The Cost-Effectiveness of Primary Angioplasty Compared to Thrombolytic Therapy for Acute Myocardial Infarction in the UK NHS.

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1. INTRODUCTION

Coronary heart disease (CHD) is the single commonest cause of premature death in the UK and is associated with significant impairment in quality of life; there is also evidence that this burden is inequitably distributed in society[1] The National Service Framework (NSF) for CHD outlines several key stages in addressing the burden of CHD, including the need to specify the most appropriate interventions and models of care. [1] Since NHS resources are inevitably limited, there is a requirement to identify interventions that provide the greatest health benefit for a reasonable cost (i.e. those that are cost-effective). The use of cost-effectiveness analysis has now become an integral component of decision-making, including public reimbursement of health care interventions, in many countries. In the UK, the National Institute of Health and Clinical Excellence (NICE) explicitly considers the available clinical and economic evidence before issuing guidance to the National Health Service (NHS).

The effective and cost-effective management of CHD in the UK is a NHS priority. In particular, the appropriate management of acute myocardial infarction (AMI) or "heart attack" comprises a cornerstone of the NSF for CHD. Although one objective of the NSF is to avoid the occurrence of AMI altogether (e.g. through lifestyle changes and use of appropriate medication such as aspirin, beta-blockers and cholesterol-lowering therapies), for those patients who suffer an AMI it is vital that they are managed in a timely and efficient manner. Figures from the NSF suggest that approximately 300,000 people suffer a heart attack each year in the UK and about 140,000 die. [1] While the management of AMI has improved in the UK, with an associated 16% reduction in mortality between 1999 and 2001, [2] many of these deaths are still considered to be potentially preventable.

Facilitating access to the correct care in the first minutes and hours after the onset of symptoms of AMI has been central to the improvements seen in the management of AMI. Pharmacological treatment with thrombolysis aims to dissolve the clot and re-open the artery, if possible before irreversible damage has occurred to the heart muscle deprived of oxygen downstream from the occlusion. The administration of thrombolysis as soon as possible after the onset of an AMI has been demonstrated to significantly reduce the risk of death and disability. The proportion of people treated within 60 minutes of calling for help is now 58% compared with 24% before the NSF. [3]

Although thrombolysis forms the mainstay of first line treatment in the UK, its use has several well-documented limitations. Only 60-80% of the presenting population are eligible for treatment as there are important contraindications related to the risk of bleeding and hypertension. [4] Even when treatment is suitable, normal coronary flow is restored to between only a quarter and a half of patients depending on whether streptokinase or a fibrin-specific agent such as alteplase is used. [5]

The increased use of primary angioplasty for the management of AMI has been suggested as one approach to provide further improvement in the management of patients with AMI. Primary angioplasty is defined as the use of angioplasty as the main or first line treatment for patients with AMI. It is widely seen as the main reperfusion option in patients ineligible for thrombolytic treatment, the other alternative being surgical bypass by emergency coronary artery bypass graft (CABG). A substantial evidence-base exists demonstrating significant clinical benefits of primary angioplasty compared to patients receiving in-hospital thrombolysis in terms of reductions in rates of mortality, non-fatal reinfarction and stroke. Despite this evidence, the issue of whether primary angioplasty should become the first line treatment is still the subject of considerable debate in the UK and beyond. [4]

The use of interventional techniques following AMI has traditionally been low in the UK NHS compared to that in other developed countries. The NSF for CHD (2000) [1] set targets for treatment with thrombolytics within 20-30 minutes of hospital arrival. As a result, NHS Trusts have introduced changes in their management strategies to achieve this target. Apart from the practical and economic implications derived from any structural change in health care provision, one possible reason for the limited use of primary angioplasty in the NHS is the lack of evidence regarding its cost-effectiveness. The objective of this report is to fill this evidence gap by developing a comprehensive cost-effectiveness model of primary angioplasty in the UK NHS.

2. AIMS AND OBJECTIVES

To date there have been no cost-effectiveness analyses undertaken in the UK to establish whether the additional cost of primary angioplasty, relative to medical management with thrombolytics, is justified in terms of long-term generic outcomes (e.g. life-years gained or quality-adjusted life years). Indeed, the cost-effectiveness evidence is lacking internationally. A systematic literature search of the area found only one UK short-term cost-effectiveness study [6] and two international studies. [7, 8] Consequently the long-term cost-effectiveness of primary angioplasty in the UK NHS has not been adequately addressed in published studies. This report details the results of a decision analytic model developed to address this question.

The aim of this project was to develop a UK specific cost-effectiveness model of primary angioplasty compared to medical management with thrombolytics. A central component of this model was to quantitatively address two of the major sources of uncertainty relating to the use of primary angioplasty: (1) the impact of treatment delay and (2) the long-term costs and outcomes compared to treatment with thrombolysis. Specific objectives were:

- To structure an appropriate decision model to characterise patients' care and lifetime prognosis
- To populate this model with the most appropriate data identified systematically from published literature and routine sources
- To characterise uncertainty in the data used to populate the model
- To estimate the mean cost-effectiveness of primary PCI in terms of lifetime NHS costs and quality-adjusted survival, and to establish the uncertainty in those mean estimates
- To use the model to identify priorities for future research

The analysis adheres to the recently updated methodological guidance for economic evaluation from NICE. [9] Although the use of primary angioplasty is not currently listed as a technology for appraisal by NICE, the methods guidelines provide a useful summary of good practice in the field. In particular, the systematic approach to model building, evidence gathering and synthesis, and the rigorous methods of analysis represent what is currently considered to be 'best practice' in the field. Furthermore, adhering to these guidelines will be worthwhile if NICE considers primary angioplasty in the future.

3. OVERVIEW OF THE DECISION MODEL

3.1 Analytic framework

In health technology assessment there is an increasing role for decision analysis for synthesising data, identifying optimal treatment decisions under conditions of uncertainty and prioritising additional research. [10] The use of Bayesian decision theory to establish expected payoffs for alternative treatment strategies has been accepted as a rational basis for decision making for some time. [11, 12] More recently, a Bayesian decision theoretic framework for the economic evaluation of health care programmes has been presented. [13, 14] This framework suggests that the choice between mutually exclusive health care programmes should be distinguished from the conceptually separate question of whether more information should be acquired to inform this decision in the future

Within this framework, the choice between programmes should be based on expected payoffs, with uncertainties surrounding the outcome of interest considered only to establish the value of acquiring additional information by conducting further research. Bayesian decision theory and value of information (VOI) analysis provides an explicit and rigorous framework within which both the decision problems posed in health technology assessment can be addressed. There are a number of examples of the application of these approaches to priority setting in the evaluation of health care technologies. [15, 16]

The application of these methods requires two main tasks to be completed:

1. Construction of a probabilistic decision analytic model to represent the decision problem and to characterise the current decision uncertainty;

2. Establishing the value of additional information to inform this decision in the future.

The model presented within this report incorporates both of these requirements. The basic model structure is discussed in the remainder of this section. This is followed (Section 4) by a description of the process and approach used to complete the first task, describing the Bayesian evidence synthesis used to inform the clinical effectiveness parameters for the short-term model. Section 5 provides further details

of the structure of both the short and long term elements of the model, providing an overview of the key assumptions, data sources and the methods used to conduct the probabilistic analysis. Section 6 details the main cost-effectiveness results and explores the robustness of these results to a series of alternative assumptions. Finally, Section 7 addresses the second task by establishing the value of acquiring additional information to reduce current decision uncertainty.

3.2 Model structure

The model structure aims to reflect the nature of the decision problem and characterise patients' care and lifetime prognosis. As a result it comprises two main elements. The first consists of a short-term component that captures the main short-term events and costs associated with the management of AMI using either thrombolysis or primary angioplasty. This short-term model, which comprises a basic decision analysis tree up to 6 months after initial AMI, evaluates costs and effects over this period which matches the period of follow-up reported in many of the trials. The second element involves a long-term extrapolation using a Markov model, which extends the analysis from 6 months to a lifetime time horizon (assumed to be a maximum of 40 years). The results of the short-term model informs the particular health states in which patients will enter the long-term model, that is, the proportion of AMI patients that survive, die, or who have a non-fatal event (e.g. stroke or reinfarction) after 6 months. The results from the long-term model provide an estimate of the lifetime costs and quality-adjusted survival conditional on patients surviving the first 6 months.

The model considers the costs from the perspective of the National Health Service and Personal Social Services (NHS & PSS) and is expressed in UK £ sterling at a 2003/4 price base. The primary outcome measure for the economic evaluation is quality adjusted life years (QALYs). Costs and benefits were discounted using a 3.5% annual discount rate, in line with current guidelines. [9]

The model was populated using the best available data identified systematically from published literature and routine sources. All stages of the work were informed by an external advisory group comprised of clinicians experienced in the management of AMI patients. The advisory group met periodically in order to provide feedback on specific aspects of the analysis such as the model structure, data inputs and analysis.

3.3 Treatment strategies under comparison

Primary angioplasty was compared to pharmacological treatment with thrombolytic drugs (streptokinase or fibrin-specific agents) which is currently considered to be first line treatment in the UK for AMI. Short-term effectiveness estimates are based on an average of all streptokinase and fibrin-specific (mostly accelerated t-pa) trials in cluded in the meta-analysis. Full details are reported in Section 4.

4. EVIDENCE SYNTHESIS

4.1 Aim of the meta-analysis

The aim of the meta-analysis was to estimate the relative effectiveness of primary angioplasty, compared to thrombolysis, for a variety of different major cardiovascular events (death, re-infarction and stroke) over a range of PCI related time delays (hereafter referred to as PCI-time delay). Data was obtained by updating the most comprehensive published meta-analysis of randomised trials comparing thrombolysis with primary angioplasty in AMI. [17] This involved aggregating data from twenty-two trials, reporting at two different time endpoints: 1 month (which could be anything from 30 days to 6 weeks) and 6 months. Bayesian meta-regression was used to enable the simultaneous estimation of posterior distributions and correlational structure for major cardiovascular events (death, re-infarction and stroke) and different time endpoints (30 days and 6 months). The impact of PCI-time delay to was analysed using the mean (and associated uncertainty) additional time delay compared to thrombolytics administration as a covariate of the random effects model. The probabilistic decision analytic modelling was done using a Bayesian software package (WinBUGS).

4.2 Previous published meta-analyses

Our literature search identified four recent contemporary meta-analyses. [18-21] Cucherat et al. 2004 [19] is a Cochrane review amended in 2003 in which the biggest and most recent trial is the GUSTO-II [22] and trials published after 1997 are not included. Dalby 2003 [20] focused on transfer for primary angioplasty versus immediate thrombolysis and PCAT 2002 [21] analysed individual patient data from eleven trials with six-month follow-up. Despite their different aims and number of trials included, all analyses consistently found that primary angioplasty is more effective than thrombolytic therapy for the treatment of ST-segment elevation acute myocardial infarction.

The largest and most comprehensive of the meta-analyses was undertaken by Keeley et al. [18] There are a number of concerns over the methods used by Keeley et al. review including: the use of a single database for their search strategy, the lack of trial quality assessment, the inclusion of unpublished studies and the statistical handling of zero values and heterogeneity. [23-28] Our updated meta-analysis builds

on the review undertaken by Keeley et al. [18] Perhaps most importantly our study includes the results of two of the largest studies published in this area, [29, 30] which were only available to Keeley as conference abstracts. In addition, our Bayesian framework allows us to incorporate the analysis of uncertainty and the correlation between clinical efficacy at 4-6 weeks and 6 months. We also consider the impact of PCI-related time delay on the results by including this as covariate in the analysis.

4.3 Methods

4.3.1 Literature search

In order to systematically identify randomised trials comparing intravenous thrombolytic drug therapy with primary PCI published since the Keeley study, [18] we searched the following resources: the Cochrane Controlled Trials Register (CCTR), the National Research Register (NRR), Medline, Embase, the Database of Abstracts of Reviews of Effects (DARE), the NHS Economic Evaluation Databases (NHS EED) and the HTA Database. The searches were restricted to English language studies published between 2002 and 2004.

4.3.2 Study inclusion criteria

The inclusion criteria specified comparisons of primary PCI with hospital thrombolysis in patients with acute MI. These are consistent with the selection criteria used by both the Keeley study and the latest Cochrane review on this topic. [19] The definition of eligible patients differed between studies but typically required ischaemic symptoms and ST segment elevation, no major contraindications for the use of thrombolytic drugs and randomisation within 6 and 12 hours of suspected coronary occlusion. We excluded trial arms that specifically addressed transfer for primary angioplasty after thrombolytics (facilitated PCI) or inter-hospital transfer. [29-31]

Table 1 lists the studies included in our updated review of Keeley et al 2003. [18] Results from recent published studies are reported instead of previous conference abstracts used in the Keeley study. [29, 30, 32] One additional trial was identified subsequent to Keeley et al. [33]

Akhras 1997 [34] was excluded from our meta-analysis as it did not report mean time delays to treatment. The SHOCK study [35] was also excluded as it enrolled a high-risk group of patients with MI complicated by cardiogenic shock and compared

emergency revascularisation (angioplasty 64%, surgery 36%) without differentiating results by type of intervention. As such, the results were not directly comparable with the primary angioplasty strategy considered in the rest of trials.

4.3.3 End points and definitions

All 22 trials reported outcomes between 30 days and 6 weeks. Ten out of the total 22 (45%) trials also reported outcomes at 6 months after the initial MI episode. Clinical outcomes considered in the analysis were death, non-fatal re-infarction and non-fatal stroke. The combined endpoint was not considered because of definition discrepancies between the studies. All clinical end-points were analysed according to the intention to treat principle. We also considered data on the need for repeated reperfusion (CABG or angioplasty for the thrombolytic branch; CABG or repeated angioplasty for the primary angioplasty branch) and PCI-related mean time delay.

PCI-related time delay was defined as the mean (or median) difference between time-to-balloon in primary angioplasty and time-to-needle in thrombolytic therapy. Importantly, this definition emphasises the differences in the time to initiation of treatment between the two reperfusion strategies; thus disparities in specific definitions across the studies (i.e. from onset of symptoms, from admission, from randomisation etc.) become inconsequential. Time was measured from hospital admission or randomisation to balloon/needle when available and in all cases the same definition was used within each trial, so that no comparison bias between the two treatment groups was introduced. The 22 included trials had an average PCI-time delay of 54 minutes relative to thrombolytics.

Two researchers (YB, CA) selected the studies for the review and systematically extracted the clinical data. Differences between our data extraction and that reported in Keeley et al. 2003 were investigated in detail. The majority of these differences were due to the use of preliminary results from conference abstracts by Keeley et al 2003, compared to our own extraction that used the final published results. Some other differences between the data extraction could not be resolved and appear to be due to inaccuracies in the data extraction reported in Keeley et al. 2003 (see e. g. Nallamothu et al). [36] Discrepancies were resolved by consensus and a third party (SP) was consulted when necessary. Data inconsistencies between our results and Keeley's reported data were also resolved by consensus.

4.4 Overview of trials

Table 2 shows a summary of the main outcomes of the 22 trials assessed. Short-term major adverse events are also shown in table 2 (4-6 weeks). See Appendix 2 for a description of the main characteristics of the included trials.

There were eight trials comparing primary angioplasty versus streptokinase and fourteen versus fibrin-specific agents (most commonly the use of accelerated t-pa). The use of stents and glycoprotein IIb/IIIa antagonists (GPAs) reflected standard of care in current practice (the majority of trials published in the late 90s onwards report their use to a greater or lesser extent).

The clinical characteristics of angioplasty and thrombolysis patients were comparable in terms of age and although the definition of eligible patients differed between trials, although typically they required ischaemic symptoms and ST segment elevation of at least 1mm in two contiguous leads or a left bundle branch block (LBBB). Patients with contraindications for the use thrombolytic therapy were excluded in all studies.

There is, however, some variability in terms of patient risk. Ribichini 1998 [37] and García 1999 [38] enrolled high-risk patients, with inferior AMI (ST-segment elevation in the inferior leads and ST-segment depression in the precordial leads) and anterior AMI, respectively. Vermeer 1999 [31] included a relatively large proportion of patients with anterior infarction (total ST segment elevation and depression at least 1.5 mV or 15 mm). Finally, seven studies enrolled patients with LBBB, an unfavourable prognostic marker of mortality.

Both the PRAGUE [39] and the LIMI trials [31] included a third group of patients who received thrombolytic therapy followed by transfer to angioplasty (n= 1000 and n=74, respectively); both groups were excluded from our analyses.

Outcomes as defined by each individual trial were used. Because clinical outcomes were not available for every study at the same time point (i.e. hospital discharge, 30 days, 6 weeks, 6 and 12 months), we defined short-term as 4 to 6 weeks and 6 months, when available, as the primary time points of interest. Only one selected trial reports outcomes at 12 months.

Overall, the trials suggested that angioplasty provides a short-term (in-hospital to 30 days) clinical advantage over thrombolytic therapy. Differences in event-free survival between groups seemed to be minimal beyond 6 months. The main advantage of primary angioplasty over thrombolysis in low risk patients seemed to be the reduced risk of re-infarction.

4.5 Evidence synthesis

Aggregate data from the 22 trials were formally combined using meta-analytic approaches. A Bayesian evidence synthesis was implemented [40] using specialist software (WinBUGS) [41]. A random-baseline, random-effects approach was adopted for each outcome measure (see Parmigiani 2002, [42] van Houwelingen et al 2002 [43]) incorporating a linear regression of the treatment effect on the covariate 'PCI-related time delay' [44]. The model assumptions are described step by step below. Further technical details are presented in Appendix 3.

4.5.1 Multiple outcomes

There were a sufficient number of trials to inform an evidence synthesis of the major cardiac events: death, non-fatal strokes, and non-fatal re-infarctions. With such binomial outcomes, where an event either happens or does not happen, treatment effects can be modelled as absolute or relative risk differences or as log-odds. [45] For numerical convenience, we model all treatment effects on the log-odds scale. To reflect slight differences in recruitment criteria and patient mix, the baseline event rates for each outcome are assumed to vary randomly around a common mean (random-effects model).

4.5.2 Multiple time-points

While all trials reported outcomes at the 1-month endpoint, a number of trials also reported clinical events at the 6-month endpoint. However, any event that had occurred by 1 month would still have occurred by 6 months, so these endpoints are clearly related. Statistically, such a situation can be modelled by assuming that, for each treatment arm and outcome, the 1-month and the 6-month endpoints differ by a random effect, additive on the log-odds scale. We assume that these random effects are unrelated to the covariates that may explain some of the variation in the treatment effect of primary angioplasty compared to thrombolytics.

4.5.3 Treatment effect of primary angioplasty relative to thrombolytics

For each trial and outcome, we modelled the treatment effect of primary angioplasty relative to thrombolytics as a random effect additive on the log-odds scale, respecting both the randomisation scheme of the clinical trial and the heterogeneity of treatment effects measured by different trials. We assumed that the same mean treatment effect of primary angioplasty relative to thrombolytics applied at both the 1-month and the 6-month endpoint of each trial. This assumption was supported in the trial reports, which show that most clinical events occur within a few days from the initial episode. [38, 46-48] We do not attempt to impute the 6-month data for those trials that did not report it, and therefore the average treatment effect of PCI relative to thrombolytics will be informed more strongly by the 1-month endpoint data that are reported more commonly. The mean treatment effect of primary angioplasty, relative to thrombolytics, is modelled in terms of the covariate "time delay" by linear regression [44].

