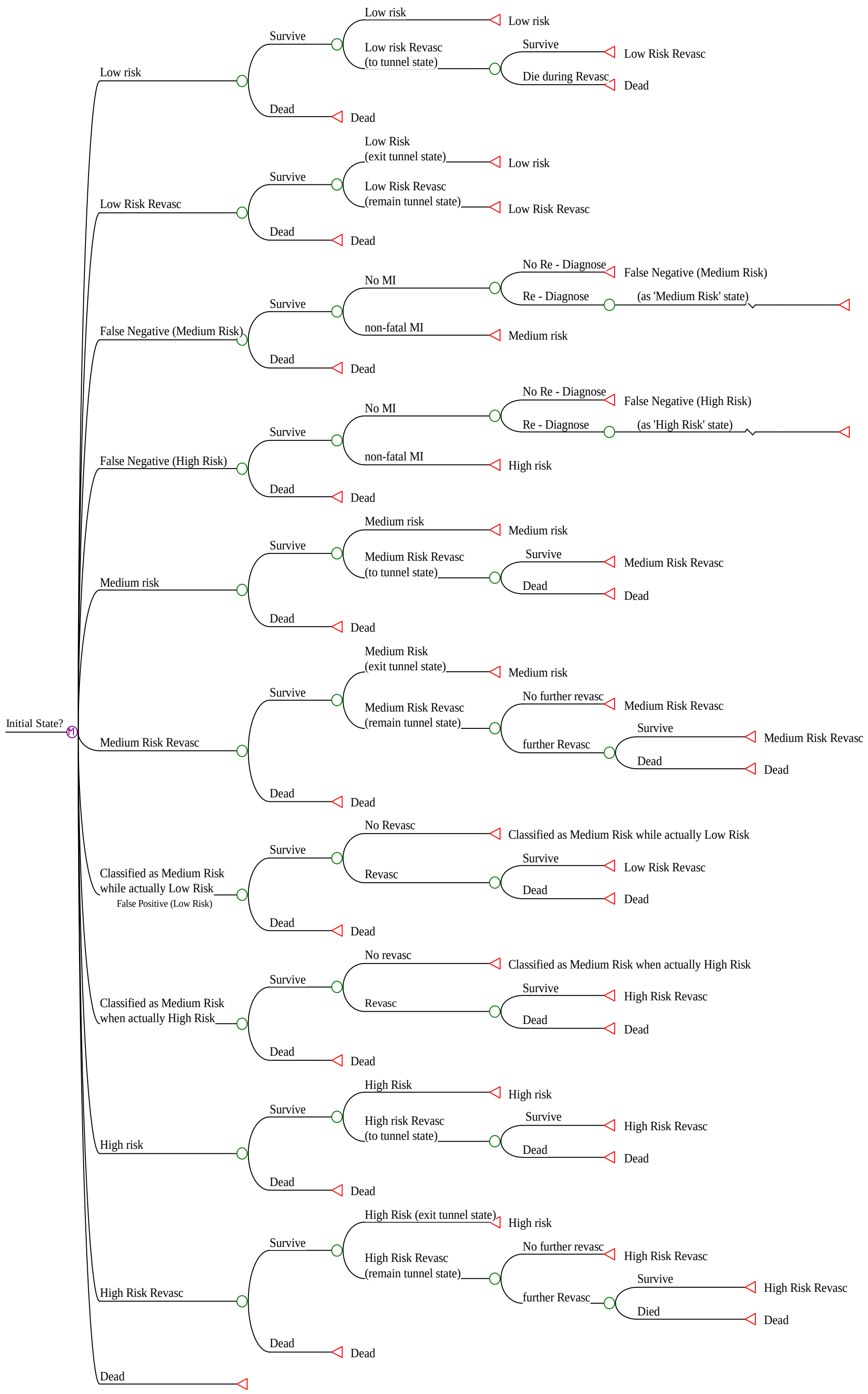
** ICER against SPECT-Coronary Angiography strategy: for 50% prevalence rate of CAD = £3,677; for 85% prevalence rate of CAD = £2,057

