UNIVERSITY OF SOUTHAMPTON

FACULTY OF LAW, ARTS AND SOCIAL SCIENCES

School of Management

A Comparative Study of Modelling Approaches for the Evaluation of Healthcare Interventions, with Reference to Coronary Heart Disease

by

Keith Cooper

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Abstract

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This dissertation presents a comparison of modelling techniques for evaluating healthcare interventions with a focus on modelling coronary heart disease interventions. Through the construction of decision tree, Markov and discrete event simulation (DES) models for simple hypothetical and realistic healthcare models, the dissertation compares the respective processes and outputs of the alternative techniques. The results are analysed and recommendations are made for theoretical guidelines for the choice of modelling technique according to various intervention classifications. This research is the first to compare the modelling techniques from an empirical perspective for several intervention types and to provide a serious comparison of the benefits or disadvantages of the modelling approaches. In addition the models for coronary heart disease provide realistic assessment of the benefits and costs of improved emergency response times, secondary prevention medication and bypass surgery. The coronary heart disease models are based upon research completed by the author as part of the UK Coronary Heart Disease Policy Model working team. In particular much of the data have been collected by other members of the group. Furthermore the modelling work here was done in consultation with other members of the group.

The interventions are shown to be good value for money according to a willingness to pay threshold of £30,000 per QALY gained. Aspirin and beta blockers are the most cost effective and have incremental cost effectiveness ratios (ICER) of less than £1000 per QALY gained. Improving thrombolysis response times is the least cost effective with an ICER of almost £30,000 per QALY gained. In order to achieve the targets from the National Service Framework (NSF), the increased spending (and consequent health benefits) would be greatest for statins and revascularisation. Implementing each of the NSF scenarios for England over the next 20 years for these interventions would result in an average annual extra cost of £400 million and will result in a saving of 65,000 life years and 70,000 QALYs each year.

The choice of the preferred model will depend on the intervention or health system, particular expertise, background and preferences of the modeller, the ease and speed of development, the complexity of the model in terms of the number of states, and the interconnectedness of the system. The modeller will need to make a judgement on the necessary complexity of the model, in term of the number of states to be included. They will need to judge whether interactions between individuals is a significant issue in the health care system and whether queuing for resources and resource constraints are relevant to the research question. The modeller will need to judge whether the preferred modelling techniques will be acceptable to the users of the model. Finally the use of population-based models and the provision of health care outcomes for the likely cost, health benefits and cost effectiveness of the interventions is recommended.

To my mother and father

Thanks for the kidney mum,
- it's still in safe hands.....

Contents

List of Tables

List of diagrams

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Abbreviations

ACI	Acute coronary incident
BARI	Bypass Angioplasty Revascularisation Investigation
BMA	Boersma et al Study
BRHS	British Regional Heart Study
CABG	Coronary Artery Bypass Graft
CHD	Coronary Heart Disease
CCU	Coronary care unit
CPLYS	Cost per life year saved
DES	Discrete event simulation
ECG	Electrocardiogram
ECHO	Echocardiogram
EMMACE	Evaluation of Methods and Management of Acute Coronary Events
FTT	Fibrinolytic Therapy Trialists' Collaborative Group
GPRD	General Practitioners Research Database
HES	Hospital Episode Statistics
HSE	Health Survey for England
ICER	Incremental cost effectiveness ratio
LMS	Left main stem
LYS	Life year saved
MI	Myocardial infarction
NCD	Non cardiac death
NSF	National Service Framework
ONS	Office of National Statistics
PET	Positron Emission Tomography
PTCA	Percutaneous Transluminal Coronary Angioplasty
SK	Strepokinase
SPECT	Single photon emission computed tomography
tPA	Tissue plasminogen activator
UKHAS	United Kingdom Heart Attack Study
QALY	Quality Adjusted Life Year
QoL	Quality of life

Chapter 1

Introduction and Outline of Thesis

This dissertation presents a comparison of modelling techniques for evaluating health care interventions with a focus on modelling coronary heart disease (CHD) interventions.

In recent years economic evaluations have become increasingly common in the health care literature and this has provided additional information for policy makers for the equitable and efficient allocation of health care resources. There has been growing concern about the quality of these studies and guidelines have been produced for both reviewers and analysts for ensuring better quality. However, the choice of modelling technique and the consequences of this choice have not been fully explored.

Through the construction of decision tree, Markov and discrete event simulation models for simple hypothetical health care models, the dissertation compares the respective processes and outputs of the alternative techniques. The results are analysed and recommendations are made for theoretical guidelines for the choice of modelling technique according to various intervention classifications.

These recommendations are considered in a wider sense by constructing realistic models of health care interventions for coronary heart disease interventions. These interventions cover a wide scope in their structure and range from short term acute interventions, long term chronic interventions to resource-constrained interventions. Coronary heart disease has been the subject of many analyses using modelling, and the models produced within this dissertation supplement these studies.

The first section of this chapter introduces the role of health care modelling and its importance to health care decision making. The second section discusses this modelling within coronary heart disease. The third section outlines the key research questions and summarises the research approaches in this dissertation. The final section outlines the structure of the remaining chapters of the thesis.

1.1 Modelling health care interventions

In the UK and other western countries, there is a scarcity of health care resources, such as money, people, time and facilities. Health service providers need to make difficult choices between different uses of these resources. Ideally these choices would be made in an objective way based on all the latest information with regard to present and future treatment.

One of the methods which is increasingly used to provide information for health care planners is often referred to as economic evaluation (Elixhauser et al. 1993; 1998). Economic evaluation attempts to compare the costs and consequences of alternative courses of action (Kupersmith et al. 1994). It assesses health improvements in terms of increased survival and / or quality of life in a single comparable measure. These analyses often use models, for example decision tree, Markov and discrete event simulation.

There has been increasing interest in improving the quality of these models (Halpern et al. 2002; Davies et al. 2002; Sculpher et al. 2000; Weinstein et al. 2003; Sonnenberg et al. 1994; McCabe and Dixon 2000; Brennan and Akehurst 2000; Weinstein et al. 1996; Siegel et al. 1996; Russell et al. 1996; Eddy 1990). However, the choice of modelling technique and the consequences of the choice have not been fully explored (Davies et al. 2003; Karnon 2003; Sonnenberg et al. 1994).