4.5.4 Correlated outcomes

We identify and model two sources of correlation between event rates. Baseline log-odds for the three outcomes are correlated across trials (e. g. high baseline mortalities may systematically coincide with elevated or reduced rates of non-fatal strokes). Also, within each outcome, we modelled correlation of the four endpoints (1-month and 6-month endpoints on two treatment arms), but we allowed the exact nature of these correlations to vary dependent on outcome. [43] We parameterise all the above correlations by multivariate normal distributions (again, on the log-odds scale).

4.5.5 Covariate 'PCI-related time delay'

To model the measurement error in the covariate 'PCI-related time delay', we model independently the delays associated with each treatment (time to needle/balloon) as measured in each trial, and calculate the value of the covariate by subtraction. For each treatment arm, the trial reports a summary statistic (i. e. mean with standard error, or median with confidence interval), which we have interpreted to obtain a prior mean and variance under the assumption of normality. For those trials that do not report the variability in times to treatment, [31, 39, 49] we used the corresponding average values from the other trials. Because treatment effect in our model only depends on the 'PCI-related time delay', it is irrelevant whether a trial measures the

time from occurrence of symptoms to reperfusion, or from randomisation to beginning of treatment as long as both arms of the trial are consistent.

The evidence synthesis model was fitted in a Bayesian framework. [41, 50, 51] We set non-informative prior distributions for all unknown model quantities and verified using sensitivity analysis that modifying the particular choices of these prior distributions do not alter our results substantially. All results of interest, i.e. baseline event rates, treatment effects and the regression of treatment effects on 'PCI-related time delay', are robust to the particular choices of non-informative priors.

4.6 Evidence synthesis results

Our results show that, for all outcomes, the mean probability of an adverse event occurring is lower for patients undergoing primary angioplasty. In particular, the incidence of mortality within 1 month is estimated to be 4.5% following primary angioplasty, but 6.4% following thrombolytics, with an odds ratio of 0.68 (95% Credibility Interval, CrI, 0.46, 1.01). From a frequentist point of view this falls just short of being significant at the 95% level. For the outcome of non-fatal re-infarction we find an odds ratio of 0.32 (0.20, 0.51), for non-fatal stroke we estimate 0.24 (0.11, 0.50), both are significant at the 95% level. See Table 3 for further details.

Because we explicitly model the additional time delay to reperfusion using primary angioplasty, we can predict how a longer or shorter additional delay would influence the superiority of angioplasty seen above and in previous studies. For assumed delays of 30, 60 or 90 minutes, the absolute probability differences and the relative risks of primary angioplasty versus thrombolytics are shown in Table 4. If primary angioplasty could be given at an additional delay of 30 minutes only, the absolute probabilities of mortality, non-fatal re-infarction and non-fatal stroke at 6 months, compared to thrombolytic treatment, would be 3.7%, 4.6% and 1.7% lower, respectively. All these are statistically significant at the 95%-level.

For any of the outcomes of death, non-fatal re-infarction and non-fatal stroke, the benefit of primary angioplasty decreases with longer additional delays (see Panel 1). In terms of mortality, primary angioplasty is superior to thrombolytics, on average, at time delays up to around 90 minutes. Moreover, from a frequentist point of view, in terms of the 1-month outcome of mortality the superiority of primary angioplasty is significant (at the 95%-level) for an additional delay of up to a little less than 60

minutes. For the 6-month outcome of mortality, a significant superiority of primary angioplasty can be asserted for delays of up to around 45 minutes only.

For the other two outcomes included in our study (non-fatal re-infarction and non-fatal stroke) primary angioplasty is superior on average, even if it requires an additional time of up to 2 hours to achieve reperfusion. For both non-fatal outcomes, the superiority of primary angioplasty is seen to be statistically significant at additional delays of up to 90 minutes at the 1-month endpoint. For the 6-month endpoint the superiority of primary angioplasty is statistically significant at delays up to 80 minutes.

5. COST-EFFECTIVENESS ANALYSIS

5.1 Short-term model

The short-term model is structured as a decision tree as shown in Figure 2. The initial decision node reflects the main alternatives being evaluated, i.e. whether a patient receives medical treatment with thrombolytics or primary angioplasty for the treatment of an initial AMI episode. The possibility of needing further revascularisations, either repeat angioplasty or CABG, are also modelled. These events are represented using chance nodes to reflect the uncertainty surrounding their occurrence. This uncertainty is conditioned upon whether a patient receives primary angioplasty or thrombolysis as part of their initial treatment. In the case of patients initially treated with thrombolytics, no distinction was made between rescue and non-rescue revascularisations up to 6 months, as there were insufficient data to apportion the revascularisation data reported in the trials to these separate categories. At the far right of the decision-tree, four mutually exclusive outcomes are modelled: repeat non-fatal MI, non-fatal stroke, alive without a further non-fatal event (stroke, repeat MI) and death. Using a similar approach as the one described for the revascularisation events, these outcomes are conditioned upon the initial treatment received by patients in the model. All short-term events and outcomes are populated directly from the evidence synthesis model outlined previously.

5.1.1. Relative treatment effect for primary angioplasty versus thrombolysis

As previously discussed, the results from the evidence synthesis were used to populate the effectiveness part of the short-term decision tree (see Section 4). The probability of various endpoints at 1 or 6 months after primary angioplasty or thrombolytic therapy, for the average observed PCI-related time delay, are shown in Table 3, alongside the associated odds ratios (O.R.) of primary angioplasty compared to thrombolysis.

The base-case analysis establishes the cost-effectiveness of primary angioplasty on the assumption that the average patient is treated as in the randomised trials included in the meta-analysis, and in centres that have the necessary infrastructure. As a result, the time-delay applied in the base-case analysis is based on the average figure reported across the trials (54.3 minutes). A series of sensitivity analyses were also undertaken to explore the impact of variation in the estimate of time delay on the cost-effectiveness results. Separate analyses were undertaken for delays of 30, 60

and 90 minutes. The absolute probability differences for the 6-month treatment effects of primary angioplasty compared to thrombolytic therapy at these different time-delays are shown in Table 4.

The probabilities of further revascularisations up to 6 months for both strategies are taken from the evidence synthesis model outlined previously. The revascularisation events and probabilities applied in the short-term model are reported in detail in Tables 5 to7.

5.1.2. Resource use and unit costs short-term model

All resource use associated with the short-term model is shown in Table 5. The resources considered include those associated with the initial interventions (e.g. drug acquisition costs, procedure costs and associated hospital length of stay) and subsequent events occurring over the following 6-month period, such as further revascularisations and major clinical events (either repeat MI or stroke). Hence, the resource use considered in the model relates directly to the clinical events shown in Figure 1.

One of the main areas considered in the model is the length of the initial hospitalisation and the effectiveness of primary angioplasty compared to thrombolysis. Both of these areas are likely to have an important effect on the overall cost differences estimated between the two strategies considered. For our base-case analysis, we use national statistics on the average length of hospital stay for patients with AMI based on Hospital Episode Statistics (HES). [52] Hence, in the absence of reliable data in which to quantify the potential impact of primary angioplasty on the length of the initial hospitalisation, we apply a conservative approach by assuming that primary angioplasty has no impact on the duration of hospitalisation. A separate sensitivity analysis is also conducted using estimates from a sample of 80 patients from Hammersmith and Charing Cross Hospital, in order to assess the robustness of the results to alternative assumptions related to length of initial hospitalisation (Dr. Kenneth Morgan, personal communication).

We also applied a conservative assumption regarding the resource use and costs for all consumables and adjunctive drugs used with primary angioplasty. For angiography we assumed that all patients undergoing primary angioplasty would require an angiogram as part of the treatment, while those treated with thrombolytic

agents would not. The base-case analysis assumed that all patients receiving primary angioplasty would receive adjunctive GPAs and stents during the initial procedure, although, in reality, the use of these adjunctive treatments is likely to vary between different hospitals. Because of uncertainty regarding the cost-effectiveness of drug-eluting stents, [53] we only included the cost of bare metal stents in our model.

Regarding the type of thrombolytic agent used, we opted to use the cost of the most expensive but increasingly more commonly used, t-pa (£600 per dose compared with £89), instead of an average price of t-pa and streptokinase.

All unit cost data used in the analysis to value resource use for the short-term model are shown in Table 8. Drug costs were taken from the British National Formulary, [54] based on licensed dosages for this particular indication. Other unit costs were obtained from national databases (NHS Reference Costs) [55] or published literature. [54-60] The costs associated with revascularisations were based on NHS Reference Costs estimates, [61] applying a weighted mean cost based on the proportion of elective and non-elective interventions. All costs were updated to 2004 prices using Hospital and Community Health Services (HCHS) prices index 2004. [62] Value added tax (VAT) is included in the cost of consumables but not for drug acquisition costs, in line with the recent NICE methods guidance (2004). [9] These unit costs (Table 8) are used together with the resource use (Table 5) to generate an overall mean cost for the two main strategies given in Figure 2.

5.2 Long-term model

Any assessment of the cost-effectiveness of strategies for MI must allow for the long-term implications in terms of cost and outcome of the initial episode treatment. This approach is necessary in order to reflect the lifetime costs and QALYs associated with the alternative strategies. The long-term model is structured as a Markov model as shown in Figure 3.The model structure aims to reflect the major clinical and resource generating events that a patient may experience throughout the course of their remaining life (taken to be 40 years).

5.2.1. Long-term model structure

Figure 3 presents the structure of the Markov model used for the long-term extrapolation, illustrating the eight possible health states (circles) and alternative pathways that a patient may experience over the course of their lifetime. The cycle length of the model determines the speed by which patients may make particular movements between the health states (referred to as transitions). A cycle length of one year was applied in this analysis, and the model was run for 40 cycles.

Patients enter the long-term model in one of the following four states: no further event (IHD), repeat non-fatal MI, non-fatal stroke or the death state (which is assumed to be cardiac related during the initial 6-month period). The short-term model informs the long-term model about the proportion of patients that enter the long-term model in each of these states. The short-term model also estimates the costs incurred during the first 6 months for each strategy.

Patients in any non-fatal Markov health state can move into the death states (cardiac or non-cardiac related) at any cycle. The two death states represent 'absorbing' states in that further transitions are not permitted following entry into this particular state. In addition, patients in the IHD state can experience a non-fatal MI or a non-fatal stroke. In these circumstances, they move to the MI state or stroke state for one year, after which they can die or move to the post-MI state or post-stroke state. In other words, the MI and stroke health states only apply for one cycle. Patients in the MI state or stroke state can die or move to the post-MI or post-stroke states (i.e. 2nd cycle onwards). Further recurrent non-fatal events incurred by patients in the post-MI and post-stroke states are fully accounted for in the model by incorporating the costs of these additional events and their impact of quality of life, although for simplicity these additional events are not illustrated graphically.

5.2.2 Populating the long term model – probabilities

In the absence of long-term trial evidence on the prognosis of patients following primary angioplasty or thrombolysis, UK registry data was used to calculate long-term transition probabilities and resource use. A number of potential UK registries for AMI patients were considered, including the Nottingham Heart Attack Registry (NHAR), Myocardial Infarction National Audit Project (MINAP) and the Global Registry of Acute Coronary Events (GRACE) registry [63-65]. For the purposes of this analysis, it was necessary to have access to patient-level data (with unique

identifiers) that could provide a longitudinal analysis of subsequent fatal and non-fatal events (e.g. further re-infarctions, stroke etc). After careful consideration, the Nottingham Heart Attack Register (NHAR) was selected because extensive follow-up data had been collected and provided detailed information on both the frequency and timing of recurrent events. In addition, follow-up for the NHAR was the longest available of the registries considered (5-years).

The NHAR was initially set up in 1973 to audit the development of a new paramedic service in Nottingham. It has since been developed extensively, and now collects some 175 data points on each patient covering pre-hospital and in-hospital events, admission and discharge data, risk factor profiles and follow-up plans [65].

The NHAR data was derived from the 1992 cohort. In order to correspond with our model structure, patients were selected based on initial AMI episode and survival to 6 months. A total of 627 patients with 5 years follow-up of survival and subsequent MI or stroke (i.e. recurrent event) were analysed. All transition probabilities were calculated from data from 6 months after the initial episode.The annual transition probabilities obtained using survival analysis techniques are presented in Table 9.

The notation 'NF Event' includes stroke or repeated myocardial infarction. Transition probabilities were modelled using a piecewise exponential model for each of the transitions from the IHD and 'NF Event' states. The first 'piece' corresponds to the first year following MI to reflect the higher probability of experiencing major cardiac events (both fatal and non-fatal) in this period. Although event rates were substantially higher in the first year, the subsequent estimates for the second year and beyond were remarkably similar. Thus, these years were modelled together as the 2nd 'piece', with the assumption that event rates remained constant during this period.

Data for patients experiencing a non-fatal stroke in the NHAR data were combined with data for patients experiencing recurrent MI in order to estimate the transition probabilities for the non-fatal stroke state, due to the small number of events in the data. Transitions to and from this state were thus estimated statistically using a single combined 'Non-Fatal Event' state. For the purposes of the decision model, the proportion of patients in the 'Non-Fatal Event' state experiencing a recurrent MI or stroke were apportioned on the basis of the proportion of patients experiencing these particular events in the NHAR data. This approach enabled the separate costs and

quality of life impacts of these different events to be fully captured by the model, but meant that subsequent transitions (e.g. either to a further recurrent episode or to the death state) were assumed to be the same. Table 10 relates the probabilities associated with stroke and recurrent events.

In addition to the data from NHAR, external estimates were also utilised in an attempt to fully quantify the resource implication and quality of life impact of these additional non-fatal events in the long-term. In particular, it was necessary to try and reflect the disability level and potential impact on non-NHS providers for patients who had experienced a non-fatal stroke in order to account for the potential long term costs outside of the hospital setting. Neither of these areas could be suitably informed by the NHAR data and hence estimates were derived based on previous research undertaken in this area. [58, 66] These external estimates were used to estimate the probability that a non-fatal stroke resulted in significant disability and the probability that stroke patients would be discharged home or to institutional care.

Only death for cardiac reasons was estimated using the NHAR data. Although other causes of mortality were reported, due to the small number of these events the probability of non-cardiac mortality was estimated using life-table data. A life-table for non-cardiac death for the UK population is presented in Table 11. The life tables were calculated eliminating deaths caused by cardiovascular disease (ICD10: I00 to I99 excluded). The cause elimination was calculated using standard methods by the ONS and based on their latest mortality statistics (2002). [2] The corresponding yearly probability of dying from a non-cardiovascular death is simply estimated by the number of deaths in each strata divided by the total starting in each strata. Mean probabilities in each age strata together with 95% confidence intervals are shown.

The full transition probability matrix, for the complete range of possible transitions applied in the long-term model, is presented in Table 12.

5.2.3. Populating the long-term model - resource use and unit costs

Estimates of the probability and number of hospitalisations for MI, post-MI and other causes (including non-cardiac hospitalisations) were obtained for each state directly from NHAR. These probabilities were combined with external estimates of the length of such hospitalizations taken from previous work undertaken in this area. [67-69] This external evidence was also used to estimate the resource use and costs

associated with outpatient and daypatient attendances for each of the health states considered. The resource use and unit costs used in the long-term model are detailed in Tables 13 and 14.

Mean annual costs for each non-fatal state (IHD, non-fatal MI, post-MI, non-fatal stroke and post-stroke) have been applied to the model. These annual costs were estimated by applying the average number of days in the IHD (449), MI (268) and Post-MI (200) states calculated from the NHAR dataset. Table 15 summarises the mean annual costs for each of the health states. In addition, a one-off 'transition cost' is applied to patients dying from cardiovascular reasons. This cost is based on the probability of dying in hospital and the associated length of stay.

The uncertainty in resource use in the long-term model is characterised by beta distributions (to reflect the proportion of patients utilizing a particular resource item) and a gamma distribution (to reflect the intensity of use). These estimates are then multiplied by the relevant unit costs, in order to estimate the total costs for each state.

5.3 Adjustment for Quality of Life

In order to estimate QALYs, it is necessary to quality-adjust the period of time the average patient is alive within the model using an appropriate utility or preference score. In the absence of utility data from the trials and the NHAR, external estimates of utility data were sought in order to differentiate between the health status of patients in the IHD, MI, post-MI, stroke and post-stroke states of the long-term model. The estimates applied in our analysis were based on the results of a previous systematic review and economic model undertaken to evaluate alternative treatments for the prevention of occlusive vascular events. [68] As part of this previous work, a separate systematic search and critical appraisal of studies reporting utility values for these particular health states had been undertaken. These estimates were considered the most reliable source for the model. Table 16 reports these data in detail.

For the first year of the IHD (no event) state, we estimated a utility value weighted on the basis that half of this period would be covered by the estimate derived for the 1st year after an MI, and half the period would be covered by the value for the post-MI state. This approach was necessary in order to reflect that patients entered the long-term model 6-months after their initial event. A single utility score for stroke patients

was applied which was weighted by the probability of having a disabling stroke. The uncertainty associated with utility scores was characterised by beta distributions. [70]

5.4 Sensitivity analysis

A series of sensitivity analysis were undertaken to test the robustness of the results of the base-case model to the use of alternative assumptions. The sensitivity analyses have been divided into three main sections:

1. variation in the additional time-delay required for primary angioplasty;
2. variation in the length of hospital stay;
3. variation in the trials used to populate the model.

An overview of the alternative assumptions applied in each of these analyses is reported in Table 17. A brief description of the approaches is reported below.

(1) Time-delay

The base-case assumed that the primary event occurs at a mean age of 61 and that primary angioplasty took on average 54.3 minutes longer to administer than thrombolysis. These assumptions reflect the average estimate of the additional delay reported across the 22 trials included in the evidence synthesis. A sensitivity analysis of alternative time-delays was conducted using estimates of 30, 60 and 90 minutes.

(2) Length of hospital stay

In the sensitivity analysis we relaxed the conservative approach taken regarding the length of initial hospitalisation to consider the potential impact of primary angioplasty in terms of reducing the length of the initial hospitalisation compared to patients receiving thrombolytic therapy.

(3) Trials incorporated

Finally, we conducted a series of alternative scenarios in order to explore the impact of excluding the trials where streptokinase was administered, in order to compare primary angioplasty with the more effective thrombolytic drugs.

6. COST- EFFECTIVENESS RESULTS

The model is run for a period of 40 cycles (equivalent to 40 years), after which the vast majority of patients will have died. Therefore, the mean life-years and QALYs per patient can be calculated for each strategy, as well as the mean lifetime costs. The model does not formally include any particular sub-group of patients, and therefore reflects the balance of baseline clinical characteristics as seen in the trials and the NHAR.

Incremental cost-effectiveness is calculated from the expected (mean) costs and QALYs estimated by the model. If dominance does not exist the incremental cost-effectiveness ratio (ICER) is calculated. [71] This shows the mean additional cost of generating one additional QALY by the more effective intervention. Whether this additional cost is worth paying for requires a judgement on the part of NHS decision makers. However, interventions with incremental cost-effectiveness ratios in the region of £20,000 - £40,000 per QALY have been considered to provide value for money in the NHS. [72]

The model has been developed as a comprehensive decision-analytic model using Bayesian methods and WinBUGS software. All input parameters were entered as probability distributions to reflect their imprecision in the estimates. Monte Carlo simulation was used to propagate the parameter uncertainty through the model. [73] Three parallel chains were run for 5,000 iterations of burn-in, which visual inspection of the Gelman-Rubin convergence statistic indicated to be sufficient for convergence. To remedy the observed autocorrelation of the chains, only every 10th of the 6,000 subsequent draws from each of the chains was recorded to generate the results. The Monte-Carlo simulation was run for 10,000 iterations

In addition to presenting estimates of the ICER we present the uncertainty in these results and the decision uncertainty. This is presented using cost-effectiveness acceptability curves which show the probability of primary PCI being cost-effective conditional on a range of possible threshold values which NHS decision makers attach to an additional QALY. [74]

6.1 Results short-term model

Table 18 details the expected short-term (up to 6 months after the initial AMI episode) costs for each strategy. Primary angioplasty is more expensive, costing an average of £6,600 per patient as opposed to thrombolytic therapy, which costs around £3,620. This difference is primarily due to the additional cost of initial treatment associated with primary angioplasty (cost difference of £3,760). This additional cost is reduced, but not offset, by a cost-saving of £780 associated with fewer revascularisations for patients receiving primary angioplasty.