Figure 1: *Decision Tree Model (short term diagnosis model)*



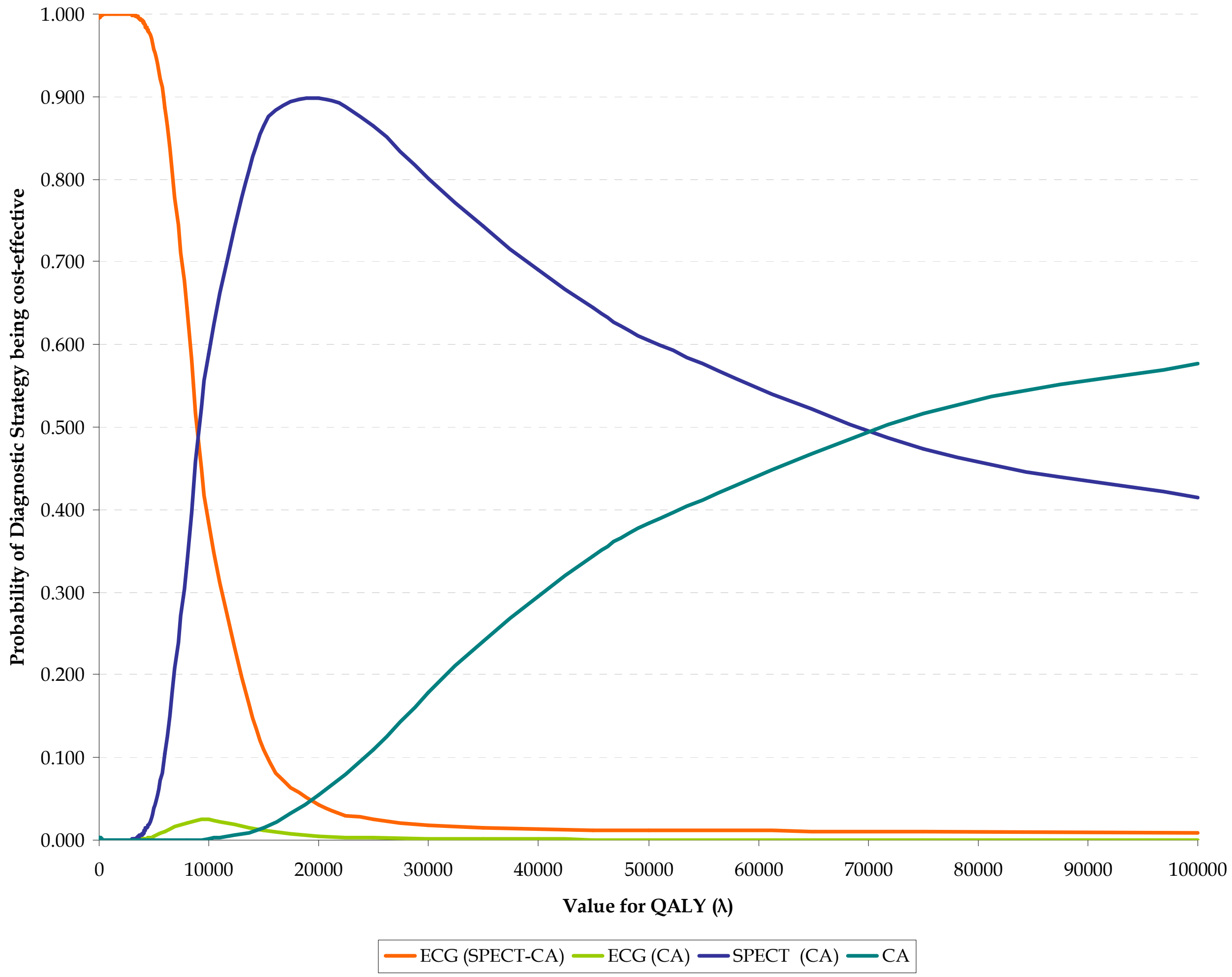
Stepwise approach: if first test inconclusive or positive result, a further test looking for more information is performed. ECG = stress electrocardiography; SPECT = single photon emission computed tomography myocardial perfusion scintigraphy; CA= coronary angiography. In brackets (i.e. 'False Positive (Low Risk)') the true state of the disease.