This research expands the work of Karnon (2003) which compared the processes and outputs from a Markov model and a discrete event simulation model. The models described an economic evaluation comparing alternative adjuvant therapies for early breast cancer. Recommendations were made for the use of the modelling techniques, although these may not be generalisable to other modelling studies. Sonnenberg et al. (1994) and Barton et al. (2004) provided broad recommendations for the use of models for different model structures, although these recommendations have not been based on analytical or empirical studies.

Through the construction of decision tree, Markov and discrete event simulation models for simple hypothetical health care models, the dissertation compares the respective processes and outputs of the alternative techniques. The results are analysed and recommendations are made for theoretical guidelines for the choice of modelling technique according to various intervention classifications.

1.2 Modelling coronary heart disease interventions

The recommendations for choosing the type of model are considered in a wider sense by constructing realistic, working models of health care interventions for coronary heart disease interventions. These interventions cover a wide scope in their structure and range from short term acute interventions, long term chronic interventions to resource-constrained interventions.

Coronary heart disease is one of the leading causes in death in the UK. Every year, more than 100,000 die from heart related conditions (Office for National Statistics 1999). Patients with coronary heart disease usually have coronary arteries which have narrowed. They may suffer from angina pectoris, a chest pain brought on by exercise. If one of the coronary arteries become blocked a heart attack or cardiac arrest may occur.

Coronary heart disease has been the subject of many economic evaluations using modelling (Kupersmith et al. 1995), and the models produced within this dissertation supplement these studies. The models constructed are concerned with the treatment rather than the prevention of CHD, ie they are populated by individuals who have CHD.

The majority of the models for Coronary Heart Disease have been developed in the US. Many of the models have used the Coronary Heart Disease model developed by Weinstein et al. (1987) in the mid 1980s. This model has become somewhat outdated with the great clinical changes in CHD in the last 20 years. For example the introduction of secondary prevention drugs such as statins and the introduction of surgical procedures such as angioplasty. There are relatively few models for the treatment of CHD in the UK and the majority of these have been developed to evaluate the use of cholesterol lowering drugs (statins), for example Ebrahim et al. (1999).

In this dissertation, models are developed for CHD to evaluate improved ambulance and thrombolysis response times, secondary prevention drugs and surgical procedures.

The interventions for faster ambulance and thrombolysis response times are examples of acute interventions as these will impact on the short term survival of patients who suffer a heart attack or cardiac arrest. The interventions for secondary prevention drugs, eg statins, aspirin, beta blockers, ACE inhibitors, are examples of continuous or chronic interventions as these will impact on the long term survival of patients. The revascularisation interventions are examples of resource-constrained interventions. In these models, there are limited resources and patients are allocated according to the severity of their health condition and other criterion.

1.3 Key research question and research approach

This thesis comprises the following related research themes:

i) Development of models for evaluating coronary heart disease interventions

ii) Modelling techniques for evaluating health care interventions

This research develops models for coronary heart disease interventions. Although models for coronary heart disease have been developed before, the UK Coronary Heart Disease Policy model is the most comprehensive model developed for the prevention and treatment of coronary heart disease in the UK. The author has been the main modeller on this project for the treatment part of this model with guidance from his supervisor and with advice from other members of the Coronary Heart Disease modelling team. The data for the model was collected by other members of the team but the author has carried out extensive work on deriving the parameters for use in the model. In addition he has contributed to the structure of the model and produced all validation and model results. The summary of shared work for the Coronary Heart Disease Simulation Project and the agreement of work to be used in the PhD thesis is shown in Appendix I.

In this thesis interventions for faster ambulance and thrombolysis response times, secondary prevention drugs and revascularisation are evaluated. The modelling in this thesis is able to model these different interventions using the same data and assumptions for a disease which makes more these evaluations more readily comparable. Furthermore these analyses are extended to estimate the likely costs and benefits for increasing provision for these interventions according to the guidelines set out in the National Service Framework for coronary heart disease.

The second key research question to be addressed is: What is the appropriate modelling technique to be used to evaluate a given health care intervention? This question is to be addressed for a variety of types of health care interventions.

Davies et al (2003) '*many spreadsheet flow models are published in the medical literature but there have been no serious comparisons of their benefits with respect to other modelling approaches*'.

This dissertation seeks to contribute to the existing knowledge on appropriate model selection for health care interventions using the case study approach. The case study approach is a useful method of investigating the current theory for model selection in a practical way. In particular by building models using each of the techniques it is possible to gain insights into the comparative ease of development and results of the models. This research uses commonly used software for health care modelling. The contribution of this research is the development of comprehensive models for coronary heart disease, and the use of these models for an empirical analysis of model selection for a variety of related health care interventions. The insights gained from this research are used to develop a framework for choosing between the models according to the complexity of the models and the health care intervention characteristics.

1.4 Structure of the thesis

Chapter 2 introduces the modelling methodology for evaluating health care models. It gives a theoretical basis for the evaluation of health care interventions using modelling techniques. It also introduces current methods commonly used for economic evaluation

of health care interventions, such as decision tree, Markov process and discrete event simulation models.

Chapter 3 provides a review of the literature of models for coronary heart disease interventions in the context of the choice of modelling technique. It gives a contextual background for subsequent chapters on modelling coronary heart disease.

Chapter 4 presents a review of methodological issues for modelling health care interventions. It gives a summary of the best practice for building models and then investigates the issues concerning appropriate model selection according to the characteristics of the health care intervention.
Chapter 5 provides an empirical analysis of modelling techniques for health care interventions. Simple models of health care interventions are constructed, using modelling technique, for each of the main intervention structures which affect model choice. A theoretical framework is devised for the recommendation of model choice based on these model structures.

Chapter 6 presents the theoretical basis of a model for coronary heart disease interventions. It presents the analysis and derivation of main parameters of the coronary heart disease models described in this thesis. A coronary heart disease model using these parameters is validated for the main outcomes against national data.

Chapter 7 to 9 describe models built for coronary heart disease interventions for each of the main intervention structures previously examined. In each chapter models are built using each technique and the results collected for the likely costs, benefits and cost effectiveness of these interventions. Using these case studies the theoretical recommendations for the appropriate modelling technique are examined.

Chapter 7 describes models built for the acute treatment intervention of ambulance and thrombolysis response times. Chapter 8 describes models built for chronic treatment interventions of secondary prevention medication. Chapter 9 describes models built for resource-constrained interventions for coronary revascularisation. It also develops a framework for choosing between the Markov and simulation models, according to the complexity of the model.