6.2 Base-case results of the long-term model

Table 19 presents the basecase results for the long-term model in terms of costs, QALYs and the ICER. Primary angioplasty is the most expensive option (£12,760 compared to £10,080 mean cost for thrombolytics), but it is also associated with a mean QALY gain of 0.29 (7.12 mean QALYs for primary angioplasty compared to 6.83 mean QALYs for the thrombolytics strategy). The ICER associated with primary angioplasty compared to thrombolytics is £9,241 per QALY. Hence, primary PCI is the optimal decision provided that the decision-maker is prepared to pay at least this amount per additional QALY.

While the results of the ICER can be used to determine the optimal decision based on a comparison of mean costs and QALYs, they do not incorporate the uncertainty surrounding this decision. Figure 4 presents the uncertainty in the costs and effects on the incremental cost-effectiveness plane. The estimate of the mean incremental cost and effect is indicated and the ellipse shows the 95% confidence interval of the expected incremental costs and QALY values. Figure 5 presents the base-case results in the form of a cost-effectiveness acceptability curve (CEAC). The CEAC demonstrates that if society is prepared to pay £10,000 per additional QALY, the probability that primary PCI is cost-effective is around 0.55 increasing to almost 1 if the maximum willingness-to-pay (WTP) is beyond £30,000.

6.3 Sensitivity analyses

The robustness of the results to variations in time delay were tested through sensitivity analysis using 30, 60 and 90 minutes. In addition, alternative scenarios were used to explore the implications of using a differential length of hospital stay for patients administered thrombolytics or undergoing primary angioplasty (S1),

comparing primary angioplasty with the most effective thrombolytic type (S2) and a combination of both (S3). Results are reported also for time delays at 30, 60 and 90 minutes, in order to assess the robustness of the basecase results to this issue.

6.3.1. Variation in the additional time-delay required for primary angioplasty

Table 20 presents cost-effectiveness results associated with different time delays (30, 60 and 90 minutes), in order to assess the robustness of the base-case model results to variation in time delay to treatment. Figure 6 presents the results for different time delays on the incremental cost-effectiveness plane and Figure 7 presents the related CEACs.

Reducing the time delay to 30 minutes results in an improvement in the estimate of cost-effectiveness with a reduction of the ICER to £6,850 per QALY. Furthermore, the probability that this strategy is cost-effective increases from 0.55 to 0.82 at a maximum WTP of £10,000 per QALY. For higher thresholds, primary angioplasty is associated with a very small error probability (0.02 for a £20,000 WTP and 0.01 for a £30,000 WTP). The results at 60 minutes are very similar to those for the base-case analysis, as expected given the base case delay of 54.3 minutes. There is, however, a slight increase in the ICER (£10,269 per QALY) and a slightly smaller probability of being cost-effective at £10,000 (0.43).Increasing the time-delay up to 90 minutes resulted in a six-fold increase in the base-case ICER (£64,750 per QALY) and substantial reduction in the probability that primary angioplasty was considered cost-effective (0.13 for a WTP of £10,000). This analysis clearly demonstrates the relevance of time-delay on the cost-effectiveness results of both treatments.

6.3.2 Variation in the length of hospital stay

The scenario S1 of the sensitivity analysis explores the independent effect of hospital length of stay on the cost-effectiveness results. Instead of the average length of stay based on HES estimates (10 days), we used differential lengths of stay (5.76 for primary angioplasty compared to 12.12 days for the thrombolytic strategy) based on estimates from a sample of 80 patients from Hammersmith Hub site and Charing Cross Hospitals (Dr. Kenneth Morgan personal communication). The results show that, for the average time delay (54.3 minutes), the ICER for primary angioplasty decreases to £5,488 (compared to the £9,241 for the base-case analysis). As a

consequence, the probability of primary angioplasty being cost-effective for a threshold of £10,000 increases from 0.55 (base-case) to 0.85.

The results at 60 minutes are closer to the base case (£6,038 compared to £9,241 base-case). However, at 90 minutes the ICER increases to £37,250 per QALY. This result is not surprising if we take into account the effect of PCI-time delay on short-term effectiveness for the different outcomes: while results at 60 minutes show primary angioplasty as the most effective strategy (RR 0.75 for death, 0.38 for non fatal reinfarction and 0.26 for non fatal stroke), this is not the case at 90 minutes, especially for the prevention of death (RR 1.05, 0.50 and 0.35, respectively). See Table 3 and 4 for further details.

6.3.3. Variation in the trials used to populate the model

As expected, when primary angioplasty is compared with the most effective thrombolytic drug (S2 scenario), instead of averaging efficacy across all streptokinase and t-pa trials, the ICER for primary angioplasty increases slightly (from £9,241 base-case to £9,833). When this is coupled with a change in the average time-delay to 90 minutes, primary angioplasty is dominated by thrombolytics (i.e. it is, on average, more expensive and less effective). This result is explained by the effect of PCI-time delay on the effectiveness of PCI. Appendix 5 presents the short-term effectiveness results at different time delays based on the t-pa trials. As observed with all trials the results show that at 60 minutes primary angioplasty is the most effective strategy (RR 0.77 for death, 0.45 for non fatal reinfarction and 0.28 for non fatal stroke), but at 90 minutes the results worsen considerably, especially in the case of death (RR 1.11, 0.38 and 0.66, respectively).

When we combine both scenarios (S3), the reduction in mean cost associated with primary angioplasty due to shorter hospitalization compensates the better effectiveness associated with t-pa for the base-case time-delay with an ICER of £5,778 per QALY and a probability that primary angioplasty is the most cost-effective treatment of 0.72 for a £10,000 WTP. The results of this scenario are very similar to those reported to Scenario S1, when only the differential length of stay was examined. However, the real difference is again observed at 90 minutes, where the reduced effectiveness ensures that primary angioplasty is dominated.

The CEACs associated with these alternative scenarios are shown in Figures 8-10.

6.4. Conclusions

The results indicate that primary angioplasty is cost-effective for treatment of AMI based on a lifetime horizon. The ICER of primary angioplasty in the base-case analysis was £9,241. These results were based on the average time delay reported across the trials (54.3 minutes). In addition, primary angioplasty was demonstrated to be cost-effective even though a number of conservative assumptions were applied to the resource use and costing assumptions

These findings are explained by the superior mortality benefit associated with primary angioplasty when compared to thrombolytics for delays of up to 1 hour, and the prevention of non-fatal re-infarction and non-fatal strokes for delays of more than 80 minutes. The sensitivity analyses show that results are most sensitive to the time-delay factor. Even with a significant reduction in mean costs (S1), primary angioplasty is shown not to be cost-effective for delays of up to 90 minutes.

7. VALUE OF INFORMATION ANALYSIS

7.1. Theoretical background

The expected cost of uncertainty surrounding the adoption decision is determined using the expected value of perfect information (EVPI). Value of information analysis involves establishing the difference between the expected value of a decision made on the basis of existing evidence and, following the collection of further information, the expected value of a decision made on the basis of new evidence. The expected value of perfect information (EVPI) values the resolution of all uncertainty, through the provision of perfect information, and provides a measure of the maximum return to further research. The EVPI represents the maximum a decision maker should be willing to pay for additional evidence to inform this decision in the future. If the EVPI exceeds the expected costs of additional research, then it is potentially cost-effective to acquire more information by conducting such research. [13, 75]

Within the framework, the EVPI for the decision can be determined directly from the results of the probabilistic analysis with each iteration representing a possible future resolution of the existing uncertainty for which the optimal decision (the intervention which maximises net benefit) can be identified. For a decision involving j interventions where net benefit is dependent upon a set of unknown parameters θ, the EVPI is simply the difference between the expected value of the decision made on the basis of existing information (maxj [Eθ {NB(j, θ)}]) and the value of the decision made with perfect information (maxj {NB(j, θ)}) averaged over all possible realisations of uncertainty (Eθ [maxj {NB(j, θ)}]):

$$EVPI = E_\theta [\max_j \{NB(j, \theta)\}] - \max_j [E_\theta \{NB(j, \theta)\}]$$

Since Information is a public good, generation of perfect information for one instance of a decision ensures that the information is available for other instances of the decision. Hence, the overall value of perfect information surrounding a healthcare policy decision depends upon the number of times that the decision is faced over the lifetime of the technology. [13, 75] The population level EVPI is determined by scaling up the individual EVPI according to the incidence of the decision.

In addition to determining the EVPI surrounding the decision as a whole, value of information techniques can be used to particular elements of the decision in order to

direct and focus research towards the areas where the elimination of uncertainty has the most value. The partial EVPI can be calculated for individual or subsets of parameters. The process involves determining the expected value of a decision made with and without perfect information for the subset of parameters of interest. For a subset of parameters φ, the expected value of partial perfect information (EVPPI) is simply the difference between the expected value of the decision made on the basis of existing information (maxj [Eθ {NB(j, θ)}]) (as with the calculation of decision EVPI) and the value of the decision made with perfect information about φ (maxj [Eθ|φ {NB(j,θ)}]). Where perfect information about the subset of parameters has no impact on the decision the information has no value. The value of the decision made with perfect information about φ is averaged over all possible realisations of uncertainty (Eφ [maxj (Eθ|φ {NB(j,θ)}]]) to reflect the fact that the subset of parameters can resolve at any point within the distributions:

$$EVPPI_{\varphi} = E_{\varphi} [max_j (E_{\theta|\varphi} \{NB(j,\theta)\})] - max_j [E_{\theta} \{NB(j,\theta)\}]$$

7.2. Results of value of information analysis

7.2.1. Population EVPI (PEVPI)

In order to estimate the effective population for the decision we estimated the average incidence rate of MI for men and women aged 30-69 (600 per 100,000 and 200 per 100,000 respectively). [76] We applied these rates to the UK population and calculated that there were a total of 87,000 new MI cases per year (63,000 heart attacks per year in men aged under 75 living in the UK and 24,000 in women). Further, we assumed that only 70% of these patients present at hospital and are eligible for thrombolytics. We also assumed an effective lifetime of the decision of 10 years.

Table 22 presents the EVPI for the UK population of eligible MI patients over a range of threshold values. Given a willingness-to-pay of £30,000 per QALY the EVPI was estimated to be £170 million for the base-case analysis. Figure 11 illustrates the population EVPI for the base case over a range of values of the willingness-to-pay for a QALY. Initially, the population EVPI rises as WTP increases up to the point where the WTP equals the ICER. This is because both the error probability (as evidenced by the CEAC) and the valuation of the consequences of error (via the WTP) are increasing over this range. At the point where the WTP equals the ICER the decision

changes (adopt primary angioplasty) and the uncertainty falls as the WTP increases (as evidenced by the CEAC). The two effects are pulling in different directions. Over the range of WTP up to approximately £30,000 the reduced error probability overshadows the increased valuation of the consequences and the EVPI falls. Beyond this point the error probability is fairly stable and the increased valuation of the consequences of error overshadows the reduction in the error probability and the EVPI rises again.

Table 22 reports also the EVPI for the different sensitivity analysis scenarios at different time delays, which are consistent with the trend observed for the base-case. The results seem to be driven by time-delay: as PCI-time delay increases beyond 60 minutes the probability of making the wrong decision (and the EVPI) unambiguously increases. For the base case the population EVPI associated with a time-delay of 90 minutes is estimated to be £2,200 for a willingness-to-pay of £30,000 per QALY.

7.2.2. Population Partial EVPI (PEVPPI)

Table 23 presents the PEVPPI for a set of relevant group parameters (evidence synthesis and revascularisations, transition probabilities, cost and utilities). The results reveal that the evidence synthesis is driving the decision uncertainty mainly through the short-term treatment effect of primary angioplasty on mortality (£99m). Whilst the components of the long-term model are less relevant (£27m).

7.3 Conclusions

The EVPI for the clinical decision problem as a whole shows a considerable value of information of £170 million for the base-case analysis given a £30,000 WTP. Further research in this area would appear to be potentially worthwhile. The results of the partial EVPI analysis show that research should focus on the effectiveness of primary angioplasty beyond 60 minutes and, in particular its impact on mortality.

8. DISCUSSION

8.1. Summary of results

Despite the existence of a substantive evidence base for the clinical effectiveness of primary PCI, to date there has been a relative dearth of cost-effectiveness analyses suitable for informing UK decision makers. Indeed, existing cost-effectiveness evidence is lacking within both the UK and internationally. The analysis presented here attempts to address the deficiencies in the existing cost-effectiveness evidence base for primary PCI, providing a systematic and comprehensive approach to synthesising existing clinical and economic evidence on the potential cost-effectiveness of primary PCI in a UK decision-making context. The analysis represents an important contribution to the existing clinical and cost-effectiveness evidence for primary PCI. Firstly, it updates the most comprehensive recent meta-analysis of randomised trials comparing primary angioplasty and thrombolysis in patients with STEMI. Secondly, it extends the evidence synthesis by evaluating the relationship between the treatment effects of angioplasty and the mean angioplasty-related time delay (over and above time to initiation of thrombolysis). Furthermore, to our knowledge, this is the first study that explicitly models the measurement uncertainty associated with angioplasty-related time delay. Finally the use of a decision-analytic approach enables the results from the evidence synthesis of existing clinical trials to be related to longer-term costs and outcomes and hence to the cost-effectiveness of primary PCI.

This analysis builds on previous meta-analyses by extending their scope and statistical rigor. It assesses how both the treatment effect and cost-effectiveness of angioplasty on fatal and non-fatal outcomes (re-infarctions and strokes) relates to the additional delay involved in initiating angioplasty. It also considers both the short-term and longer-term outcome data reported in randomised clinical trials. Furthermore, in using Bayesian statistical methods, the analysis is able to quantify more fully the uncertainty associated with the estimated relationships.

The results demonstrate that primary PCI appears cost-effective, compared to thrombolysis, for treatment of AMI based on a lifetime horizon. These findings are strengthened since primary PCI was demonstrated to be cost-effective even though a number of conservative assumptions were applied to the resource use and costing assumptions. As seen in previous studies, the clinical advantage of angioplasty

decreases the longer the time delay to initiation of angioplasty. Clearly this has important implications for the cost-effectiveness of primary PCI. The base-case analysis was based on the average time delay reported across the trials (54.3 minutes). However, there was marked variation across the trials in the additional PCI-related time delay. The use of Bayesian meta-regression approaches enabled this potential source of heterogeneity to be quantified and enabled the cost-effectiveness of primary PCI to be established across a range of alternative time delays. In summary, primary PCI was demonstrated to be clearly cost-effective for delays up to 60 minutes, although the cost-effective advantage of this strategy was no longer apparent at a delay of 90 minutes. These findings are explained by the superior mortality benefit associated with primary angioplasty when compared to thrombolysis for delays of up to one hour, and the prevention of non-fatal re-infarction and non-fatal strokes for delays of more than 80 minutes. Results from the Bayesian meta-analysis demonstrated that the clinical superiority of primary PCI was no longer evident at delays of 90 minutes or more, which explain the cost-effectiveness results presented here.

The analysis suggests, therefore, that angioplasty performs better than thrombolysis but this clinical and cost-effectiveness superiority is related to angioplasty-related time delay. It should be emphasised, however, that no trials have been identified which show a statistically significant advantage for thrombolytic drugs at very long angioplasty-related time delays. Moreover, the PRAGUE-2 trial indicates that angioplasty performs better than thrombolytic therapy even when it involves a patient transfer of up to three hours. Without more evidence at long angioplasty-related time delays, the linear regression model estimated here will inevitably indicate that the relative treatment effect of PCI becomes negative at an unspecified delay. This is not because of data showing this effect, but simply because a consistent relationship has been observed for a range of relatively short time delays. Consequently, the lack of cost-effectiveness advantage found at longer-time delays need to be assessed against this potential limitation.

8.2. Comparative analysis with other published studies

We identified all published cost-effectiveness studies on primary PCI using a systematic review of literature. A total of seven studies were considered, although four of these did not meet the inclusion criteria, one of them was not a cost-effectiveness analysis, [77] two compared balloon angioplasty with coronary stenting

[78, 79] and another one was an economic evaluation alongside a clinical trial that compared primary angioplasty with or without stents and adjunctive abciximab. [80] Only three studies met the inclusion criteria: one UK study [6] and two international studies. [7, 8]

Hartwell et al. [6] presents a decision tree model that compares three options: primary PCI, thrombolytics, and primary PCI when thrombolysis is contraindicated. This third alternative is compared to a base case scenario of symptomatic and supportive treatment only (i.e. pain relief and beta-blockers), so the authors do not present and indirect comparison of the three management strategies. The model considers the costs from the perspective of the UK NHS. Mortality, morbidity and 'restored health' are considered as the main health outcomes of the analysis, however the methods used to calculate utilities appears arbitrary (i.e. restored health is assumed to be equivalent to discharge home and attributed the value of perfect health, 1) and results are only reported in the short-term (approximately at hospital discharge).

Müllner et al. [7] presents results of a decision tree that compares balloon angioplasty with t-pa from the perspective of the Austrian public health insurance organisations, with life years saved (LYS) as its primary outcome measure. The last one is a US study, Lieu et al. [8], that presents a decision tree with three main treatment options: balloon angioplasty, thrombolysis (SK or t-pa) and no intervention. The model considers the costs from a societal perspective and its primary outcome are QALYs.

All three previous studies reported that primary PCI appeared cost-effective compared to thrombolysis, which concurs with the findings from the base-case analysis presented here. A direct comparison of our cost-effectiveness results with the results from these studies, however, is not particularly meaningful as there exist important differences in terms of their choice of time-horizon, comparators, perspective of analysis and main outcome measures. In addition, none of these studies has considered the variation in cost-effectiveness estimates according to time-delay.

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8.3 Limitations of the model

This study has some limitations. Firstly, the lack of individual patient data precludes the analysis of how the relative effect of angioplasty varies between patient sub-groups, and whilst this analysis has taken account of the uncertainty in the average time delay, thus reducing the possibility of ecological fallacy, the presence of an ecological bias can't be entirely eliminated. However, the aim of this study is to provide some evidence that can help to take population decisions and so the generalisability of the findings at an individual level is not an issue. Analysis of individual patient data would also enable a more appropriate estimate of the impact or otherwise of time delay on outcome to be obtained. [81,82] Secondly, time-to-needle is a predictor of the success of thrombolytic treatment, but this effect could not be included in the analysis explicitly due to inconsistent reporting of the data in the trials. Hence the results are based on the *average* time-to-needle in the studies considered, which was shown to be similar to the median call to needle time (67 minutes) in the UK (personal communication, Dr John Birkhead, UK Myocardial Infarction National Audit Project). Thirdly, given this review was an update of those published earlier, neither the effect of publication bias, study quality or the influence of individual studies were formally assessed on the overall meta-analysis results.