Figure 2: *Simple Markov Model for Prognosis and Management of CHD*



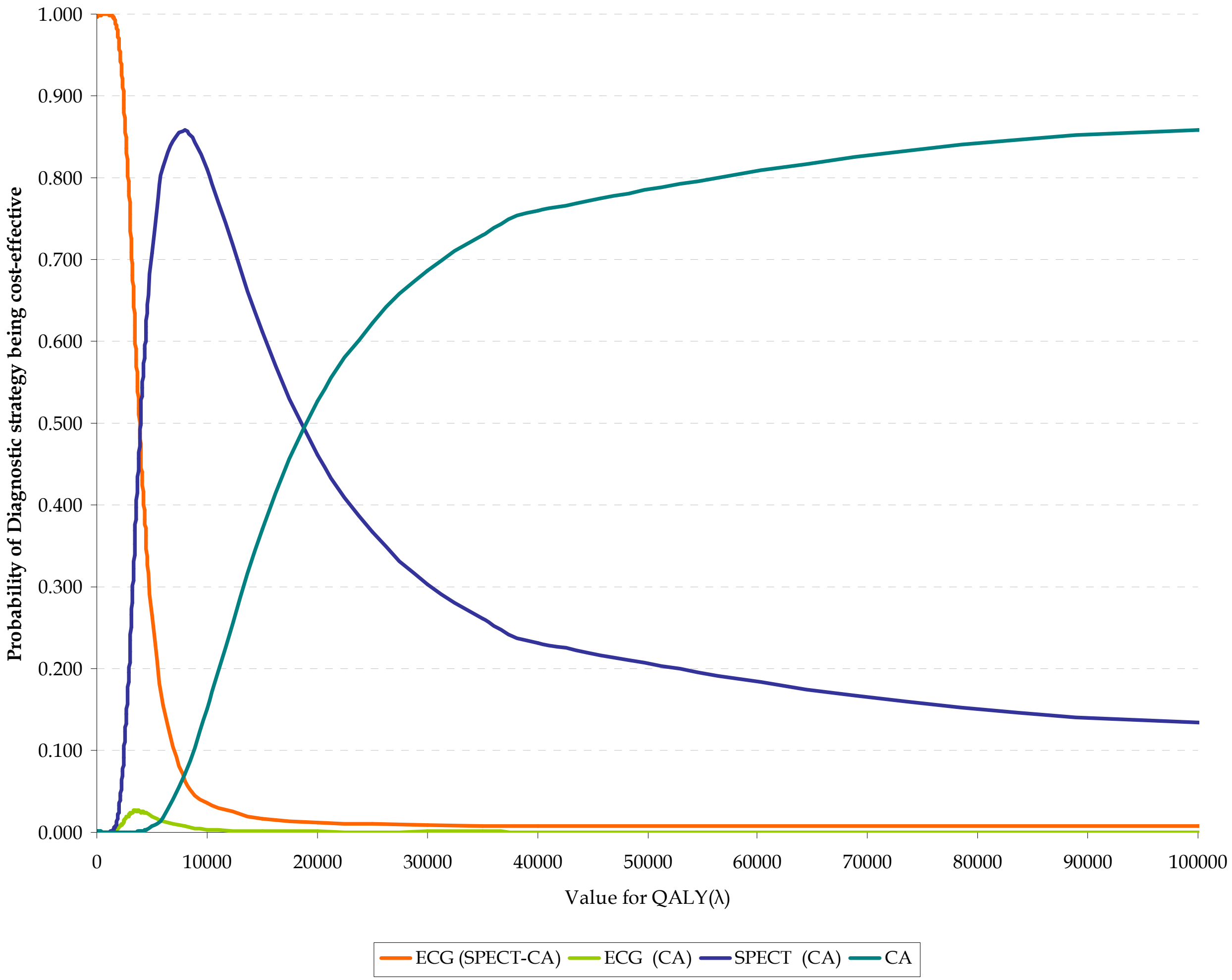
In brackets (i.e. 'False Positive (Low Risk)') the true state of the disease. All states considered MI and revascularisation quality of life and cost effects. Revascularisation effects lasts more than one cycle so modelled as state.