Chapter 10 concludes the dissertation. It discusses the coronary heart disease results from chapters 7 to 9, reviews the research questions and summarises the key contributions and limitations of this research. Finally recommendations are presented for future research.

Chapter 2

Health care Modelling Methodology

Abstract

This chapter reviews the current methodology of modelling health care interventions. It aims to give a background to the current methods used for modelling health care interventions as a basis for the research in the subsequent chapters. Economic evaluation, such as cost effectiveness analysis, provides a method for comparing health care interventions. These evaluations often use modelling techniques such as decision trees, Markov processes and discrete events simulations. This chapter introduces the concepts of economic evaluation and describes each of the modelling techniques.

Chapter 2 Health care Modelling Methodology

2.1 Introduction

In the UK and other western countries, there is a scarcity of health care resources, such as money, people, time and facilities. Health service providers need to make tough choices between different uses of these resources. Ideally these choices would be made in an objective way based on all the latest information with regard to present and future treatment.

One of the methods which is increasingly used is often referred to as economic evaluation. Economic evaluation attempts to compare alternative courses of action in terms of both their cost and consequences. It assesses health improvements in terms of increased survival and / or quality of life in a single numerical measure. In order to do this, the economic evaluation uses information on the cost and effectiveness of the courses of action, which are being compared. This information is often collected from short term trials or pilot studies. The aim of economic evaluations is to be able to directly compare all treatments whether they are related or not by putting them on the same scale. Thus health care decision makers may wish to be able to compare treatments such as coronary artery bypass surgery (CABG) with screening for breast cancer, hip replacement and any other new or existing health technology or treatment.

The most common forms of economic evaluation are cost effectiveness analysis, cost benefit analysis and cost utility analysis. These analyses use various models, for example decision tree, Markov and discrete event simulation. This chapter is in two parts. It describes the theory of economic evaluation and some of the models used are described in more detail.

2.2 Economic evaluation

In this section basic methods of economic evaluations are defined. Although attempts have been made at standardisation of methodology and terminology, for example Gold

et al. (1996), differences remain. Where these differences occur, the terminology and methodology as described by Drummond et al. (1997) is used.

2.2.1 Cost minimisation analysis

Cost minimisation compares two or more programmes or strategies on the basis of cost alone and selects the cheaper one as the most appropriate (Kupersmith et al. 1994). One assumption made is that each of the alternative programmes have equal health care consequences. In fact, it is unusual for the alternative programmes to have equivalent effectiveness and so very few studies are designed from the outset to be cost minimisation analyses (Drummond et al. 1997). Cost minimisation has been used to compare the cost of angioplasty and bypass surgery (Hlatky et al. 1990; Cohen et al. 1993).

2.2.2 Cost effectiveness analysis

In cost effectiveness analysis, the ratio of total cost to effectiveness is calculated (Kupersmith et al. 1994). Costs are those related to the particular medical interventions studied (eg drugs, interventions, outpatient visits) minus savings from prevention of events (eg stroke or MI). Indirect costs, such as costs associated with working days lost, are not normally included. The usual measure of effectiveness is increase in years of life. Alternatively, effectiveness may be related to number of lives saved, or more specific outcomes such as disease free survival, or successful treatment accomplished.

$$\text{Cost effectiveness ratio} = \frac{\Delta \text{Cost}}{\Delta \text{Life expectancy}}$$

However different treatments can only be compared if a common measure of effectiveness is used. Thus kidney transplantation can be compared to compulsory bicycle helmet legislation if the effectiveness is measured as years of life gained but not if it is measured as number of bicycle accident injuries avoided (Drummond et al. 1997).

2.2.3 Cost benefit analysis

In cost benefit analysis, health benefits, including human life, are given a monetary value (Kupersmith et al. 1994). However, valuing health outcomes is not a simple process and comes with many difficulties, for example how much is an added year of life expectancy worth. The main method used to value health outcomes is the *willingness to pay* of patients (Drummond et al. 1997). The amount a patient is willing to pay for a health service is estimated by surveying patients or potential patients. One difficulty of this approach is that people do not accurately predict what they are likely to spend, especially if it is a health service they do not understand well or if they are not directly spending the money, as is the case with treatment within the National Health Service. For these reasons, cost benefit analysis has been used far less than cost effectiveness analyses (Kupersmith et al. 1994; Drummond et al. 1997).

$$\text{Cost benefit ratio} = \frac{\Delta \, Cost\ of\ strategy}{\Delta \, Cost\ of\ benefit}$$

2.2.4 Cost utility analysis

Cost utility analysis incorporates quality and quantity of life into a cost effectiveness analysis (Kupersmith et al. 1994; Drummond et al. 1997). This is especially appropriate for assessing treatments that only or mainly improve quality of life. Outcomes are expressed in terms of quality adjusted life years (QALYs). Quality of life or utility is measured as a number between 0 and 1 where 0 and 1 represent death and perfect health respectively. Some health states that are considered by patients to be worse than death itself may have negative values. The quality of life (QoL) value for each health state is multiplied by the time in the state and then summed to calculate the number of QALYs. For example, if a patient with severe angina (QoL = 0.7) has a life expectancy of two years, they will have the equivalent of 1.4 QALYs.

$$\text{Cost utility ratio} = \frac{\Delta \, Cost}{\Delta \, QALY}$$

Quality of life or utility values are subjective to patients' perceptions of disease and health care outcomes and are estimated by linear scales such as the category rating, the standard gamble or the time trade off method, as described below.

Linear scale methodologies such as category rating or visual analogue scale use a numbered line such as a 100 point scale, where death scores 0 and perfect health scores 100 (Kupersmith et al. 1994). Subjects place a mark on the scale to indicate how desirable this health state is compared to death or perfect health.

In the standard gamble method, the subject is asked to imagine a hypothetical situation in which he is given a choice between continuing to live in this health state and gambling to live in either the perfect health state or to die (Kupersmith et al. 1994). For example suppose the patient has angina pectoris and given the gamble whereby there is 95% chance of perfect health and 5% risk of dying. In this case the patient may accept the risk. The chance of perfect health is now lowered until the point where the subject is indifferent between choosing to take the gamble or not and this is the QoL score. For example if this break even point was at 80% chance of perfect health and a 20% risk of immediate death then the utility or QoL score will be equal to 0.8.