The fourth limitation concerns the use of older streptokinase trials in the meta-analysis. Keeley *et al* were criticised[45] for including these trials in their meta-analysis because, by effectively averaging across the thrombolytic trials, the additional benefit of angioplasty may have been over-estimated. However, streptokinase is the most common form of thrombolytic therapy used in many countries and is used in about a third of patients in the UK (personal communication, Dr John Birkhead, UK Myocardial Infarction National Audit Project).

A further limitation relates to the strategies considered in the model presented here. Existing thombolytic trials of different therapies (streptokinase, t-pa etc.) were pooled together and presented as a single comparator strategy for primary PCI. In reality each therapy represented a possible comparator for primary PCI based on cost-effectiveness considerations. In order to establish the cost-effectiveness of primary PCI in relation to individual thrombolytic therapies appropriately would require consideration of additional indirect evidence from trials in which alternative thrombolytic therapies (either head-to-head or against placebo) would need to be considered. The issue of relevant comparators extends beyond the choice of

thrombolysis and would also need to consider the potential cost-effectiveness of alternative modes of thrombolytic administration (e.g. use of pre-hospital thrombolysis) and the use of facilitated-PCI (i.e the use of PCI in patients who do not respond to thrombolysis). These analyses represent significant extensions to the work presented here and are the subject of ongoing research we are undertaking in this area.

8.4. Future research recommendations

In addition to the comparator issue noted previously, the value of information analysis shows a considerable value of information (£170 million at a WTP of £30,000 per QALY). Further research in this area would thus appear to be potentially worthwhile. The results of the partial EVPI analysis show that research should focus on the effectiveness of primary angioplasty beyond 60 minutes and, in particular its impact on mortality.

Table 1. List of studies included compared to Keeley et al. and other recent meta-analyses

	Current updated review (n= 22)	Keeley 2003 (n= 23)	Cucherat 2004 (n= 10)	PCAT 2002 (n= 11)	Dalby 2003 (n= 6)
Streptokinase trials					
Zijlstra 1993[83]	√	√	-	√	-
Ribeiro 1993[84]	√	√	√	√	-
Zwolle 1994[33]	√	-	√	-	-
Grinfeld 1996 [85] ¥	-	√	√	√	-
Berrocal 2003[32]	√	-	-	-	-
Zijlstra 1997[86]	√	√	√	√	-
Akhras 1997 [34] ‡	-	√	-	√	-
Widimsky 2000[39]	√	√	-	-	√
De Boer 2002[87]	√	√	-	-	-
Widimsky 2002[88], 03[29]¥	√	√	-	-	√
Fibrin-specific trials					
De Wood 1990 [49]§	√	√	√	√	-
Grines 1993[89]	√	√	√	√	-
Gibbons 1993[90]	√	√	√	√	-
Ribichini 1998[37]	√	√	√	√	-
Garcia 1999[38]	√	√	√	√	-
GUSTOIIb 1997[22]	√	√	√	√	-
Hochman1999[35]‡	-	√	-	-	-
Le May 2001[48]	√	√	-	-	-
Bonnefoy 2002[91]	√	√	-	-	√
Schomig 2000[47]	√	√	-	-	-
Vermeer 1999[31]	√	√	-	-	√
Andersen 2002 [92], 03[30]¥	√	√	-	-	√
Kastrati 2002[93]	√	√	-	-	-
Aversano 2002[46]	√	√	-	-	-
Grines 2002[94]	√	√	-	-	√

¥ Results extracted from original conference abstracts. When available, results from recent published studies reported instead (i.e. Widimsky 2003 and Andersen 2003; Berrocal 2003 substitutes Grinfeld 1996).

§ Conference abstract, short-term results reproduced as reported in Keeley 2003.

‡ We excluded the SHOCK trial from the analysis because of the high death risk of patients with cardiogenic shock. Akhras 1997 was also excluded because it does not report time delays to treatment.

Table 2. Overview of trials and key endpoints and time to treatment for primary angioplasty (PCI) and thrombolysis (Lysis)

Study	1 month (4-6 weeks)								6 months								Covariate: Time to treatment (mins)			
	N (PCI)	N (Lysis)	Death (PCI)	Death (Lysis)	Reinf. (PCI)	Reinf. (Lysis)	NF stroke (PCI)	NF stroke (Lysis)	N (PCI)	N (Lysis)	Death (PCI)	Death (Lysis)	Reinf. (PCI)	Reinf. (Lysis)	NF stroke (PCI)	NF stroke (Lysis)	Mean (PCI)	SD or 50%-CI (PCI)	Mean (Lysis)	SD or 50%-CI (Lysis)
Zijlstra 1993§	70	72	0	4	0	9	0	2	-	-	-	-	-	-	-	-	61	22	30	15
Ribeiro 1993§	50	50	3	1	4	5	-	-	-	-	-	-	-	-	-	-	238	112	179	98
Zwolle 1994§	152	149	3	11	2	15	1	2	-	-	-	-	-	-	-	-	195	227	176	172
Berrocal 2003§	54	58	5	6	1	2	-	-	-	-	-	-	-	-	-	-	82	55, 100	15	10, 26
Zijlstra 1997§	45	50	1	0	0	8	1	2	45	50	1	0	0	8	1	2	68	21	29	17
Widimsky 2000§	101	99	7	14	1	10	0	-	-	-	-	-	-	-	-	-	96	-	90	-
de Boer 2002§	46	41	3	8	1	6	1	2	-	-	-	-	-	-	-	-	59	19	31	15
Widimsky 2003§†	429	421	29	42	6	13	1	9	-	-	-	-	-	-	-	-	97	27	12	10
DeWood 1990	46	44	3	2	-	-	-	-	-	-	-	-	-	-	-	-	126	-	84	-
Grines 1993	195	200	5	13	5	13	0	3	188	190	7	15	-	-	-	-	60	41	32	22
Gibbons 1993	47	56	2	2	-	-	-	-	47	56	3	2	0	2	-	-	277	144	232	174
Ribichini 1998	55	55	1	3	1	2	0	0	55	55	1	4	2	2	-	-	53.2	11.7	36.5	10.3
Garcia 1999	109	111	3	12	4	6	0	2	99	91	5	13	6	8	-	-	197	150, 250	150	105, 215
GUSTO IIb 1997	565	573	32	40	25	37	1	5	565	573	-	-	-	-	-	-	228	180, 318	180	120, 258
Le May 2001	62	61	3	2	3	5	1	1	62	61	3	2	4	10	1	3	77	58, 97	15	10, 21
Bonnefoy 2002	421	419	20	16	7	15	0	4	-	-	-	-	-	-	-	-	190	149, 255	130	95, 180
Schomig 2000	71	69	3	5	2	4	-	-	71	69	3	9	-	-	-	-	65	53, 85	30	23, 40
Vermeer 1999†	75	75	5	5	1	7	2	1	-	-	-	-	-	-	-	-	85	25	10	-
Kastrati 2002	81	81	2	5	0	4	1	1	70	71	5	7	-	-	-	-	75	65, 105	35	27, 45
Aversano 2002	225	226	12	16	11	20	3	8	225	226	14	16	12	24	5	9	101.5	82, 121	46	30, 65
Grines 2002	71	66	6	8	1	0	0	3	-	-	-	-	-	-	-	-	174	80	63	39
Andersen 2003: Referral*	567	562	37	48	11	35	9	11	-	-	-	-	-	-	-	-	90	74, 108	20	15, 30
Andersen 2003: Invasive*	223	220	15	13	2	14	0	5	-	-	-	-	-	-	-	-	63	49, 77	20	13, 30

Note: Reinf. = reinfarction; NF = Non fatal; SD = standard deviation; CrI = credible interval; * This trial consisted of two sub-trials, labelled 'Referral' and 'Invasive', and these are analysed as if they are two separate studies; † Includes a third group of patients who received thrombolytic therapy followed by transfer to angioplasty; this third comparator was excluded from the present analysis; § These trials used streptokinase as part the thrombolytic arm, the rest are fibrin-specific trials.

Table 3. Short term effectiveness results - Average time delay

1-month endpoints	**Primary PCI**	**Thrombolysis**	**odds ratio**
Death	4.5% (3.0%, 6.5%)	6.4% (4.5%, 9.0%)	0.68 (0.46, 1.01)
Non-fatal reinfarctions	2.0% (1.2%, 3.1%)	6.0% (4.1%, 8.5%)	0.32 (0.20, 0.51)
Non-fatal strokes	0.4% (0.2%, 0.9%)	1.8% (1.0%, 3.2%)	0.24 (0.11, 0.50)
6-month endpoints	**Primary PCI**	**Thrombolysis**	**odds ratio**
Death	5.2% (3.4%, 8.8%)	7.4% (5.0%, 11.8%)	0.69 (0.42, 1.18)
Non-fatal reinfarctions	2.4% (1.4%, 4.8%)	6.7% (4.4%, 10.7%)	0.35 (0.20, 0.67)
Non-fatal strokes	0.5% (0.2%, 1.0%)	2.2% (1.1%, 6.9%)	0.24 (0.08, 0.72)

Note: Occurrence of various endpoints 1 month or 6 months after PCI or thrombolytic therapy (median and 95%-CrI), for the average observed 'PCI-related time delay'.

Table 4: Short term effectiveness results - sensitivity analysis time delay

	30 minutes		60 minutes		90 minutes	
Endpoint	**Difference**	**RR**	**Difference**	**RR**	**Difference**	**RR**
Death	**–3.7%** (–7.2%, –0.5%)	0.53 (0.31, 0.93)	**–1.8%** (–5.6%, +1.7%)	0.75 (0.47, 1.26)	**+0.4%** (–4.6%, +8.1%)	1.05 (0.51, 2.17)
NF Reinf.	**–4.6%** (–8.2%, –2.2%)	0.30 (0.15, 0.61)	**–4.0%** (–7.5%, –1.6%)	0.38 (0.22, 0.73)	**–3.2%** (–7.1%, +1.6%)	0.50 (0.21, 1.24)
NF stroke	**–1.7%** (–5.8%, –0.5%)	0.209 (0.05, 0.69)	**–1.6%** (–5.6%, –0.4%)	0.26 (0.09, 0.75)	**–1.3%** (–5.3%, +0.8%)	0.35 (0.08, 1.41)

Note: Absolute probability differences and relative risks for the 6-month treatment effects of primary angioplasty compared to thrombolytic therapy (median and 95%-CrI) at assumed 'PCI-related time delays' of 30, 60 and 90 minutes.
NF= Non Fatal; Reinf = Re-infarction.

Table 5. Resource use associated with the short term model.

Item of resource use	Mean (SE)	Parameters gamma distribution		Comments	Source
		α	β		
Treatment initial AMI episode					
Number of stents	1.71(0.12)	203.40	0.008	n= 933; non-elective patients audit Liverpool center.	Bagust et al. 2005[57]
Hospital length of stay:					
Acute Myocardial Infarction	10	-	-	Average length of stay, non elective NHS Trusts.	Hospital Episode Statistics 2003/04[52]
(i) PCI in acute period	5.76 (1.58)	13.290	0.433	Sample of 80 patients from Hammersmith hub site and Charing Cross Hospitals, UK	Personal communication Dr. Kenneth Morgan
(ii) Thrombolytic therapy	12.12 (2.87)	17.833	0.676	Sample of 80 patients from Hammersmith hub site and Charing Cross Hospitals, UK	Personal communication Dr. Kenneth Morgan
Item of resource use	**Probability**	**Parameters of the beta distribution**		**Comments**	**Source**
		α	**β**		
Treatment additional revascularisations					
Revascularisations:					
(i) CABG in thrombolysis arm	0.071	17	221		Evidence synthesis
(ii) CABG in PCI arm	0.054	17	289		Evidence synthesis
(iii) PCI in htrombolytsis arm	0.281	26	68		Evidence synthesis
(iv) repeat PCI in PCI arm	0.054	18	318		Evidence synthesis

Note: AMI = Acute Myocardial Infarction, CABG = Coronary Artery Bypass Graft, PCI = Percutaneous Coronary Intervention.

Table 6. Revascularisations events up to 6 months for primary angioplasty (PCI) and thrombolysis (Lysis).

	N (PCI)	N (Lysis)	Rep. PCI (PCI)	PCI (Lysis)	CABG (PCI)	CABG (Lysis)
Zijlstra 1993§	70	72	3	22	7	8
Ribeiro 1993§	50	50	1	23	3	6
Zwolle 1994§	152	149	0	25	7	14
Berrocal 2003§	54	58	0	10	4	3
Zijlstra 1997§	45	50	9	30	6	7
Widimsky 2000§	101	99	4	11	3	3
de Boer 2002§	46	41	0	4	2	-
Widimsky 2003§†	429	421	0	27	3	0
DeWood 1990	46	44	-	-	-	-
Grines 1993	195	200	12	72	16	24
Gibbons 1993	47	56	1	21	6	7
Ribichini 1998	55	55	3	24	3	11
Garcia 1999	109	111	28	52	8	17
GUSTO IIb 1997	565	573	24	121	42	47
Le May 2001	62	61	5	24	5	10
Bonnefoy 2002	421	419	57	289	3	6
Schomig 2000	71	69	6	23	1	1
Vermeer 1999†	75	75	10	29	-	-
Kastrati 2002	81	81	0	5	0	3
Aversano 2002	225	226	53	112	30	44
Grines 2002	71	66	0	27	10	7
Andersen 2003*	790	782	45	144	30	20

Note: Rep.PCI = Repeated PCI; CABG = Coronary Artery Bypass Graft; * This trial consisted of two sub-trials, labelled 'Referral' and 'Invasive', and these are analysed as if they are two separate studies; † Includes a third group of patients who received thrombolytic therapy followed by transfer to angioplasty; this third comparator was excluded from the present analysis; § These trials used streptokinase as part the thrombolytic arm, the rest are fibrin-specific trials.

Table 7. Further revascularisations up to 6 months

	Primary PCI	Thrombolysis
Patients requiring PCI	5.3% (3.3% , 8.1%)	27.9% (19.5% , 37.5%)
Patients requiring CABG	5.3% (3.2% , 8.3%)	7.0% (4.3%, 10.8%)

Note: Mean (95% CrI). Both rescue and non-rescue revascularisations up to 6 months.

Table 8. Unit costs used in the short-term model

Item of resource use	Base-case value	Unit / Dosage	Comments	Source
Treatment initial AMI episode				
Cardiac ward	£173	Day	Acute services excess bed days (non elective patients, AMI w/o cc). National NHS Trusts mean reported.	Reference costs 2004[61]
Angiography	£727	Procedure only		Sculpher, Smith et al. 2002[56]
PCI	£1,614	Procedure only		Sculpher, Smith et al. 2002[56]
Guidewire	£71	Item		Sculpher, Smith et al. 2002[56]
Bare metal stent	£370	Item	Market average price	Bagust et al. 2005[57]
Guiding catheter	£42	Item		Sculpher, Smith et al. 2002[56]
Balloon	£231	Item		Sculpher, Smith et al. 2002[56]
Abciximab	£1042	Four 5mg/mL vials	ReoPro®. 0.25mg/kg intravenous infusion, followed by 0.125mcg/kg. Price 5mg vial is £260.40, we assume average weight 75 kg.	BNF no. 48 September [54]
Streptokinase (SK)	£89.72	1,500,000 IU	Streptase®. Single dose of 1.5 million IU infused over one hour. Administered intravenously	BNF no. 48 September [54]
Alteplase (rt-PA)	£600	Two 50mg vials	Actilyse®. 90 minutes (accelerated) dose regimen for MI patients < 6 hours after symptom onset	BNF no. 48 September [54]
Reteplase (r-PA)	£716.25	Two 10 U/vial	Rapilysin®. 10 U bolus dose followed by a second 10 U bolus dose 30 minutes later.	BNF no. 48 September [54]
Events & revascularisations after initial episode				
AMI	£1,055	Episode	Weighted mean reported based on the range of with and without complications, according to FCEs.	Non elective NHS Trusts, Reference Costs 2003[61]
PCI	£2,984	Procedure	Includes hospital length of stay and diagnostic procedures. Weighted mean based on elective and non-elective intervention, according to FCEs.	Reference Costs 2003[61]
CABG	£6,450	Procedure	Includes hospital length of stay and diagnostic procedures. Weighted mean based on elective and non-elective intervention, according to FCEs.	Reference Costs 2003[61]

Note: All costs updated using HCHS prices index 2004; Consumable costs include value added tax**;** AMI = Acute Myocardial Infarction, CABG = Coronary Artery Bypass Graft, PCI = Percutaneous Coronary Intervention

Table 9. Annual transition probabilities used in the long-term model

Annual probability	Mean value	95% CrI
From IHD to NF Event, Year 1	0.059	(0.041 , 0.077)
From IHD to NF Event, Year 2+	0.027	(0.019 , 0.036)
From IHD to (CV) Dead, Year 1	0.038	(0.024 , 0.055)
From IHD to (CV) Dead, Year 2+	0.032	(0.023 , 0.041)
From Event to (CV) Dead, Year 1	0.26	(0.18 , 0.352)
From Event to (CV) Dead, Year 2+	0.048	(0.021 , 0.084)

Note: 'NF Event' includes non fatal stroke or repeated myocardial infarction;
CV = Cardiovascular; CrI = Credibility Interval.

Source: original survival analysis based on the NHAR dataset.

Table 10. Probabilities associated with stroke and recurrent events in the long-term model.

Item of resource use	Probability	Parameters Beta distribution		Comments	Source
		α	β		
Stroke related probabilities					
First event after 6 months is a stroke	0.216	30.62	0.007	Only applies in order to differentiate transition probabilities for 'Event MI' and 'Event Stroke'.	NHAR
Next event is a stroke | MI state	0.062	1.266	0.049	Applies if you have an MI at any cycle followed by a stroke.	NHAR
Survivors of initial stroke who are disabled	0.309	2040	4562	Modified severity ranking 3 to 5, n= 6,602 Only applied to estimate costs and utitilities.	ESPS-2[66]
Mild stroke | Non disabled *	0.4129	-	-	Only applied to estimate long term costs.	Youman et al. 2003[58]
Discharged home | Mild stroke	1	-	-		Youman et al. 2003[58]
Discharged home | Moderate stroke	0.9917	-	-	Only applied to estimated long term costs. Adjusted by the probability of dying from a moderate stroke.	Youman et al. 2003[58]
Discharged institution | Moderate stroke	0.0083	-	-		Youman et al. 2003[58]
Death | Moderate stroke	0.0330	-	-		Youman et al. 2003[58]
Discharged home | Severe stroke	0.8097	-	-	Only applied to estimated long term costs. Adjusted by the probability of dying from a severe stroke.	Youman et al. 2003[58]
Discharged institution | Severe stroke	0.1903	-	-		Youman et al. 2003[58]
Death | Severe stroke	0.0960	-	-		Youman et al. 2003[58]
Recurrent event in a particular health state					
Recurrent event in the MI state	0.087	13	63	Recurrent events at any cycle. Total number events adjusted by annual probabilities. Only applied to estimate costs and utilities.	NHAR
Recurrent event in the stroke state	0.038	1	15		NHAR
Recurrent stroke	0.498	4.602	0.108	Probability your next event is a stroke having had a stroke before	NHAR

Note: MI = Myocardial Infarction; NHAR = Nottingham Heart Attach Registry; * A non disabling stroke can only be mild or moderate, severe strokes are assumed to be disabling.

Table 11. Life-table for non cardiovascular death, UK population.