Figure 3a: Cost-effectiveness acceptability curves: prevalence of CAD = 10.5%



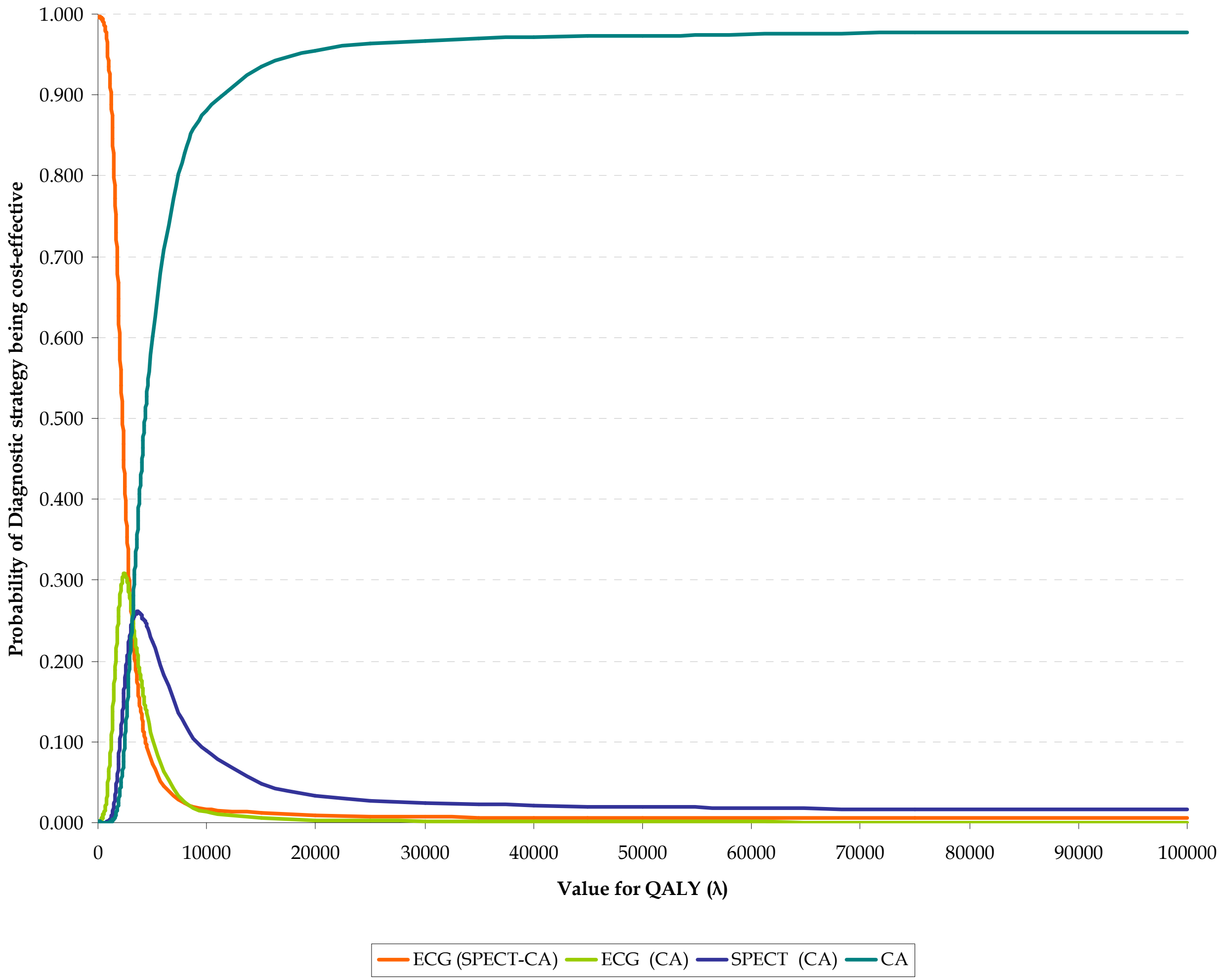
ECG = stress electrocardiography; SPECT = single photon emission computed tomography myocardial perfusion scintigraphy; CA= coronary angiography