Time trade off is the more commonly used method for estimating utilities (Kupersmith et al. 1994). Here the subject is asked how many years in perfect health would be equivalent to a fixed longer life expectancy in the health state in question. For example if the subject felt that 10 years living with angina would be equivalent to 7 years of perfect health, then the QoL or utility score would be 0.7.

Utilities may be collected from the general public, patients, nurses or physicians. There is some debate to the most appropriate source of utilities. Gold et al. (1996) recommend using utilities based on community values, ie health state weights collected from representative individuals from the general population. They justify this by maintaining that patients experiencing a disease may adapt to the condition and thus rate health states more highly than would unaffected community members. Conversely it may be true that community members may not appreciate or understand the full impact of a disease health state which they are not suffering from. Smith et al. (1993) recommend collecting utilities from patients being studied in the outcome model.

Davies et al. (2003) suggest some other major assumptions that QALYs make:

> '*..they treat mortality and quality of life (QoL), as commensurate, so that one can be traded off against the other.*'
>
> '*..the methods used surveys to elicit quality of life weights vary. For example visual analogue scale, standard gamble, time trade off and person trade off all give different values*'

They conclude that

> '*A prerequisite for using QALYs for a condition is that the utility for that condition should be well established and based on sound research. Unfortunately most health states do not have reliable QALYs*'.

Nevertheless, QALYs are widely used in cost effectiveness analyses. Bell et al. (2001) has compiled a database of QoL scores used in cost effectiveness studies. A more detailed discussion of utility theory is given by Torrance and Feeny (1989).

2.2.5 Discounting

Discounting methods are used to express future costs and benefits in terms of their net present value. Generally people would prefer to enjoy health benefits now rather than in the future, hence the saying 'a bird in the hand is worth two in the bush' (Krahn and Gafni 1993). They would wish to delay payment of these benefits rather than having to pay now. In addition, over the last few decades, the trend has been for positive economic growth. This means that a dollar today would be worth a higher value in the future (Drummond et al. 1997). For these reasons, it is widely accepted that costs and benefits should be discounted (Davies et al. 2002; Krahn and Gafni 1993; Drummond et al. 1997).

There is some debate amongst health economists about the discounting rate that should be used. Furthermore some recommend equal discount rates for costs and benefits (Olsen 1993; Fuchs and Zeckhauser 1987; Parsonage and Neuberger 1991) whilst other recommend lower rates for benefits (Sheldon 1992; Van Hout 1998). Krahn and Gafni (1993) present the theory behind discounting and the arguments for and against adopting the same discount rate for costs and benefits in more detail. The Washington panel (Gold et al. 1996) argue that costs and benefits should be discounted at an equal

rate of 3%. They also note that a 5% rate has commonly been used in the medical literature and studies should undertake sensitivity analysis for this rate.

The calculation to find net present value is as follows. If P is present value, C_n, future cost at year n, and r is the annual discount rate, then

$$P = \sum_{n=1}^{n} \frac{C_n}{(1+r)^n}$$

2.2.6 Population based and cohort based models

Models built for health care modelling can be either cohort or population based models. The cohort based method is the most commonly described method in the economic evaluation literature. Indeed in the literature review in chapter 3, all but five studies used a cohort approach. In this method, a cohort that developed a particular health impairment is studied over its lifetime. The costs and health status of the cohort are aggregated over the cohort lifetime and this information is used to estimate the likely benefits of introducing a new treatment for an individual patient. This method is described in more detail in section 2.3.2.

The prevalence-based or population method estimates the costs and health status of all in the population with a specific disease or condition during a specific year, irrespective of how long they have had the disease. In this method, the model begins with the prevalent diseased population which may include several subgroups or populations of people. Each year of the model run, a new incident population of people who develop the disease or condition will be added to the model population. The model will be run for a short term period (eg 1,5,10 years) to show the tangible impact of the treatment in the studied population in terms of costs and health benefits.

In general, most economic evaluation studies give a measure of the cost effectiveness of an intervention for different subgroups or populations. Whilst this is useful for choosing between treatments, decision makers also need to know the likely impact of introducing the new treatment in terms of change in costs and health benefits. Mauskopf (1998) comments that very few published economic evaluations give this information despite its obvious benefits for health care planners and furthermore it is rarely discussed or

recommended in methodological guides to economic evaluation such as Gold et al. (1996).

Mauskopf (1998) comments that estimates of the effect of the new drug on cost and health outcomes would be

> '*very valuable in giving policy makers an understanding of the likely impact of a new drug on the annual burden of the disease for the economy or for their covered population'.*

This would allow the health care decision maker to evaluate the expected health care benefits and

> '*insure that their budgets are sufficient to allow them to add the new drug'.*

Birch and Gafni (2004) illustrate this point with the following example.

> *Consider the new technologies aimed at treating four different conditions in Table 2.2.1. Each technology is described in terms of the additional effects and additional costs as compared to the current way of treating these conditions with the Incremental Cost Effectiveness Ratio (ICER). Suppose the National Institute for Clinical Excellence (NICE) decides on an ICER threshold of £50,000 per QALY as acceptable and the government provides a budget of £20 million for new technology. Under the threshold approach* (ie ICER estimate only), *NICE approves technology A but none of the other technologies are approved. Total health benefits increase by 360 QALYs. However technologies B and C, although failing to meet the NICE threshold , generate 388 additional QALYs, from the same additional resources, ie more health improvements than produced by investing the resources in technology A. Choosing technology A, 2 million pounds remains unspent (and hence unproductive). Even if these resources were to be used, however, they are only sufficient to support technology D (which fails to meet the ICER threshold) and hence generate a total health improvement of 380 QALYs. In other words, the threshold approach fails to maximise the health improvements produced from a fixed technology budget.*

Table 2.2.1 Evaluating the efficiency of four different technologies (From Birch and Gafni, 2004)

	Technology			
	A	**B**	**C**	**D**
Health gain (QALYs)	360	312	76	20
Costs (£millions)	18	16	4	2
ICER (£000s per QALY)	50	51.3	52.6	100

In the literature review in chapter 3, few studies included information on the likely impact on costs and health benefits for introducing the drug into a specific population. Furthermore, regulatory bodies responsible for the assessment of new drugs and treatment, advise on the inclusion of this information, for example the National Institute of Clinical Excellence (NICE) (1999).

According to Mauskopf (1998), there is a large volume of published cost effectiveness studies but these have

'rarely been used to inform health care decisions'.