Annual probability	Mean value	95% CI
Age 15 to 24 years-old	0.05%	(0.0 , 0.1)
Age 25 to 34 years-old	0.07%	(0.1 , 0.1)
Age 35 to 44 years-old	0.11%	(0.1 , 0.1)
Age 45 to 54 years-old	0.24%	(0.2 , 0.2)
Age 55 to 64 years-old	0.58%	(0.6 , 0.6)
Age 65 to 74 years-old	1.43%	(1.4 , 1.4)
Age 75 to 84 years-old	3.81%	(3.8 , 3.8)
Age 85+ years-old	10.51%	(10.4 , 10.6)

Note: ICD10 I00 to I99 excluded, cause elimination calculated using the Office of National Statistics, standard methods.

Source: Office for National Statistics, latest mortality statistics 2002.

Table 12. Transition probability matrix

Transition from:	Transition to:						
	IHD	**IHD ≥ 2nd cycle**	**MI**	**POST-MI**	**STROKE**	**POST-STROKE**	**DEATH**
IHD	0	1 – [0.059 + 0.038 + P(d)]	0.059 * (1- P(St)) (0.041 , 0.077)	0	0.059 * P(St) (0.041 , 0.077)	0	0.038 + P(d) (0.024 , 0.055)
IHD ≥ 2nd cycle	0	1 – [0.027 + 0.032 + P(d)]	0.027 * (1- P(St) (0.019 , 0.036)	0	0.027* P(St) (0.019 , 0.036)	0	0.032+ P(d) (0.023, 0.041
MI	0	0	0	1 – [MI to Stroke + + MI to death]	(1 – 0.26 – P(d)) * P(ReSt)	0	0.26 + P(d) (0.18 , 0.352)
POST-MI	0	0	0	1 – [PostMI to Stroke + + PostMI to death]	(1 – 0.48 – P(d)) * P(ReSt)	0	0.048 + P(d) (0.021 , 0.084)
STROKE	0	0	0	0	0	1 – [0.26 + P(d)]	0.26 + P(d) (0.18 , 0.352)
POST-STROKE	0	0	0	0	0	1 – [0.48 + P(d)]	0.048 + P(d) (0.021 , 0.084)
DEATH	0	0	0	0	0	0	1

Note:

P(d) = Probability of dying from non cardiac reasons, assumed to be a function of cycle number (i.e. related to age). See further details in table 11.
P(St) = probability that the first event after 6 months is a stroke. See further details in table 9.
P(ReSt) = probability next event is a stroke. See further details in table 9.

Table 13. Resource use associated with the long-term model

Item of resource use	Probability	Parameters Beta distribution		Mean value (days or visits)	Parameters gamma distribution		Source
		α	β		α	β	
IHD health state							
Year 1 – Non cardiac hospital admission	0.38	227	363	0.073	-	-	NHAR
Oupatient cardiac visit	0.46	115	137	3.44	1.89	1.82	Palmer et al. 2002[60]
Oupatient non cardiac visit	0.55	138	114	4.86	0.98	4.96	Palmer et al. 2002[60]
Day case non cardiac	0.004	1	251	1	-	-	Palmer et al. 2002[60]
MI health state							
Year 1 – Non cardiac hospital admission	0.46	51	58	0.226	-	-	NHAR
Oupatient cardiac visit	0.78	21	6	3.43	1.26	2.73	Palmer et al. 2002[60]
Oupatient non cardiac visit	0.56	15	12	3.27	0.90	3.64	Palmer et al. 2002[60]
Day case cardiac	0	-	-	-	-	-	Palmer et al. 2002[60]
Day case non cardiac	0	-	-	-	-	-	Palmer et al. 2002[60]
Post MI health state							
Year 2+ – Non cardiac hospital admission	0.46	51	58	0.226	-	-	NHAR
Oupatient cardiac visit	0.53	8	7	2.88	2.77	1.04	Palmer et al. 2002[60]
Oupatient non cardiac visit	0.60	9	6	2.33	3.12	0.75	Palmer et al. 2002[60]
Day case cardiac	0	-	-	-	-	-	Palmer et al. 2002[60]
Day case non cardiac	0	-	-	-	-	-	Palmer et al. 2002[60]

Note: IHD = Ischaemic Heart Disease; MI = Myocardial Infarction; NHAR = Nottingham Heart Attack Registry.

Table 14. Unit costs used in long term model

Item of resource use	Unit / Dosage	Base-case value	Parameters gamma distribution		Comments	Source
			α	β		
Stroke related costs						
Acute event treatment | Mild	3 months	£5,388	£344	£15,672		Youman et al. 2003[58]
Acute event treatment | Moderate	3 months	£5,089	£531	£9,578		Youman et al. 2003[58]
Acute event treatment | Severe	3 months	£11,153	£446	£25,028		Youman et al. 2003[58]
Cost ongoing care at home	3 months	£344	£24	£14,480		Youman et al. 2003[58]
Cost ongoing care in an institution	3 months	£4,091	£161	£25,404		Youman et al. 2003[58]
Other long term costs						
Inpatient – Cardiac	Episode	£1055	-	-	Only applied to recurrent MI episodes	Non elective NHS Trusts, Reference Costs 2003[61]
Inpatient – Non cardiac *	Episode	£1285	-	-	Average general surgery and other medicine inpatient cost per episode.	CIPFA 2003/04[59]
Outpatient – Cardiac	Visit	£107	-	-		CIPFA 2003/04[59]
Outpatient – Non Cardiac	Visit	£122	-	-	Average general surgery and other medicine outpatient cost per attendance.	CIPFA 2003/04[59]
Day case – Non Cardiac	Day	£495	-	-		Reference Costs 2003[61]
Cardiac death	Person	£143	-	-	Based on the likelihood of dying in hospital and the associated length of hospital stay.	Palmer et al. 2002[60]
Non Cardiac death	Person	£0	-	-		Assumption

Note: All costs updated using HCHS prices index 2004; Consumable costs include value added tax; MI = Myocardial Infarction; CIPFA= The Chartered Institute of Public Finance and Accountancy.
* All other hospitalisations including 'other cardiosvascular' but heart failure.

Table 15. Mean annual costs by health state

Health state	Mean value	95% CI
IHD	£431	(£99 , £1,209)
MI Year 1	£1,964	(£1,368 , £3,150)
MI Year 2+	£691	(£375 , £1,188)
Stroke Year 1	£8,786	(£8,244 , £9,395)
Stroke Year 2+	£2,318	(£1,826 , £2,933)

Note: MI = Myocardial Infarction; IHD = Ischaemic Heart Disease.
All annual costs adjusted by average number of days in the Well (449), MI (268), PostMI (200) state based on NHAR dataset.

Table 16. EQ-5D utilities of health states used in the model

Health state	Mean utility	Parameters Beta distribution		Comments	Source
		α	β		
IHD – 1 year cycle	0.701	-	-	Combined estimate of 6 months MI year utility and 6 months post-MI utility. For 2nd cycle onwards we assume utility for IHD equals that of post-MI state.	Assumption
MI year 1	0.683	623.09	289.19		Lacey & Walters, 2003[95]
MI post-year 1	0.718	563.08	221.15		Lacey & Walters, 2003[95]
Non disabled stroke (Year 1 and Year 2+)	0.740	218.04	76.61		Tengs & Lin 2003[96]
Disabled stroke (Year 1 and Year 2+)	0.380	42.08	68.66		Tengs & Lin 2003[96]
Combined stroke	0.612	-	-	Assuming 30.9% disabled based on ESPS-2	Tengs & Lin 2003[96]; ESPS-2[66, 96]

Note: EQ-5D = Euro-Qol-5D; MI = Myocardial Infarction; IHD = Ischaemic Heart Disease

Table 17. Base-case and alternative scenarios

	Base-case scenario	Alternative scenarios		
		S1	S2	S3
Trials selection	All 22 trials	All 22 trials	Only t-pa trials (n= 14)	Only t-pa trials (n= 14)
Hospital length of stay after initial AMI episode	10 days both groups	5.76 after PCI 12.12 thrombolysis	10 days both groups	5.76 after PCI 12.12 thrombolysis

Note: AMI = Acute Myocardial Infarction; t-pa = tissue plasminogen activator.

Table 18. Short-term costs results - Base case

	Primary PCI (£ UK)	Thrombolysis (£ UK)	Dfference (£ UK)
Treatment of initial MI episode	£6,090 (£6,000 , £6,180)	£2,330 (£2,210 , £2,560)	£3,760
Additional revascularisations	£510 (£350 , £710)	£1,290 (£970 , £1,660)	-£780
Total short term costs	£6,600 (£6,420, £6,810)	£3,620 (£3,300, £3,990)	£2,980

Note: MI = Myocardial Infarction.

Table 19. Base-case probabilistic results

Time delay	Treatment	Mean costs	Mean QALYs	ICER	Probability cost-effective for threshold of:		
					£10,000	£20,000	£30,000
Average trials	PCI	£12,760	7.12	£9,241	0.55	0.90	0.95
(54.3 minutes)	Lysis	£10,080	6.83	NA	0.45	0.10	0.05

Note: QALYs = Quality Adjusted Life Years; ICER = Incremental Cost-Effectiveness Ratio.

Table 20. Base-case probabilistic results at different time delays

Time delay	Treatment	Mean costs	Mean QALYs	ICER	Probability cost-effective for threshold of:		
					£10,000	£20,000	£30,000
30 minutes	PCI	£12,820	7.23	£6,850	0.82	0.98	0.99
	Lysis	£10,080	6.83	NA	0.18	0.02	0.01
60 minutes	PCI	£12,750	7.09	£10,269	0.43	0.83	0.91
	Lysis	£10,080	6.83	NA	0.57	0.17	0.09
90 minutes	PCI	£12,670	6.87	£64,750	0.13	0.36	0.45
	Lysis	£10,080	6.83	NA	0.87	0.64	0.55

Note: QALYs = Quality Adjusted Life Years; ICER = Incremental Cost-Effectiveness Ratio.

Table 21. Probabilistic results for alternative scenarios at different time delays

Time delay	Treatment	Mean costs	Mean QALYs	ICER	Probability cost-effective for threshold of:		
					£10,000	£20,000	£30,000
Scenario S1: All trials, differential length of stay in hospital							
Average trials (54.3 minutes)	Primary PCI	£12,030	7.12	£5,448	0.82	0.95	0.97
	Thrombolysis	£10,450	6.83	NA	0.18	0.05	0.03
30 minutes	Primary PCI	£12,085	7.23	£4,087	0.95	0.99	0.99
	Thrombolysis	£10,450	6.83	NA	0.05	0.01	0.01
60 minutes	Primary PCI	£12,020	7.09	£6,038	0.75	0.91	0.99
	Thrombolysis	£10,450	6.83	NA	0.25	0.09	0.01
90 minutes	Primary PCI	£11,940	6.87	£37,250	0.32	0.47	0.52
	Thrombolysis	£10,450	6.83	NA	0.68	0.53	0.48
Scenario S2: only t-pa trials, same length of stay in hospital							
Average trials (54.3 minutes)	Primary PCI	£12,750	7.1	£9,833	0.43	0.80	0.88
	Thrombolysis	£10,095	6.83	NA	0.57	0.20	0.12
30 minutes	Primary PCI	£12,790	7.2	£7,284	0.70	0.94	0.97
	Thrombolysis	£10,095	6.83	NA	0.30	0.06	0.03
60 minutes	Primary PCI	£12,740	7.06	£11,500	0.36	0.72	0.81
	Thrombolysis	£10,095	6.83	NA	0.64	0.28	0.19
90 minutes	Primary PCI	£12,860	6.78	DOMINATED	0.14	0.31	0.37
	Thrombolysis	£10,095	6.83	NA	0.86	0.69	0.63
Scenario S3: Only t-pa trials, differential length of stay in hospital							
Average trials (54.3 minutes)	Primary PCI	£12,020	7.1	£5,778	0.72	0.89	0.92
	Thrombolysis	£10,460	6.83	NA	0.28	0.11	0.08
30 minutes	Primary PCI	£12,060	7.2	£4,324	0.89	0.97	0.98
	Thrombolysis	£10,460	6.83	NA	0.11	0.03	0.02
60 minutes	Primary PCI	£12,010	7.06	£6,739	0.64	0.83	0.87
	Thrombolysis	£10,460	6.83	NA	0.36	0.17	0.13
90 minutes	Primary PCI	£12,120	6.78	DOMINATED	0.27	0.38	0.42
	Thrombolysis	£10,460	6.83	NA	0.73	0.62	0.58

AMI = Acute Myocardial Infarction; t-pa = tissue plasminogen activator; QALYs = Quality Adjusted Life Years; ICER = Incremental Cost-Effectiveness Ratio.

Table 22. Population EVPI– Base case at different time delays

	Value of Information at threshold of:		
scenario	**£10,000**	**£20,000**	**£30,000**
base-case	480	190	170
30 min	140	55	60
60 min	570	310	290
90 min	220	1,100	2,200
S1	170	110	130
30 min	50	43	53
60 min	250	180	210
90 min	510	1,600	2,800
S2	710	360	320
30 min	280	100	88
60 min	600	610	590
90 min	260	1,100	2,200
S3	280	200	210
30 min	95	57	59
60 min	420	370	420
90 min	510	1,500	2,600

Table 23. Population EVPI for parameters

	Value of Information at threshold of:		
Parameter group	**£10,000**	**£20,000**	**£30,000**
Value of Information Analysis (VOI)	480	190	170
Evidence synthesis and revascularisations	450	110	77
all mortality	320	82	62
baseline mortality	230	0	0
treatment effect on mortality	290	110	99
all re-infarctions	19	0	0
baseline re-infarctions	9.0	0	0
treatment effect on re-infarctions	8.0	0	0
all stroke	90	0	0
baseline stroke	110	0	0
treatment effect on stroke	31	6.2	4.6
all baselines	450	1.7	0
all treatment effects	310	140	130
Markov transition probabilities and life-table	0.4	91	27
All cost and utility parameters	0	0	0

Table 24. Characteristics of main economic evaluations on PCI vs. thrombolysis

Study	Hartwell et al. 2003[6]	Müllner M et al. 1999[7]	Lieu T et al. 1997[8]
Modelling approach	Decision tree model	Decision tree model	Decision tree model
Currency (year)*	UK sterling (2002)	Austrian schilling converted to ECU. A single price year was not reported.	US dollars (1993)
Perspective used	UK NHS	Health care system (Public health insurance organisations in Austria)	Societal perspective
Timeframe	Short-term model. Main outcomes after hospital discharge.	Not explicitly stated. Survival until hospital discharge is the main benefit measure used in the economic analysis, extrapolated in terms of life years gained for an undetermined time horizon.	10 years
Comparators	Three alternatives: PCI, thrombolysis and PCI when thrombolysis is contraindicated. The third alternative is compared to a base case scenario of supportive treatment only.	100mg tissue plasminogen activator (t-pa)	Thrombolysis (either SK or t-pa); "No intervention" defined as all patients suspected of AMI receiving neither thrombolysis nor primary angioplasty but still admitted to hospital for standard care.
Summary of effectiveness results	Mortality, morbidity and "restored health" (i.e. discharge to home) are considered. Discharge home is arbitrarily assigned the equivalent of full health score (1). Morbidity assigned the equivalent utility of "non fatal disabling stroke" (0.10, range 0.05 to 0.5). Mean utility of PCI group is 0.73 compared to 0.52 for thrombolysis group.	Hospital survival rate was 95.2% in MI patients treated with primary PCI vs. 93.4% for patients treated with thrombolytics.	0.0514 discounted QALYs gained relative to thrombolytics. Primary PCI was predicted to 22% more lives and to reduce nonfatal disabling strokes by one-third compared to thrombolytics.
Summary of cost results	Results point at a saving of £1,163 to £2,657 per case with thrombolysis treatment.	Total expected costs of the two interventions as derived from each branch in the decision model were not reported.	Primary PCI procedure has a slightly lower cost than that of t-pa ($160 per patient). Even after the costs of lifetime medical care for hospital survivors were included, primary PCI would lead to savings.
Summary of cost-effectiveness results	ICER reported for primary PCI is £8,707 to £12,171 but the comparator is not clear.	The incremental cost per life year saved was 274 ECU (95% CI 213 to 318). Results were sensitive to the probability of having a further revascularisation, especially for patients in the thrombolytic group.	Primary PCI dominated thrombolysis. The ICER is expressed in cost/QALY compared with the no intervention option ($12,000). Primary PCI would be reasonably cost-effective provided by hospitals with cardiac catheterisation laboratories.

* Year to which costs apply. ECU= European currency unit, international monetary unit used by the European Monetary System until 1999.
Source: Own elaboration based on original papers.