Figure 3b: Cost-effectiveness acceptability curves: prevalence of CAD =30%



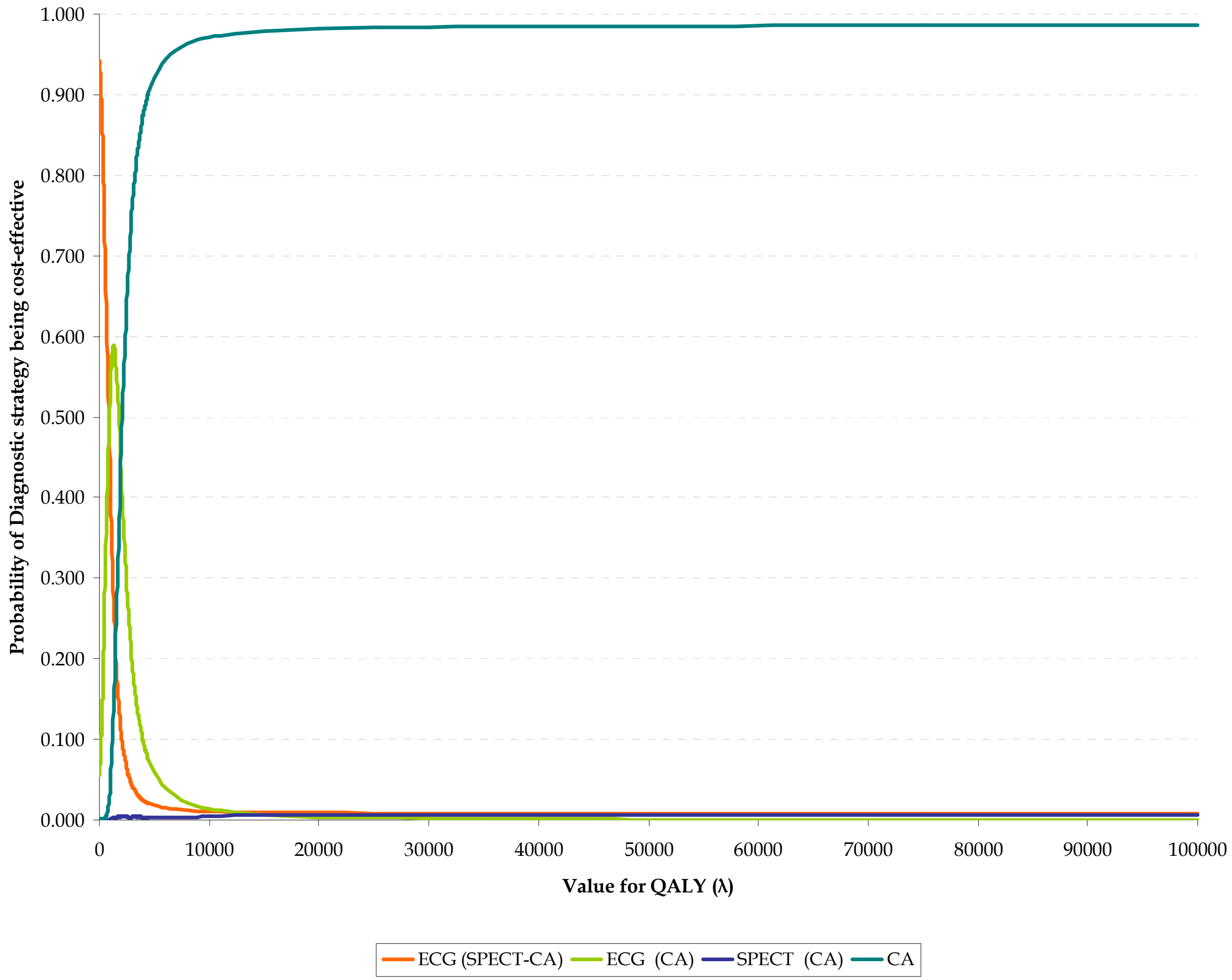
ECG = stress electrocardiography; SPECT = single photon emission computed tomography myocardial perfusion scintigraphy; CA= coronary angiography

Figure 3c: Cost-effectiveness acceptability curves: prevalence of CAD = 50%



ECG = stress electrocardiography; SPECT = single photon emission computed tomography myocardial perfusion scintigraphy; CA= coronary angiography

Figure 3d: Cost-effectiveness acceptability curves: prevalence of CAD = 85%



ECG = stress electrocardiography; SPECT = single photon emission computed tomography myocardial perfusion scintigraphy; CA= coronary angiography