Indeed Russell et al. (1996) states that,

'CEA is rarely used to inform decisions about health services in the United States'.

This view is also shared by Davies et al. (1994) and Sloan and Conover (1995) who conducted a survey showing the low impact of this type of analysis on health care policy.

As Mauskopf (1998) points out, this does raise the question about the usefulness of the cost effectiveness studies. She surmises that economic evaluation studies may not be having their intended impact because they may not be in a format that is

'useable and/or understandable by non-economists, or researchers may be answering questions that are from a perspective different from that of the decision maker in terms of the range of outcomes included, the time horizon considered, and the population included'.

Mauskopf (1998) gives several reasons for the reluctance of health care modellers to perform population based evaluations rather than cohort based evaluations. Firstly,

results from population models are specific to the size and case mix of the population and this necessitates the collection of more data and is likely to increase the complexity of the analysis. Secondly, within the health care community there is a tradition of population based analyses performed retrospectively by using large databases or observational studies, rather than prospectively at the time the new drug is first introduced. Finally since she suggests that there may be a conscious or subconscious reluctance to quantify prospectively the likely increase in costs associated with the new treatment. The reluctance to perform population based evaluation is also likely to be due to the fact that population models are more complex and less suited to Markov and decision tree models than cohort models and there is a tradition of cohort based models for cost effectiveness.

On the basis of the evidence in this section the first two assumptions are concluded:

A1) A population analysis provides a more comprehensive summary of the value of the intervention for the health care planner than a cohort analysis.

A2) The cost and health benefit outcomes of an intervention are as important an output as cost effectiveness.

2.3 Types of models used

There are several types of models used for health care modelling (Davies 1985). These may be either deterministic where there is no randomness or variability or stochastic where natural variability is taken into account by the use of probability distributions. Most of the health care models used in CHD modelling are deterministic (Halpern et al. 1998). The most commonly used models for health care evaluation are decision trees, Markov or other state transition models and discrete event simulation models and these are the models compared in this thesis. Other models such as system dynamics and semi-Markov have rarely been used although this is not a criticism of their ability to evaluate health care. Indeed Davies et al. (2003) suggests that

> '*system dynamics models have been found to be particularly good for modelling infectious diseases*'.

Due to the time needed to model each of these model types, it was decided to concentrate on the three most common and relevant model techniques to coronary heart disease interventions in this thesis.

2.3.1 Decision trees

A decision tree is a commonly used model for health care evaluations. According to Sonnenberg and Beck (1993) the decision tree

> '*models the prognosis of a patient subsequent to the choice of a management strategy*'.

An example of a decision tree is shown in Figure 2.3.1. The tree flows from left to right beginning with an initial clinical choice or decision, which is represented in the tree by a box.

As a result of the decision made, branches lead to chance nodes, which are represented by circles. From the chance nodes there are branches representing the possible events with their respective probabilities. The sum of the probabilities at a chance node add up to one. These probabilities may depend on the patient characteristics as well as the different strategies. These branches may lead to further chance nodes.

At the end of the tree, each path leads to an outcome such as survival or death at the terminal nodes represented by a triangle in the Figure. This outcome will have a payoff or reward associated with it. This payoff represents the net value of a particular scenario, ie the series of events leading up to this endpoint and may be a cost or a utility. The decision tree calculates, for each alternative action, the expected value of the clinical outcome. This is calculated as a weighted average of all possible outcomes, applying the path probabilities as weights.

The decision tree may be extended for more than one time period. In this way, events that happen more than once can be modelled. Sonnenberg and Beck (1993) describes a *recursive tree* where the simple decision tree is repeated at each of the terminal nodes of the decision tree (except the dead state nodes). However, after only a few repetitions the size of the tree may have many hundreds of terminal nodes (Sonnenberg and Beck 1993). They conclude that a recursive tree model of this type is suitable only for a short

time horizon. Often in decision tree models, long term outcome measures such as life years and QALYs are incorporated at the terminal node of a decision tree. These long term outcomes are average values for the cohort considered (Karnon and Brown 1998).

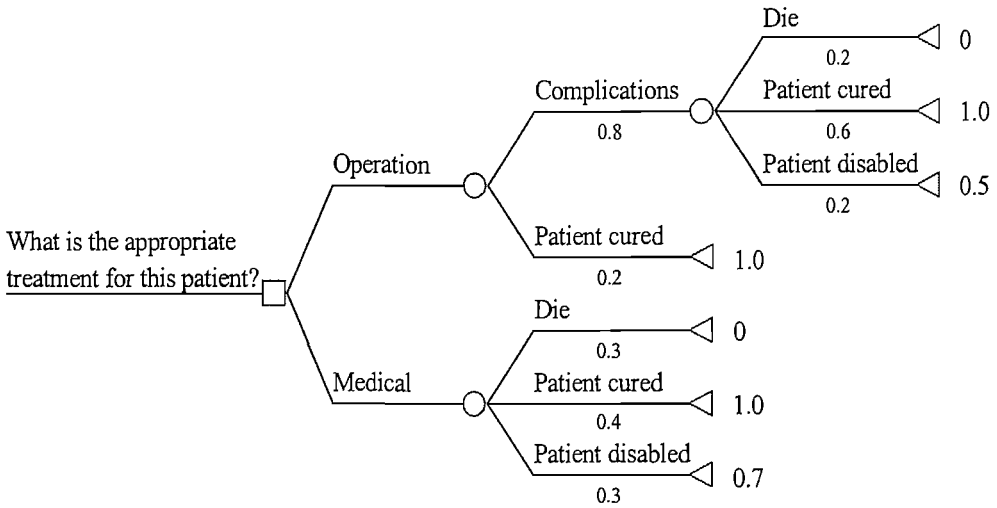

Figure 2.3.1 Example of decision tree

Figure 2.3.1 shows a simple example of a decision tree using the software package TREEAGE Data 4.0. In this example, a patient with a serious acute illness has arrived at hospital and the doctor can choose to treat him surgically or medically.

If the doctor chooses to operate, there are risks involved and the best estimate is that there is a 20% chance of complete success. If there are complications, however, the patient will be treated further and there is a probability of 20% he will die, 20% he will survive but with long term complications and 60% he will be completely cured.

On the other hand, if the patient is treated medically, there is a probability of 30% he will die, 40% he will be cured completely and 30% he will survive with long term complications.