Panel 1. Treatment effect of PCI relative to thrombolytic therapy

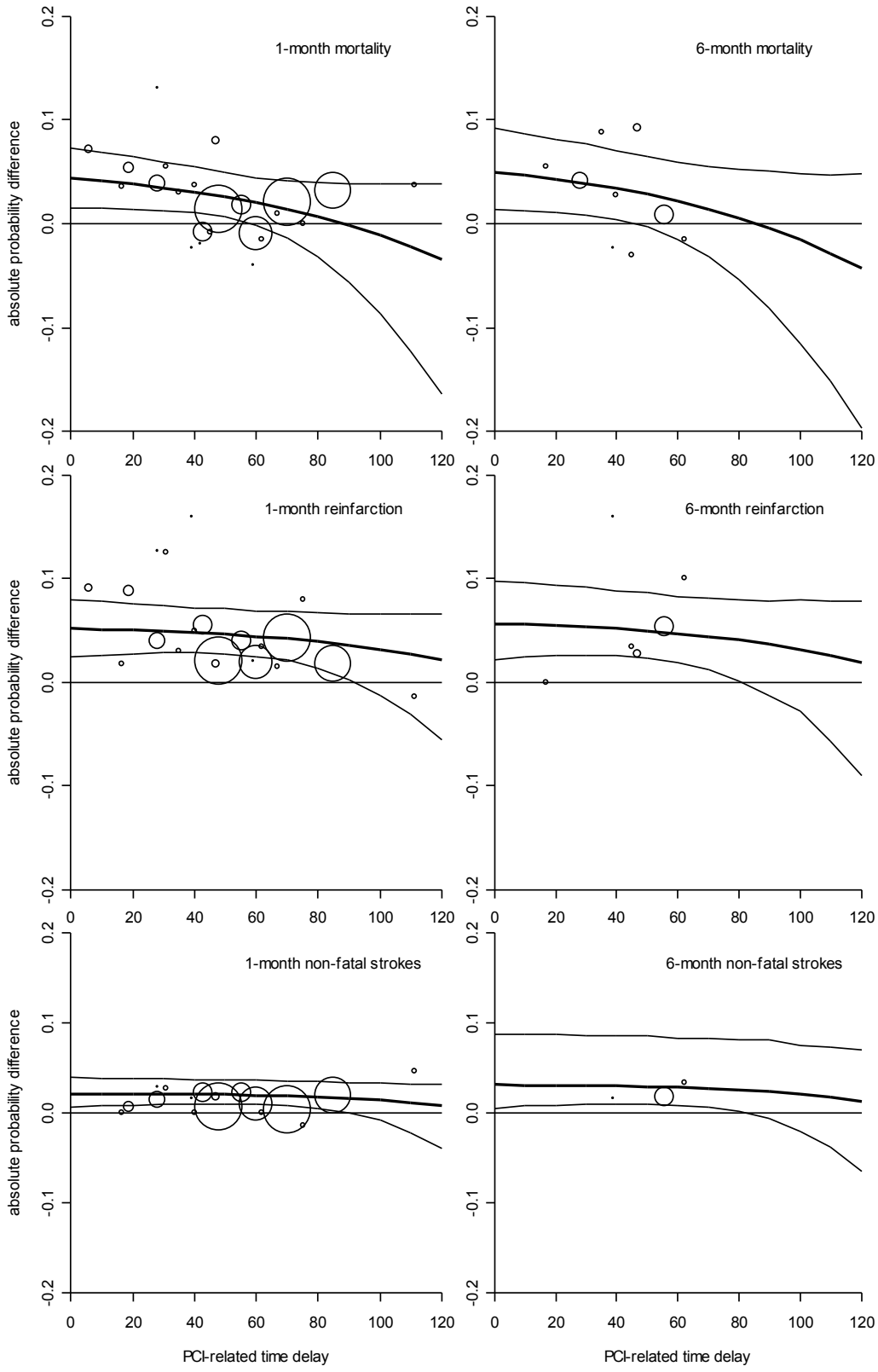


Figure 1. Model structure

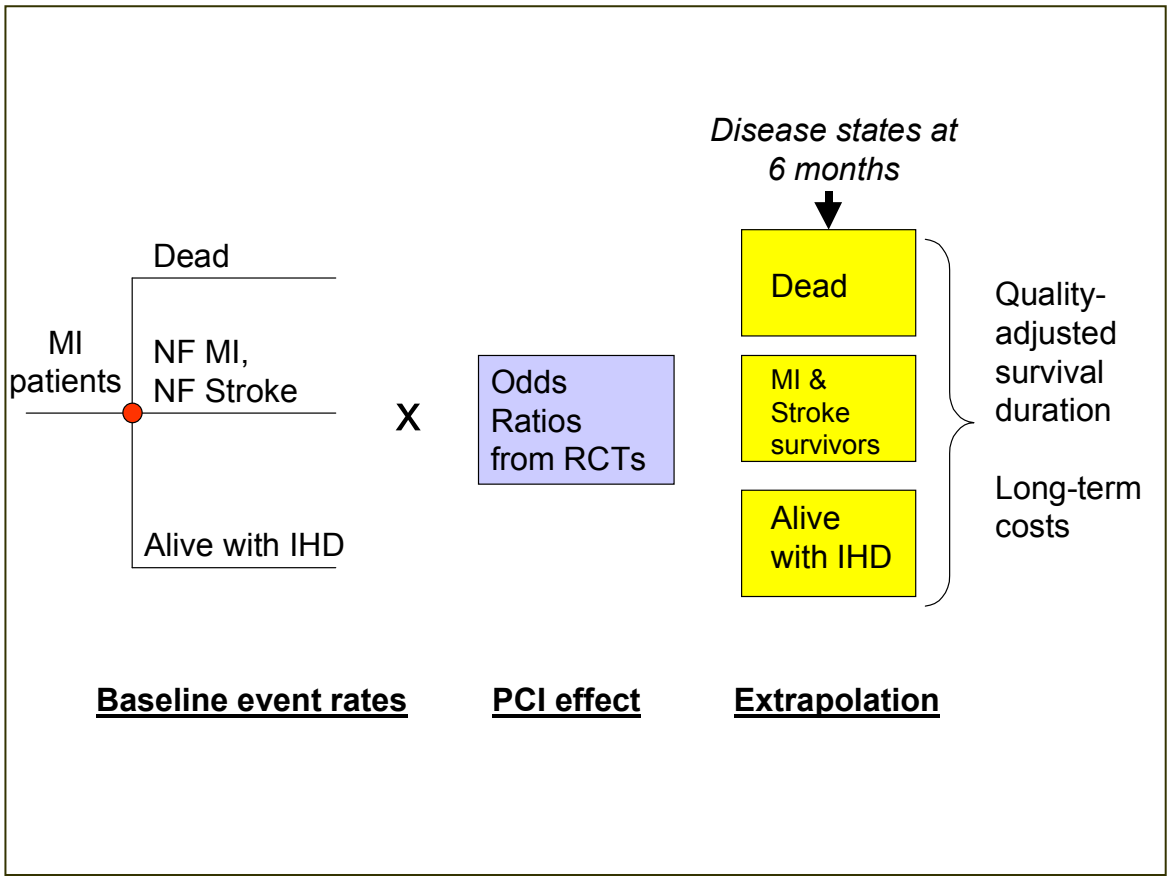
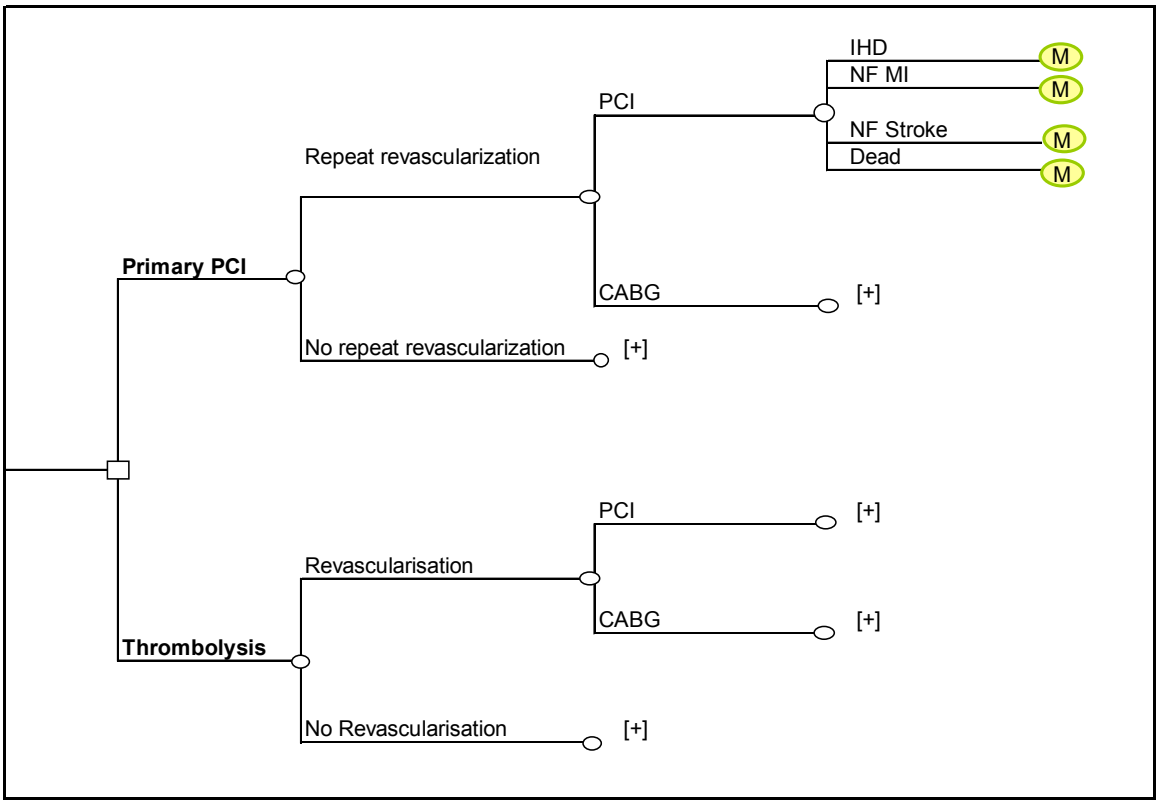
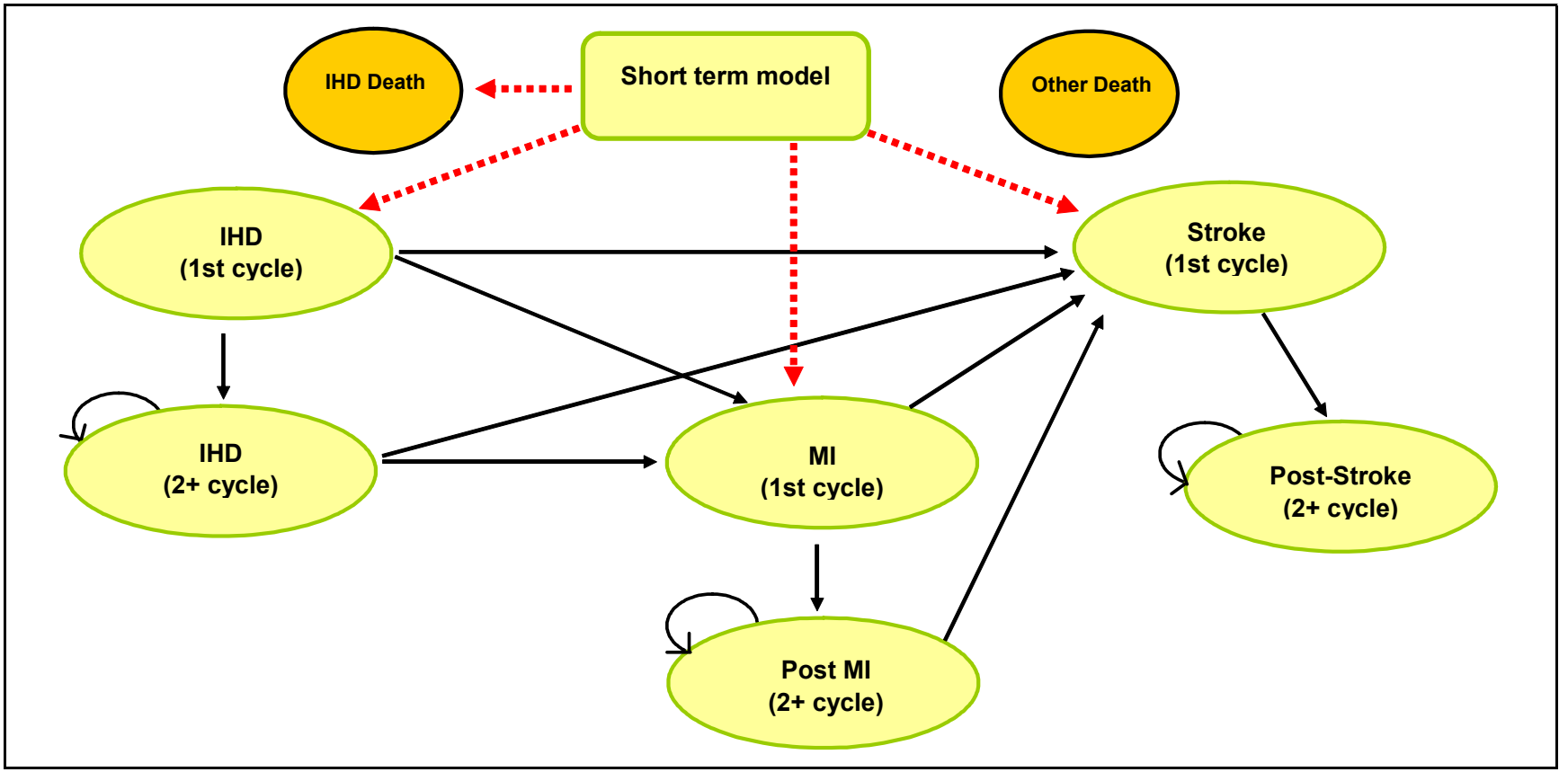


Figure 2. Structure of the short-term decision tree



[+] This symbol indicates that the ending of the node is equal to the above one, linking the different events to the Markov model (M).

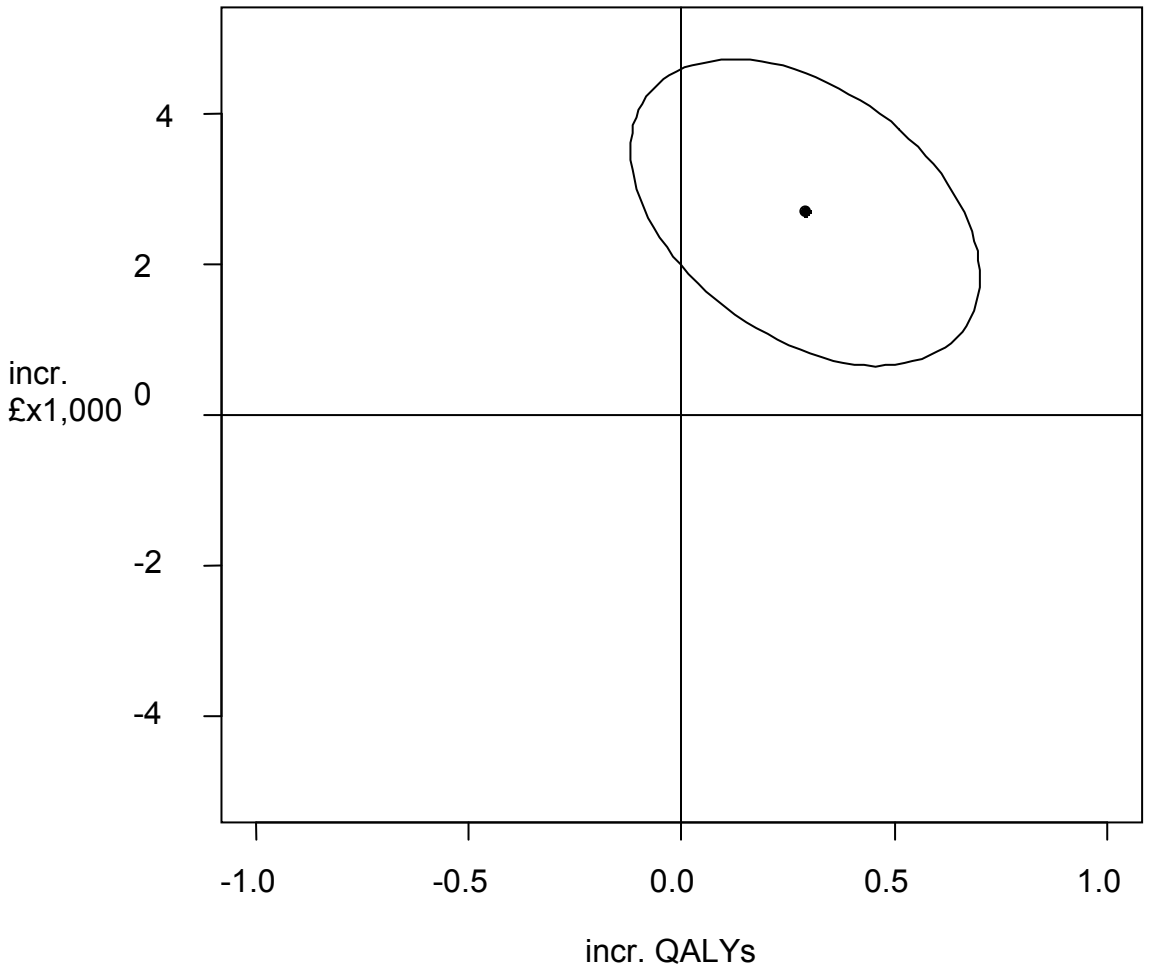
Figure 3. Structure of the Markov model



Proportion of patients ending the 6 month period in the different health states.
Long-term transition probabilities between different health states

Note that patients in any health state can move into the IHD death or other death state at any cycle. It is assumed that patients up to 6 months (i.e. short term model) can only die from cardiovascular reasons.

Figure 4. Base-case cost-effectiveness plane



Note: The points indicate the expected values, ellipses show 95%-CrI under the assumption of multivariate normality.

Figure 5. Base-case cost-effectiveness acceptability curve

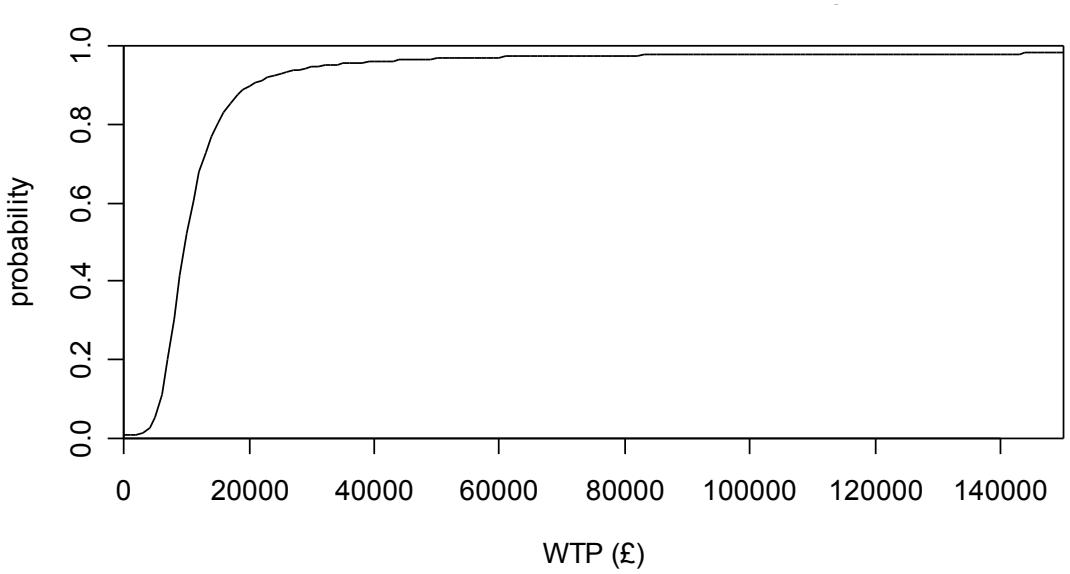
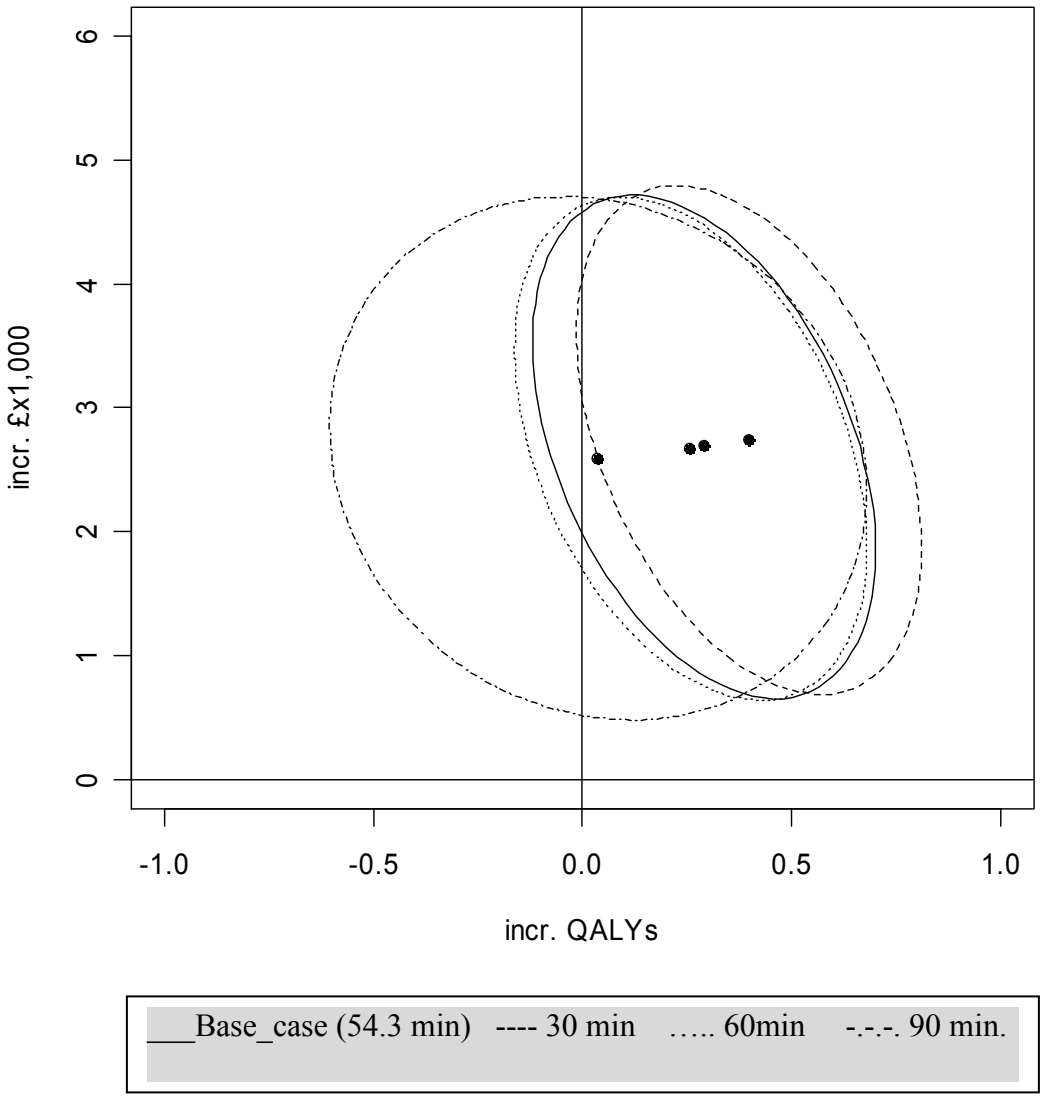


Figure 6. Base-case cost-effectiveness planes at different time delays



Note: The points indicate the expected values, ellipses show 95%-CrI under the assumption of multivariate normality.

Figure 7. Family of CEACs for the base-case scenario at different time delays

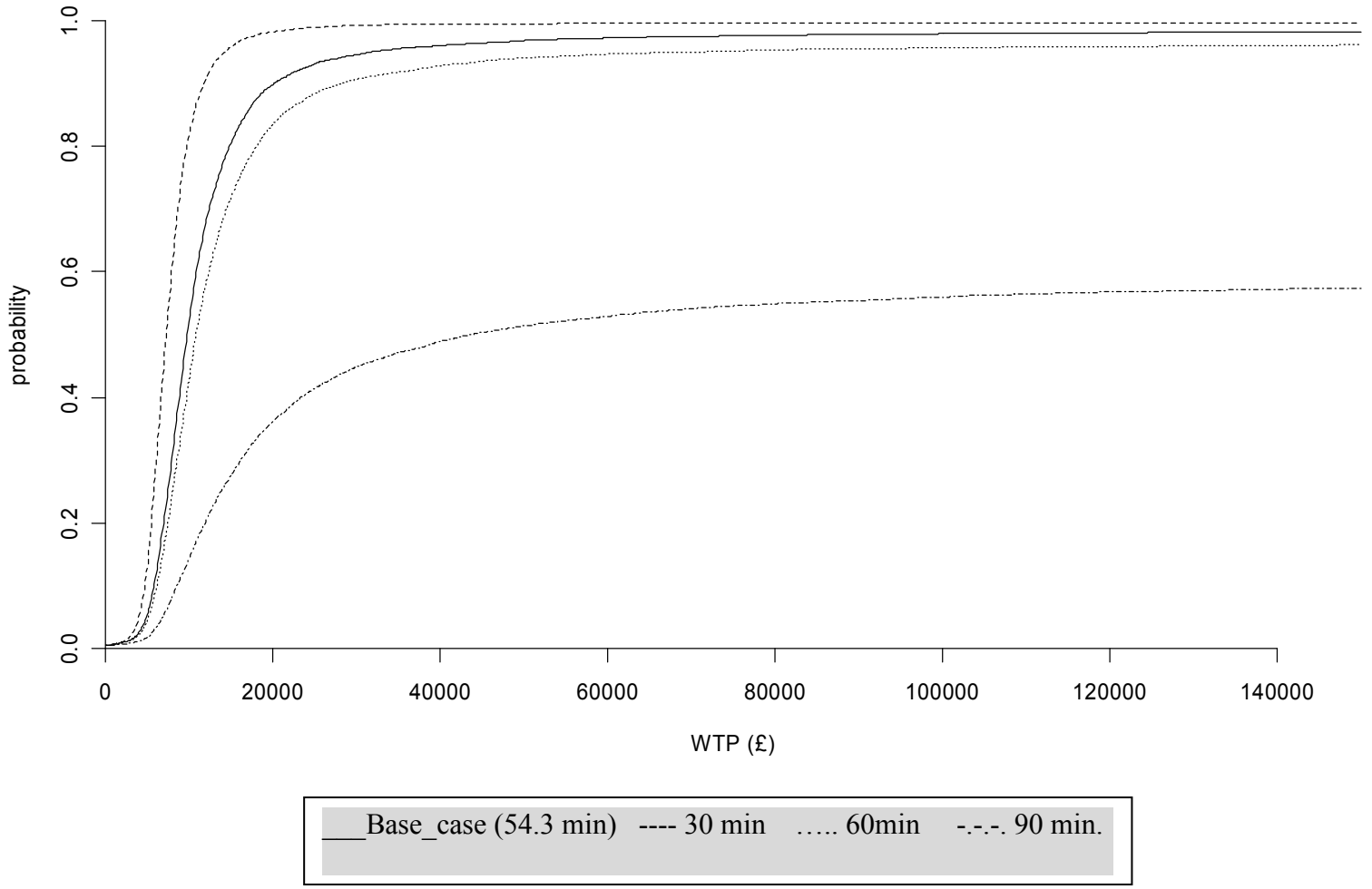


Figure 8. Family of CEACs for scenario S1 at different PCI-time delays

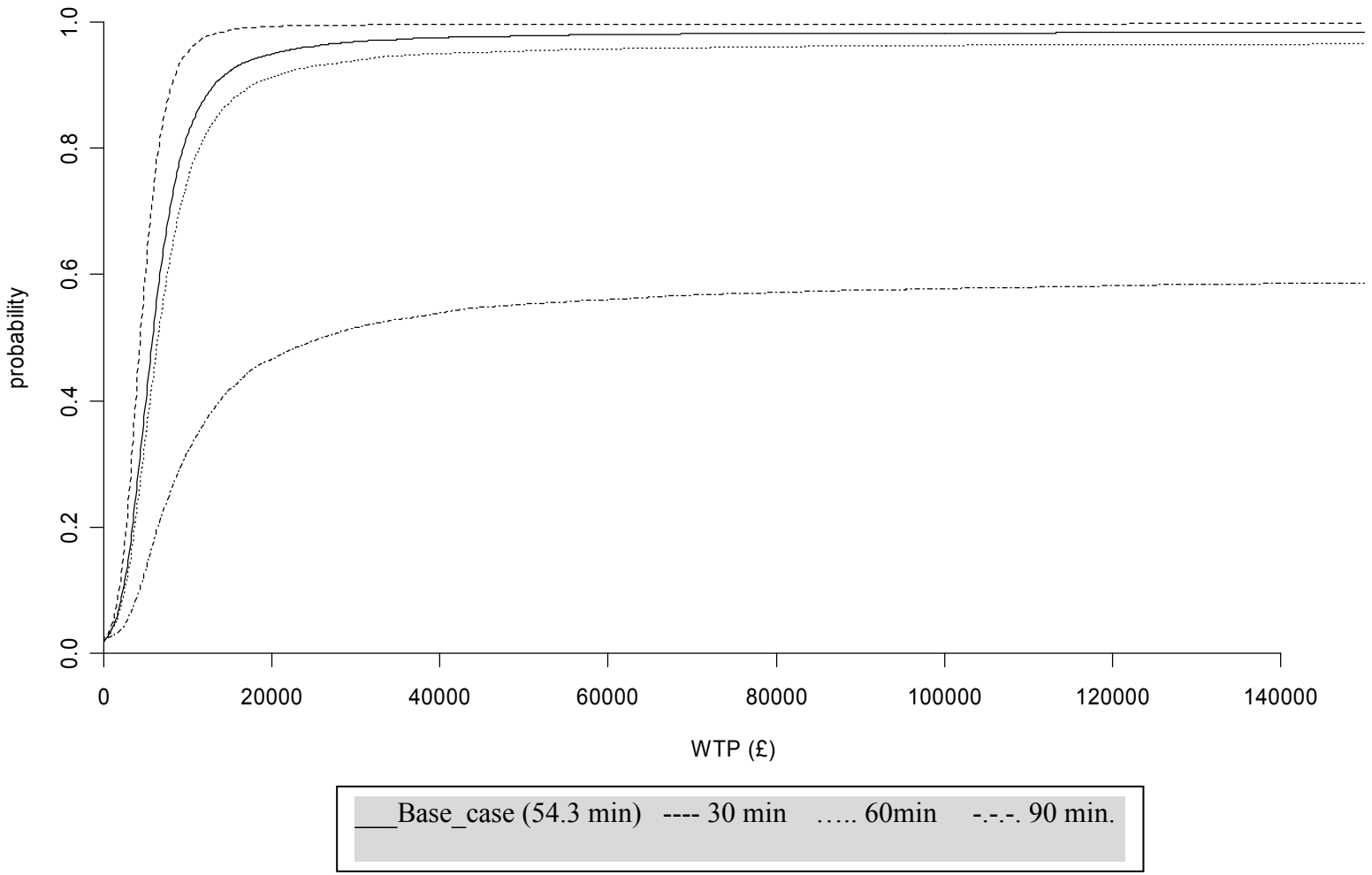


Figure 9. Family of CEACs for scenario S2 at different PCI-time delays

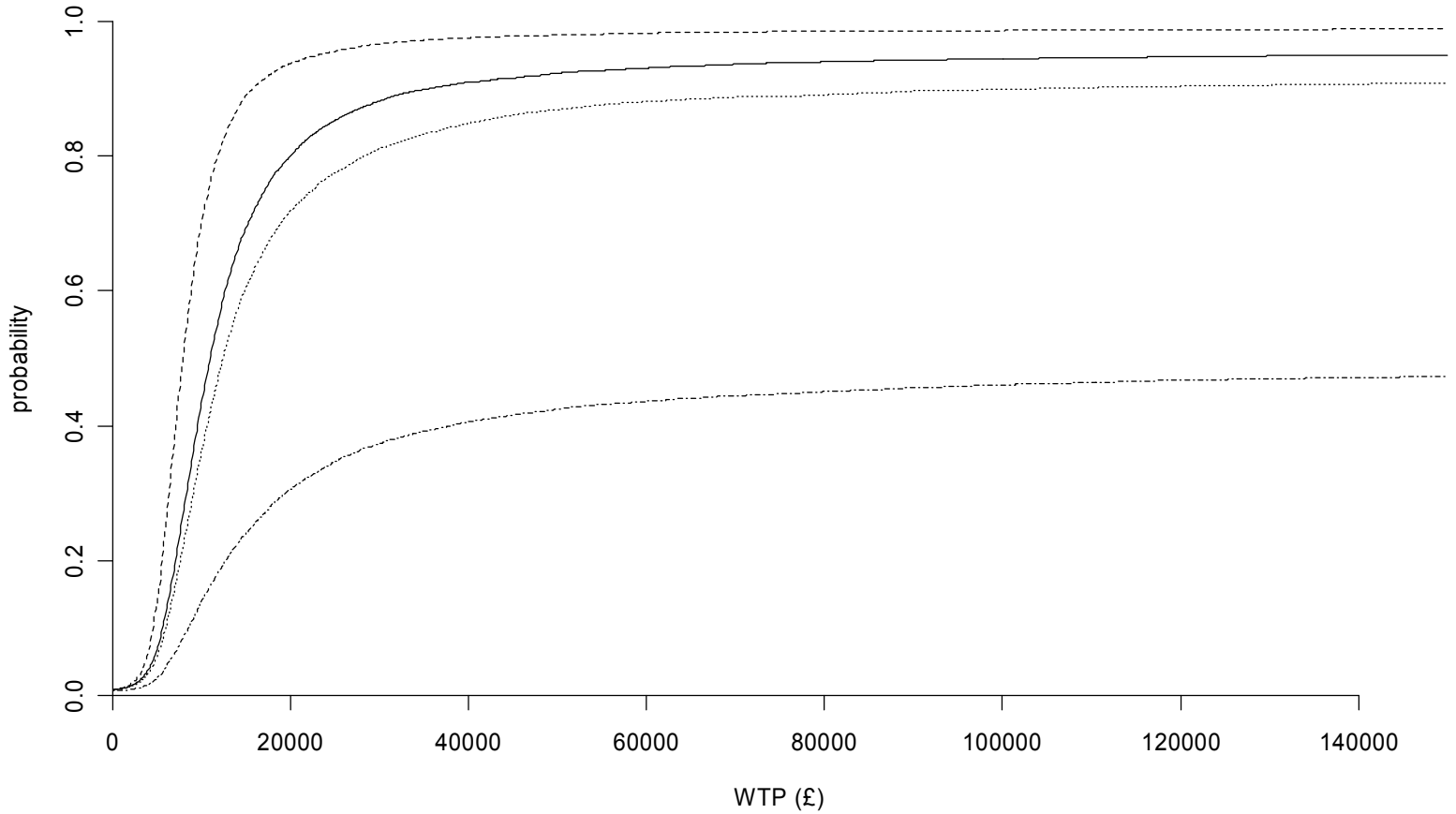


Figure 10. Family of CEACs for scenario S3 at different PCI-time delays

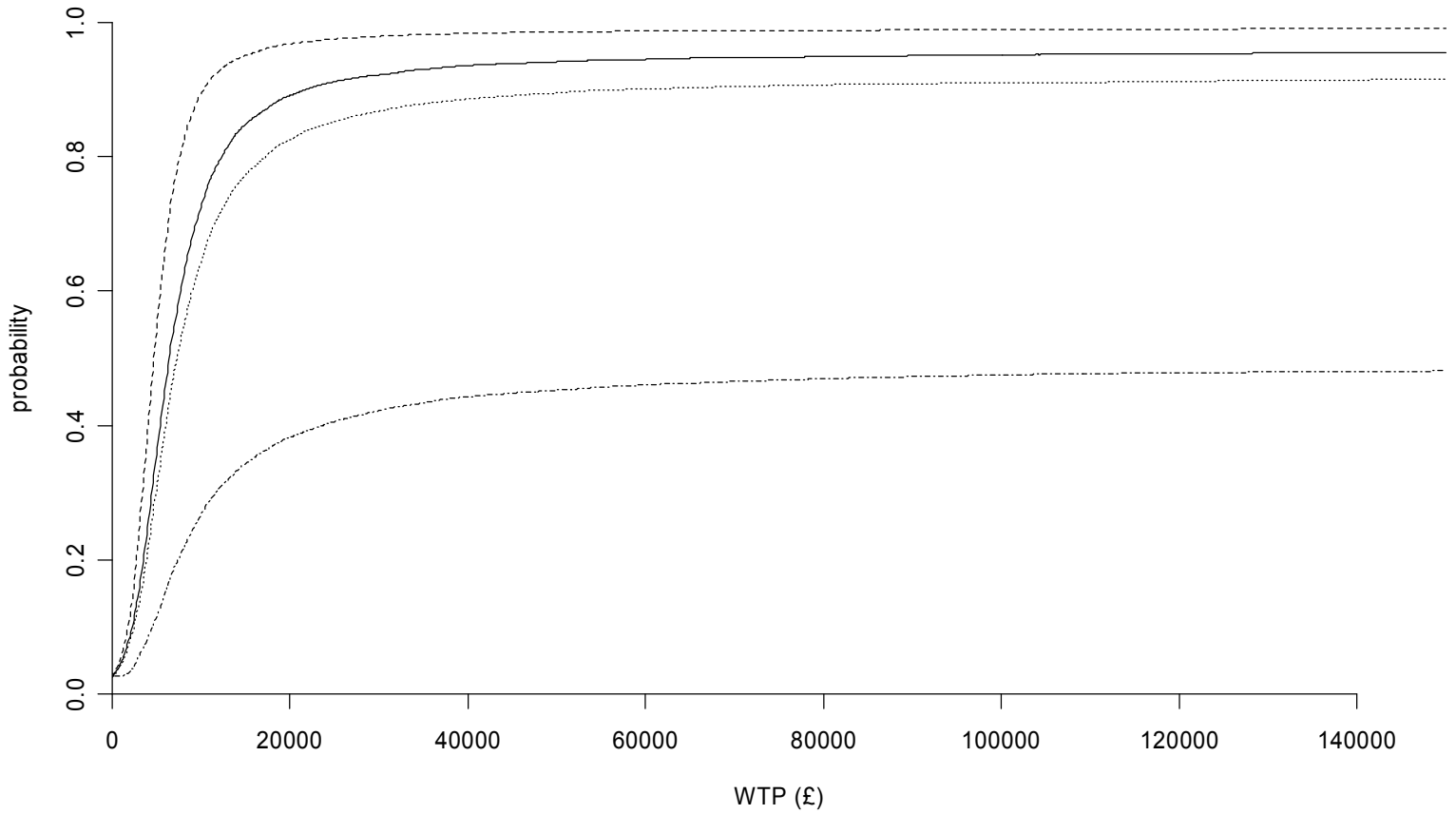
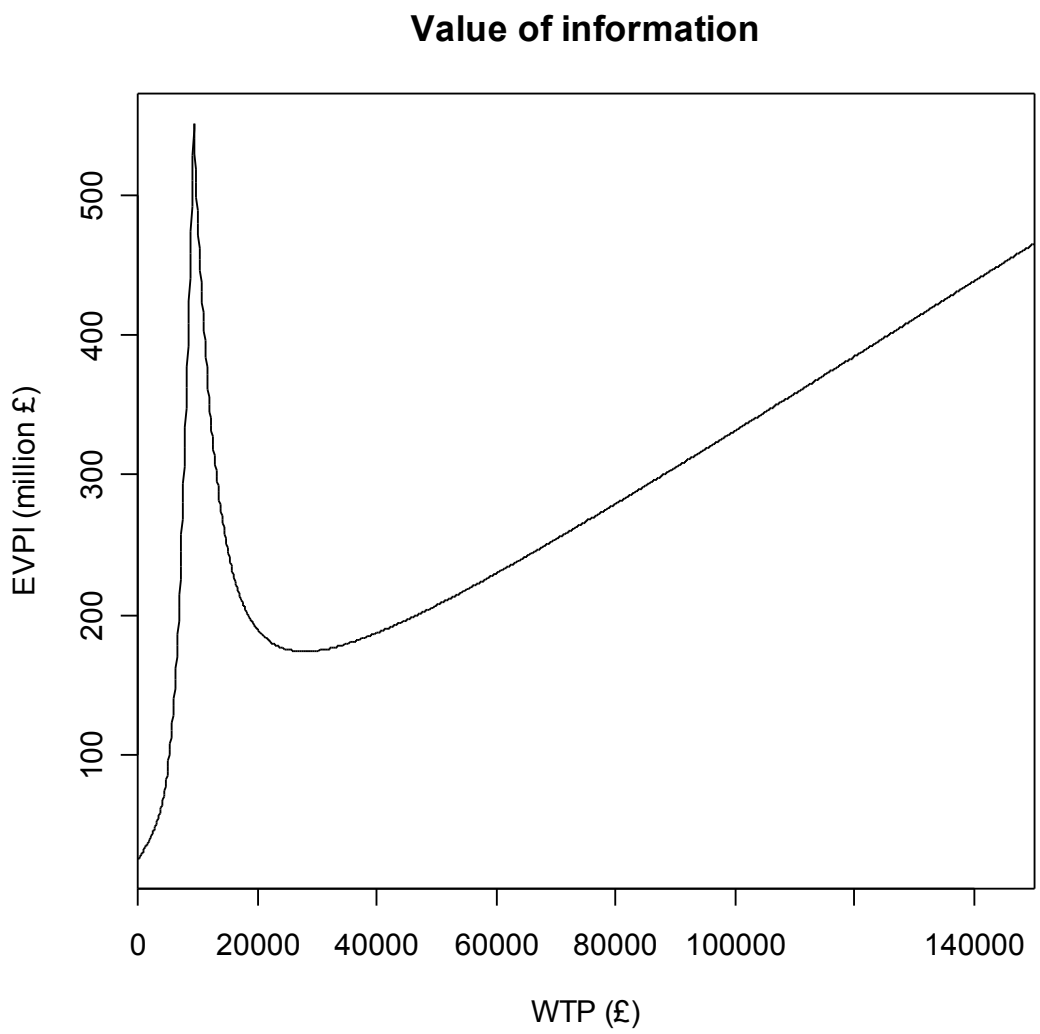