For each of the final outcomes shown at the terminal nodes, there is an associated payoff which in this case is the utility of the patient. For example, after the operation if the patient is completely cured he has a utility of 1.0 whereas if he is left disabled he has a utility of 0.5.

The expected utility of each of the decision choices Operation and Medical is calculated by the sum of the probabilities times the payoff for the chance nodes, working back from the terminal nodes.

Expected value (EV) of Operation = 0.8 * EV of Complications + 0.2 * EV of Patient cured = 0.8 * (0.2*0 + 0.6*1 + 0.2*0.5) + 0.2 * 1.0 = 0.76.
Expected value (EV) of Medical = 0.3*0 + 0.4*1.0 + 0.3*0.7 = 0.61

In this case the expected utility value of the operation is shown to be higher than that for the medical treatment and this would be the preferred treatment.

2.3.2 Markov models

An article by Sonnenberg and Beck (1993) gives a good overview of Markov modelling for health care applications. In their view the Markov model provided a

> *'far more convenient way of modelling prognosis for clinical problems with ongoing risk'* (than the decision tree).

Furthermore, Karnon and Brown (1998) state that these models are,

> *'particularly suited to modelling programmes in which the events occur over a long period of time'.*

In a Markov model, patients move between health states over time. At any time they are assumed to be in one of a finite number of states of health. A patient in a given state can only make a single state transition during a cycle, either 1) remain in their current health state, 2) move to another health state, or 3) die, according to the transition probabilities per time period between the states. The cycle time is chosen according to the time horizon being studied in the model. For example for a model for the whole of a patient's life time where there are few events of interest, a cycle length of one year is satisfactory (Sonnenberg and Beck 1993).

Markov processes all obey the Markovian assumption or Markov property. According to this assumption the model only has knowledge concerning the patients' current health states and would not know where they were in previous time periods. This assumption forces the creation of separate states for each subset of the cohort that has a distinct property or utility. The evaluation of a Markov process yields the average numbers of

cycles (or time) spent in each state and the associated utilities and costs. If the Markov process incorporates a decision node or different strategies, then cost effectiveness may be calculated.

If the transition probabilities are constant over time the Markov process will be a Markov chain. If it has an absorbing state, its behaviour over time can be found analytically. However, in the majority of Markov processes used in health care, the transition probabilities change over time, eg an older person has a higher risk of death (Sonnenberg and Beck 1993). Markov process models with transition probabilities, which are not constant over time, may be more difficult to solve analytically or may even be insoluble. These models are often represented by the Markov cohort model (Sonnenberg and Beck 1993).

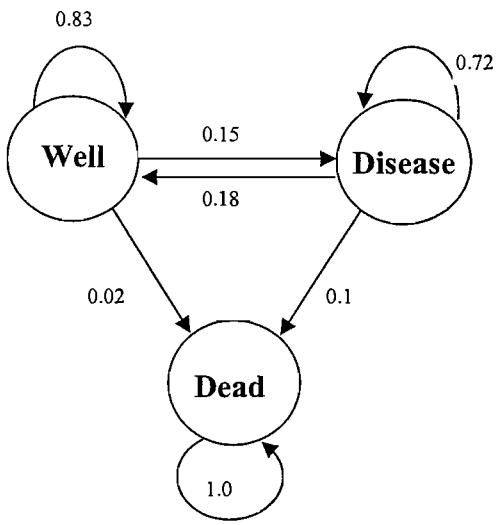

Figure 2.3.2 Example of Markov model

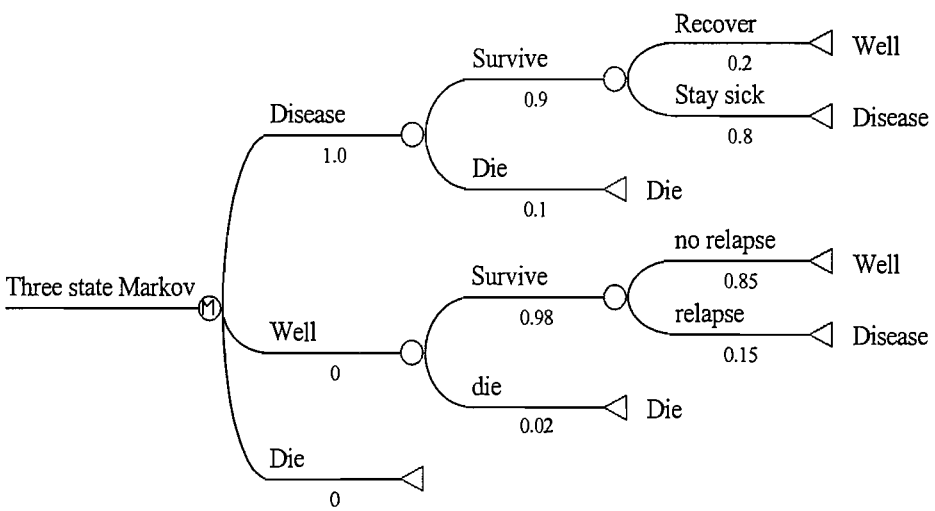

Figure 2.3.3 Example of Markov model

The Markov cohort model follows a hypothetical cohort of patients moving between health states. Each cycle a proportion of patients move between states according to the transition probabilities. This results in a new distribution of the cohort among the various states for the subsequent cycle. In the subsequent cycle the age of the cohort will have increased by the cycle period length. The model is run for enough cycles so that the entire cohort is in the dead state. The life expectancies can be found by summing the numbers of patients who remain alive for each cycle and dividing by the initial cohort size.

Figure 2.3.2 shows a simple Markov model using the standard representation. Here a circle represents each state and arrows represent transitions between states. A transition arrow pointing back to the state from which it originates denotes that patients may remain in the same state in consecutive cycles. The numbers along the arrows are the transition probabilities between the states at either end of the arrow. For any state, the transition probabilities from that state to all other states must add up to one. In the example shown the model has a cycle time of one year.

2.3.2.1 Markov cycle tree

The TREEAGE Data 4.0 software used to build Markov models represents this system in a different way. Figure 2.3.3 shows the same system in a graphical form that is similar to the decision tree format and is known as a cycle tree. The cycle tree is distinguished from the decision tree by arcs instead of straight lines.

The probabilities on the branches of the cycle tree in Figure 2.3.3 are equivalent to those in Figure 2.3.2. The transition probability between states is the product of the probabilities along the branches from the starting branch to the appropriate terminal node. For example the transition probability for disease to well would be the three uppermost branches in the cycle tree, ie $0.9*0.2 = 0.18$. The values shown under the branches immediately after the starting node are the starting proportion for each of the states.

In this example, a cohort of people start in the states well, disease and dead. Those who are well at the beginning may develop a disease, die or remain well. Those who have the

disease may get better, remain ill or die. Death is known as an absorbing state, ie people cannot move out of this state.

Each cycle a proportion of patients moves between states according to the transition probabilities. This results in a new distribution of the cohort among the various states for the subsequent cycle. This continues for many cycles until the entire cohort have reached the dead state.

Each of the states will have a reward or payoff associated with it. This reward represents whatever outcome measure is being calculated, for example costs or QALYs. For each cycle the total payoff is calculated by multiplying the proportion of the cohort in each state at the end of the cycle by the associated reward, and summing for all the states. In this example the total life expectancy of the cohort is calculated. Consequently the dead state will have a payoff of zero and the well and disease states have a payoff of 1.0.

Table 2.3.1 shows the first 10 cycles of the Markov cohort model for this example. The life expectancy of the cohort is found by dividing the total stage reward at the end of the model by the number in the cohort. The Markov process approximation is improved by incorporating the half cycle correction. This is calculated by adding to the total reward half the starting proportion of the cohort. This is done so that events occur in the middle of the cycle time rather than at the end. In this example when the model is run for 100 cycles, the expected life expectancy is 16.5 years.

As mentioned above, different reward outcomes can be collected, for example costs and utilities. If different scenarios are modelled using the Markov cohort method, different life expectancies are obtained and these can be combined with cost data to derive cost effectiveness of the scenarios.

Figure 2.3.4 shows an example where a treatment has been developed for diseased patients. The treatment results in halving the probability that a patient will stay diseased from one cycle to the next. The cost for this treatment is £2000 per year. In this case, the life expectancy calculated is 24.5 years (ie increase of 8 years) at an extra cost of £9889. The cost effectiveness of this treatment is thus £1236 per life years saved.

Table 2.3.1 First 10 cycles for the Markov cohort model

Stage	Stage reward	Total stage reward	% Disease	% Well	% Dead	Reward Disease	Reward Well	Reward Dead
0	0.5	0.5	1	0	0	0.5	0	0
1	0.9	1.4	0.72	0.18	0.1	0.72	0.18	0
2	0.82	2.22	0.54	0.28	0.18	0.54	0.28	0
3	0.76	2.99	0.43	0.33	0.24	0.43	0.33	0
4	0.71	3.70	0.36	0.35	0.29	0.36	0.35	0
5	0.67	4.37	0.31	0.36	0.33	0.31	0.36	0
6	0.63	5.01	0.28	0.36	0.37	0.28	0.36	0
7	0.60	5.61	0.25	0.35	0.40	0.25	0.35	0
8	0.57	6.17	0.23	0.33	0.43	0.23	0.33	0
9	0.54	6.71	0.22	0.32	0.46	0.22	0.32	0
10	0.51	7.22	0.20	0.31	0.49	0.20	0.31	0

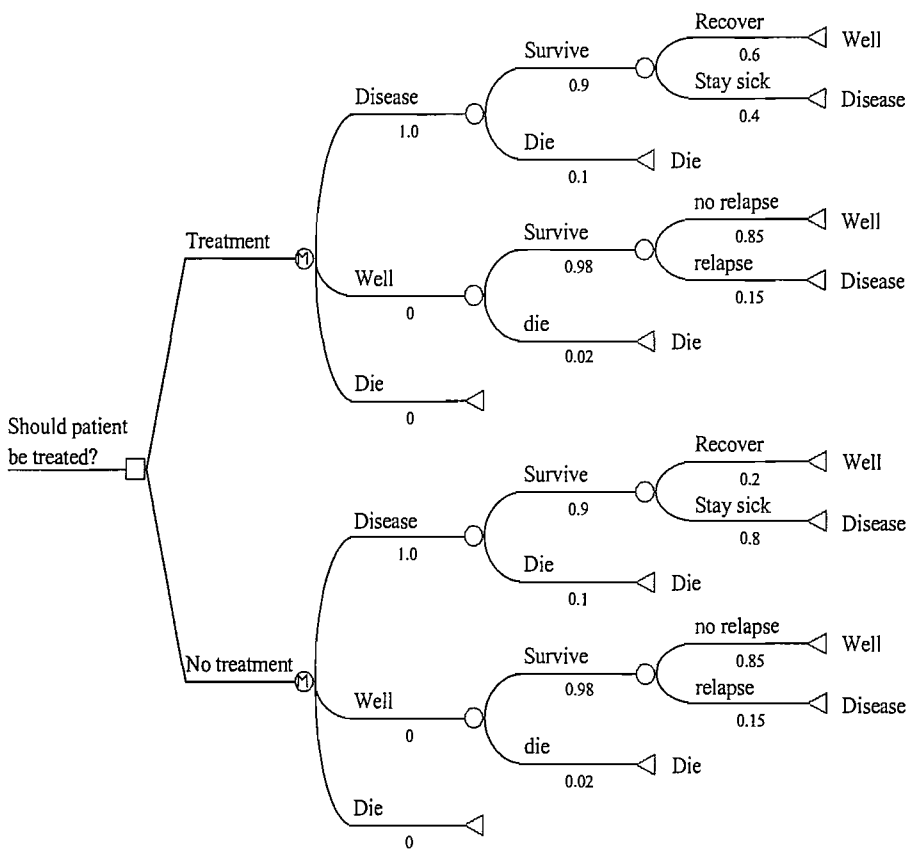

Figure 2.3.4 Markov cohort model comparing treatment or no treatment of diseased patients.

The Markov cycle tree incorporates a probability tree within each cycle. Sonnenberg and Beck (1993) suggest that Markov cycle trees allow the analyst to

'break up a large problem into smaller, more manageable ones'.

They suggest that this provides clarification of the problem and makes it more flexible to change or refine.

In the example for the Markov cohort model, a probability tree could be incorporated to describe the outcomes from relapse by splitting this state into some treatment events, which had variable results. However, by including this probability it should be ensured that the state transitions as set above remain unchanged.