Figure 11. Population EVPI – Base case



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Appendix 1. Search strategies used

1. Update PCI searches for Hartwell et al HTA report

Endnote library pci stents trials.enl
No. refs 703
Date range 2002-2004
Custom 4 pci trials update
Limits English language only

a. RCTs

CCTR
(angioplast* or pci or percutaneous coronary intervention)
(myocardial next infarction)
(#1 and #2)
FIBRINOLYTIC AGENTS explode all trees (MeSH)
THROMBOLYTIC THERAPY explode all trees (MeSH)
(fibrinol* or thromboly*)
(#4 or #5 or #6)
(#3 and #7)

NRR

((((ANGIOPLAST* or PCI) OR (PERCUTANEOUS AND (CORONARY and INTERVENTION))) OR (MYOCARDIAL NEXT INFARCTION)) AND ((FIBRINOLYTIC-AGENTS*:ME OR THROMBOLYTIC-THERAPY*:ME) OR (FIBRINOL* OR THROMBOLY*)))

b. Observational studies

MEDLINE

1 (angioplast$ or pci or percutaneous coronary intervention).mp. [mp=title, abstract, name of substance, mesh subject heading]
2 exp Myocardial Infarction/
3 (acute adj5 (mi or myocardial infarction)).mp. [mp=title, abstract, name of substance, mesh subject heading]
4 1 and 2 and 3
5 exp Cohort Studies/
6 exp "Outcome Assessment (Health Care)"/
7 5 or 6
8 4 and 7
9 randomized controlled trial.pt.
10 8 not 9
11 10
12 limit 11 to (english language and yr=2002-2004)

c. Economic Evaluations

MEDLINE

1 (angioplast$ or pci or percutaneous coronary intervention).mp. [mp=title, abstract, name of substance, mesh subject heading]
2 exp ECONOMICS/
3 exp Quality-Adjusted Life Years/
4 exp Quality of Life/
5 (cost$ or economic$).mp. [mp=title, abstract, name of substance, mesh subject heading]

6 (wellbeing or well-being).mp. [mp=title, abstract, name of substance, mesh subject heading]
7 (hrqol or qol or hr-qol or euroqol or euro-qol or health utilit$).mp. [mp=title, abstract, name of substance, mesh subject heading]
8 ((quality adj2 life) or qaly$).mp. [mp=title, abstract, name of substance, mesh subject heading]
9 or/2-8
10 1 and 9
11 exp Myocardial Infarction/
12 myocardial infarction.mp. [mp=title, abstract, name of substance, mesh subject heading]
13 11 or 12
14 10 and 13
15 14
16 limit 15 to (english language and yr=2002-2004)

EMBASE

1 (angioplast$ or pci or percutaneous coronary intervention).mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name]
2 exp Quality of Life/
3 exp Quality Adjusted Life Year/
4 exp Health Economics/
5 exp ECONOMICS/
6 (cost$ or economic$).mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name]
7 (hrqol or qol or hr-qol or euroqol or euro-qol or health utilit$).mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name]
8 ((quality adj3 life) or qaly$).mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name]
9 (wellbeing or well-being).mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name]
10 or/2-9
11 1 and 10
12 exp Heart Infarction/
13 myocardial infarction.mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name]
14 12 or 13
15 11 and 14
16 15
17 limit 16 to (english language and yr=2002-2004)

NHS EED

s angioplasty$ and myocardial(w)infarction
s @18jul2002:02feb2004/xid
s s1 and s2

2. Stents RCT searches

Endnote library	pci stents trials.enl
No. refs	252
Date range	1995-2004
Custom 4	stent trials
Limits	English language only

CCTR

#1 STENTS explode all trees (MeSH)
#2 paclitaxel or sirolimus or everolimus or actinomycin or stent or stents
#3 #1 or #2

#4 MYOCARDIAL INFARCTION explode all trees (MeSH)
#5 myocardial infarction
#6 #4 or #5
#7 #3 and #6

MEDLINE

1 exp STENTS/
2 (paclitaxel or sirolimus or everolimus or actinomycin or stent or stents).mp. [mp=title, abstract, name of substance, mesh subject heading]
3 1 or 2
4 exp myocardial infarction/
5 myocardial infarction.mp. [mp=title, abstract, name of substance, mesh subject heading]
6 4 or 5
7 3 and 6
8 randomized controlled trial.pt.
9 7 and 8
10 9
11 limit 10 to (english language and yr=1995-2004)

NRR

(STENTS*:ME OR STENT OR STENTS OR paclitaxel or sirolimus or everolimus or actinomycin) AND (MYOCARDIAL-INFARCTION*:ME OR MYOCARDIAL INFARCTION)

3. PCI/Stents in myocardial infarction - economic evaluations

Endnote library pci stents econ evals.enl
No. refs 188
Date range 1995-2004
Custom 4 pci stents econ evals
Limits English language only

NHS EED (admin database)

s angioplast$ or pci or percutaneous(w)coronary(w)intervention
s myocardial(w)infarction
s s1 or s2
s fibrinol$ or thromboly$
s s3 and s4
s paclitaxel or sirolimus or everolimus or actinomycin or stent or stents
s myocardial(w)infarction
s s6 and s7
s s5 or s8
s (1995 or 1996 or 1997 or 1998 or 1999 or 2000 or 2001 or 2002 or 2003 or 2004)/dat
s s9 and s10

4. Thrombolysis in MI - systematic reviews

Endnote library thrombolysis SRs.enl
No. refs 123
Date range 2000-2004
Custom 4 thrombolysis SRs
Limits English language only

CDSR

MYOCARDIAL INFARCTION explode all trees (MeSH)
(myocardial next infarction)

(#1 or #2)
FIBRINOLYTIC AGENTS explode all trees (MeSH)
THROMBOLYTIC THERAPY explode all trees (MeSH)
(fibrinol* or thromboly*)
(#4 or #5 or #6)
(#3 and #7)
#8 (2000 to current date)

DARE (Admin database)

s myocardial(w)infarction
s fibrinol$ or thromboly$
s s1 and s2
(2000 or 2001 or 2002 or 2003 or 2004)/dat
s s3 and s4

HTA Database

s myocardial(w)infarction
s fibrinol$ or thromboly$
s s1 and s2
s (2000 or 2001 or 2002 or 2003 or 2004)/xyr
s s3 and s4
s review
s s5 and s6

Appendix 2. Main characteristics clinical trials

Study	Patients' characteristics	Country	Stents (%)	GPAs (%)	N in PCI group	N in Lysis group
Zijlstra 1993	Age <75; ST elevation	Netherlands	No	No	70	72
Ribeiro 1993	Age <75; ST elevation	Brazil	No	No	50	50
Zwolle 1994	Age <76; ST elevation	Netherlands	No	No	152	149
Berrocal 2003	ST elevation	Argentina	No	No	54	58
Zijlstra 1997	ST elevation; low risk	Netherlands	No	No	45	50
Widimsky 2000	ST elevation, LBBB	Czech Rep.	Yes	No	101	99
de Boer 2002	Age >76; ST elevation	Netherlands	Yes	No	46	41
Widimsky 2003	ST elevation	Czech Rep.	Yes	Yes	429	421
DeWood 1990	Age <76; ST elevation	US	No	No	46	44
Grines 1993	Age <75; ST elevation	US	No	No	195	200
Gibbons 1993	Age <80; ST elevation	US	No	No	47	56
Ribichini 1998	Age <80; anterior ST depression	Italy	No	No	55	55
Garcia 1999	Anterior MI ST elevation	Spain	Yes (13)	No	109	111
GUSTOIIb 1997	ST elevation; LBBB	international	Yes (5)	No	565	573
Le May 2001	ST elevation; LBBB	Canada	Yes (81)	Yes (19)	62	61
Bonnefoy 2001	ST elevation	France	Yes (72)	Yes (23)	421	419
Schomig 2000	ST elevation	Germany	Yes (91)	Yes (91)	71	69
Vermeer 1999	Age <80; ST elevation	Netherlands	Yes (17)	No	75	75
Andersen 2003	No age limits; ST elevation	Denmark	Yes	Yes	790	782
Kastrati 2002	ST elevation; LBBB	Germany	Yes (95)	Yes (95)	81	81
Aversano 2002	ST elevation	US	Yes (63)	Yes (76)	225	226
Grines 2002	Age >70; ST elevation; LBBB	Argentina	Yes	Yes	71	66

Note: new studies in italics. *Median time to treatment, otherwise mean time.

NF stroke= Non fatal stroke; NF RI= Non fatal re-infarction; LBBB= Left bundle branch block; GPAs = Glycoproteins IIb/IIIa antagonists used as primary PCI adjunctive treatment.

Appendix 3: Equations

Model component	**Equations** (for all i, j, x, where appropriate)
Trial data	$r_{i,i}^{x} \sim Bin\left(\pi_{i,j}^{x}, n_{j}^{x}\right)$ and $R_{i,i}^{x} \sim Bin\left(\Pi_{i,j}^{x}, N_{j}^{x}\right)$
Probabilities on logit scale	$\log\left(\pi_{i,j}^{x} \Big/ 1-\pi_{i,j}^{x}\right) = \lambda_{i,j}^{x}$ and $\log\left(\Pi_{i,j}^{x} \Big/ 1-\Pi_{i,j}^{x}\right) = \Lambda_{i,j}^{x}$
Correlated within-outcome errors	$\begin{pmatrix} \lambda_{i,j}^{T} \\ \lambda_{i,j}^{P} \\ \Lambda_{i,j}^{T} \\ \Lambda_{i,j}^{P} \end{pmatrix} \sim MVN\left(\begin{pmatrix} \overline{\lambda}_{i,j}^{T} \\ \overline{\lambda}_{i,j}^{P} \\ \overline{\Lambda}_{i,j}^{T} \\ \overline{\Lambda}_{i,j}^{P} \end{pmatrix}, X_{i}\right)$
Explain treatment effects	$\overline{\Lambda}_{i,j}^{x} = \overline{\lambda}_{i,j}^{x} + \omega_{i}^{x}$ to relate 1-month and 6-month outcomes, $\overline{\lambda}_{i,j}^{P} = \overline{\lambda}_{i,j}^{T} + \alpha_{i} + \beta_{i} \cdot \partial_{j}$ for the 1-month treatment effect,
Random baselines	$\begin{pmatrix} \overline{\lambda}_{i=1,j}^{T} \\ \overline{\lambda}_{i=2,j}^{T} \\ \overline{\lambda}_{i=3,j}^{T} \end{pmatrix} \sim MVN\left(\begin{pmatrix} \mu_{1} \\ \mu_{2} \\ \mu_{3} \end{pmatrix}, Y\right)$
time delay covariate	$\partial_{j} = \overline{\delta}_{j}^{P} - \overline{\delta}_{j}^{T}$
Measurement error in time delay	$\delta_{j}^{x} \sim N\left(\overline{\delta}_{j}^{x}, v_{j}^{x}\right)$

Notation: Throughout, let j index the 23 trials and i index the three endpoints. Also, let capital letters N, R stand for the 6-month endpoint data, and small letters n, r denote 1-month endpoint data from the trials, for the two arms $x = P, T$ (PCI or thrombolytics). Probabilities π are estimated on the log-odds scale. Baseline probability log-odds are denoted by μ. Random effects are modelled as additive on the log-odds scale, and the mean underlying probabilities shall be denoted by $\overline{\lambda}$. The log-odds differences between 1-month and 6-month probabilities are denoted by ω. Time delays, as measured in each trial arm, shall be written as δ, their means as $\overline{\delta}$, and the observed variance as v. I denote the covariate "PCI-related time delay" by ∂, and the coefficients of the linear regression by α (intercept) and β (slope).

Appendix 4. t-PA trials short term effectiveness results – Average time delay

1-month endpoints	probability (PCI)	probability (Lysis)	odds ratio
Death	4.4% (2.7%, 7.2%)	6.2% (3.9%, 9.4%)	0.71 (0.44, 1.16)
non-fatal reinfarctions	2.1% (1.1%, 3.7%)	4.9% (2.8%, 8.0%)	0.41 (0.23, 0.71)
non-fatal strokes	0.4% (0.1%, 0.9%)	1.6% (0.7%, 3.3%)	0.23 (0.08, 0.57)
6-month endpoints	**probability (PCI)**	**probability (Lysis)**	**odds ratio**
Death	5.4% (3.2%, 9.7%)	7.5% (4.6%, 13.2%)	0.70 (0.39, 1.30)
non-fatal reinfarctions	2.6% (1.3%, 5.8%)	5.7% (3.2%, 10.3%)	0.45 (0.23, 0.94)
non-fatal strokes	0.5% (0.2%, 2.2%)	2.0% (0.9%, 8.2%)	0.23 (0.06, 0.83)

Note: Mean (95% CrI)

Appendix 5. t-PA trials short term effectiveness results –sensitivity analysis time delay

	30 min		60 min		90 min	
endpoint	**Difference**	**RR**	**Difference**	**RR**	**Difference**	**RR**
Death	**–3.4%** (–8.5%, +0.2%)	0.53 (0.27, 1.04)	**–1.7%** (–6.3%, +2.6%)	0.77 (0.43, 1.41)	**+0.8%** (–5.5%, +13.2%)	1.11 (0.44, 2.89)
NF Reinf.	**–2.5%** (–6.8%, +1.3%)	0.54 (0.22, 1.26)	**–3.0%** (–7.1%, –0.2%)	0.45 (0.23, 0.95)	**–3.3%** (–7.8%, +1.6%)	0.38 (0.11, 1.29)
NF stroke	**–1.7%** (–7.5%, –0.4%)	0.12 (0.01, 0.70)	**–1.4%** (–6.9%, –0.1%)	0.28 (0.08, 0.96)	**–0.6%** (–5.6%, +8.1%)	0.66 (0.10, 4.77)

Note: Absolute probability differences and relative risks for the 6-month treatment effects of primary angioplasty compared to thrombolytic therapy (median and 95%-CrI) at assumed 'PCI-related time delays' of 30, 60 and 90 minutes. NF= Non Fatal; Reinf = Re-infarction; RR = Relative Risk.

Appendix 6. Short-term costs for alternative scenarios

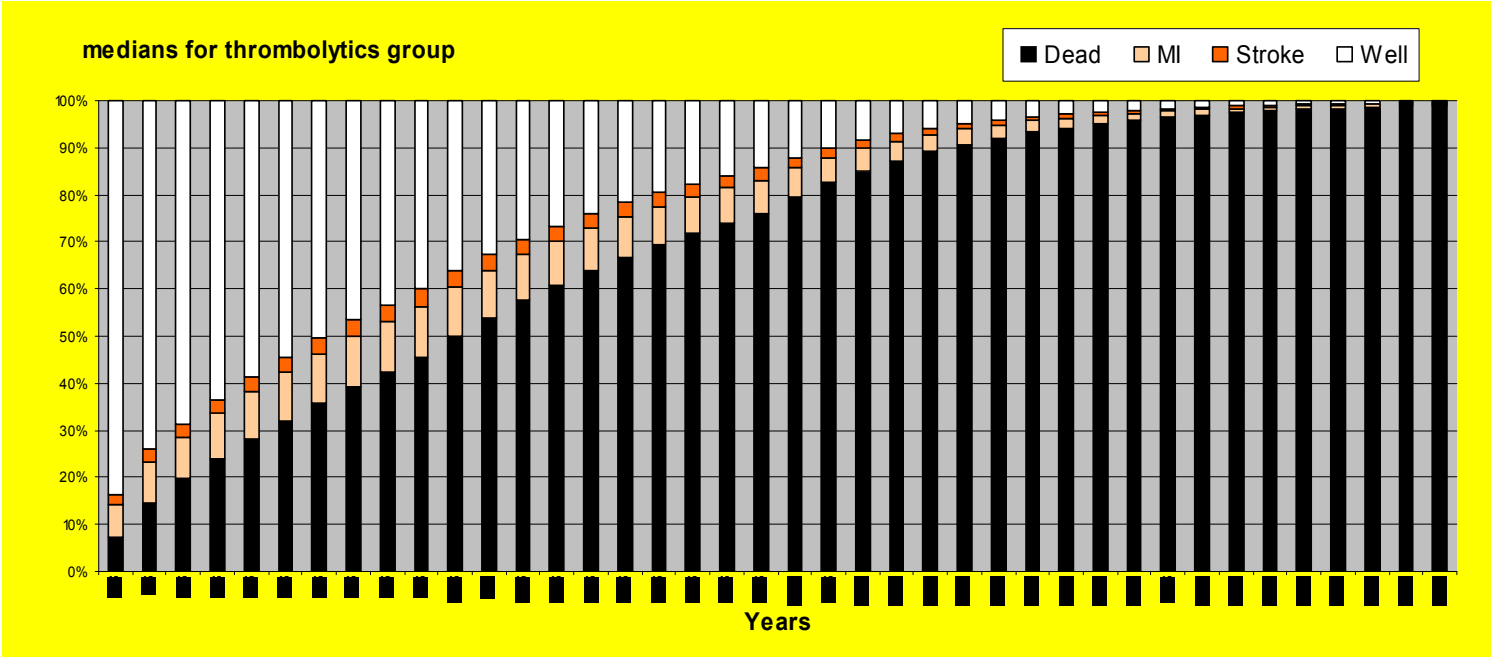
S1 SCENARIO	Primary PCI (£ UK)	Thrombolytics (£ UK)
Treatment of initial MI episode	£5,360 (£4,890 , £5,980)	£2,700 (£1,850 , £3,770)
Additional revascularizations	£510 (£350 , £710)	£1,290 (£970 , £1,660)
Total short term costs	£5,860 (£5,360, £6,510)	£3,990 (£3,060, £5,120)

S2 SCENARIO	Primary PCI (£ UK)	Thrombolytics (£ UK)
Treatment of initial MI episode	£6,090 (£6,010 , £6,180)	£2,330 (£1,950 , £2,720)
Additional revascularizations	£520 (£300 , £860)	£1,340 (£900 , £1,890)
Total short term costs	£6,600 (£6,370, £6,970)	£3,670 (£3,230, £4,220)

S3 SCENARIO	Primary PCI (£ UK)	Thrombolytics (£ UK)
Treatment of initial MI episode	£5,360 (£4,890 , £5,980)	£2,700 (£1,850 , £3,770)
Additional revascularizations	£520 (£300 , £860)	£1,340 (£900 , £1,890)
Total short term costs	£5,880 (£5,340, £6,560)	£4,040 (£3,060, £5,230)

Note: Mean (95% CrI)

Appendix 7. Thrombolytics group- Accumulated proportions of patients in each health state between 6 months and 40 years



Appendix 8. Primary PCI group- Accumulated proportions of patients in each health state between 6 months and 40 years