2.3.2.2 Population based approach for Markov models

In the example shown above, the cohort method was used where a cohort is studied over its lifetime. Although this method is useful for describing the cost effectiveness of an intervention, it is not able to give accurate information on expected year on year costs and benefits for a population. As mentioned above in section 2.2.6, Mauskopf (1998) recommends the use of a *prevalence based* or population based approach to provide this information. This information is important because health planners and decision makers typically need to choose between alternative treatment on the basis of their budget constraints as well as the efficacy of the treatments.

The population based method for Markov models uses the information from the cohort model. It starts with a prevalent based cohort and adds an incident cohort for each of the subsequent years. This is demonstrated in Table 2.3.2 which uses the transitions from the cohort model in Table 2.3.1.

The cohort model calculated the proportion of the cohort in subsequent time periods and is shown in column a. All other cohorts will change in the same proportion. The prevalent disease cohort in column b starts with 1000 individuals and the number in subsequent years is found by multiplying the starting population size by the proportion in column a. Each year an incident population will start with 100 individuals (columns c to h) and the numbers in the incident cohort are also found by multiplying the starting

incident cohort size by the proportion in column a. For each year the total in the population is the sum of each of these cohorts.

Table 2.3.2 First 5 cycles for the population based approach of the Markov model

Stage	% Disease	Prevalent Disease	Incident Disease	Incident Disease	Incident Disease	Incident Disease	Incident Disease	Total
	a	b	c	d	e	f	g	h
		1000	100	100	100	100	100	
0	1	1000						1000
1	0.72	720	72					792
2	0.54	540	54	72				666
3	0.43	430	43	54	72			599
4	0.36	360	36	43	54	72		565
5	0.31	310	31	36	43	54	72	582

2.3.3 Monte Carlo simulation

A Monte Carlo simulation can also be used to represent the prognosis of a cohort of patients. It avoids the homogeneity of the Markov cohort model or the need to create a large number of substates to differentiate between different patients (for example old and young).

Monte Carlo simulation uses random numbers to determine the outcome of each event. Each patient begins in a predetermined starting state and at the end of each cycle, a random number generator is used with the transition probabilities to determine in which state the patient will begin the next cycle. The process is repeated a very large number of times in order to find the expected outcome with small confidence intervals. A Markov cycle tree may also be evaluated as a Monte Carlo simulation.

For our example shown in Figure 2.3.3, a Monte Carlo simulation was run 1000 times and the results collected. The life expectancy was 16.46 years with a standard deviation of 17.9. Figure 2.3.5 shows the variability or spread of the results for the life expectancy

of the 1000 patients. It shows that roughly half of the patients had a life expectancy less than 10 years. One of the useful characteristics of the Monte Carlo simulation is that it is able to give indication of the variability of the outcomes.

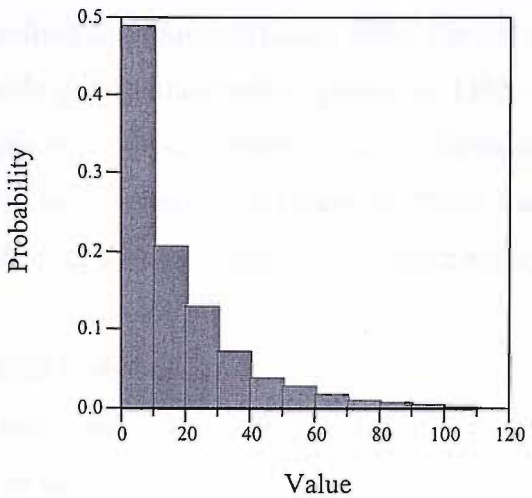

Figure 2.3.5 Probability of life expectancy for a Monte Carlo simulation with 1000 patients

In recent years there has been a development of probabilistic techniques used for Markov modelling of cost effectiveness (Briggs 2000). These techniques define the input parameters according some range or distribution. Monte Carlo methods are then used to sample starting input values for the model. A distribution of the cost effectiveness of the intervention is developed from many model runs using different starting input values. Supporters of these methods suggest that this provides further layers of variability which aid understanding of the cost effectiveness results.

2.3.4 Discrete event simulation (DES)

Discrete event simulations describe the flow of individuals through the treatment system (Karnon and Brown, 1998; Davies and Davies 1994). These individuals can be given attributes, such as age, sex and disease history, which influence their route through the simulation and the length of time between events (Davies and Davies 1994). For each individual, the time of their next event(s) is sampled from parametric or empirical

distributions. These events are added to a calendar and then these events are executed sequentially in time order. An individual's event may be a change in their disease state or a treatment or intervention. Depending on the outcome of this event, their subsequent events may be resampled.

Several articles by Davies et al. describe the advantages of modelling using DES compared to other modelling techniques (Davies 1985; Davies et al. 2003; Davies and Davies 1994). By modelling individual patient pathways, DES avoids some of the fundamental assumptions with Markov process models, for example that the population moving between states is homogeneous (Davies et al. 2003). Furthermore DES is able to take account of trends over time or resource constraints and queuing for resources (Davies et al. 2003).

According to Davies, DES is able to

> *'relate risks, survival and interventions to individuals and to their characteristics and history without proliferating the number of states'.*

DES can also be useful for determining 'bottlenecks' in a system (Davies and Davies 1994). Robinson (2003) comments that simulation is useful for describing the

> *'performance of systems that are subject to variability, interconnectedness and complexity'.*

Interconnected systems are ones where components of the system do not work in isolation but affect other parts of the system and the system may perform in a non intuitive manner as a result.

These advantages provide flexibility (Karnon and Brown 1998), which allows greater confidence in the results (Davies and Davies 1994). However it needs much data (Robinson 2003), which is often not available (Davies et al. 2003), and many more assumptions may need to be made. Costs and effects can be incorporated into a DES model with respect to patient attributes or treatment events within the model.

Figure 2.3.6 shows an example of a simulation model. In this example patients develop a disease or die from other causes. When they develop the disease they are referred to have an operation. They are then treated and some survive and others will die. In the activity flow diagram, the activities are represented by boxes, the queues are represented

by circles and the resources are represented by ovals connected to a specific activity by arrows.

At the start of the simulation a cohort of patients start who are well. It is also possible for the simulation to start with a cohort of patients and have other patients joining the simulation at various times. A time is sampled from probability distributions for them to develop the disease or die from natural causes. For each patient, whichever event happens first is then simulated. If the patient dies they experience no further events.

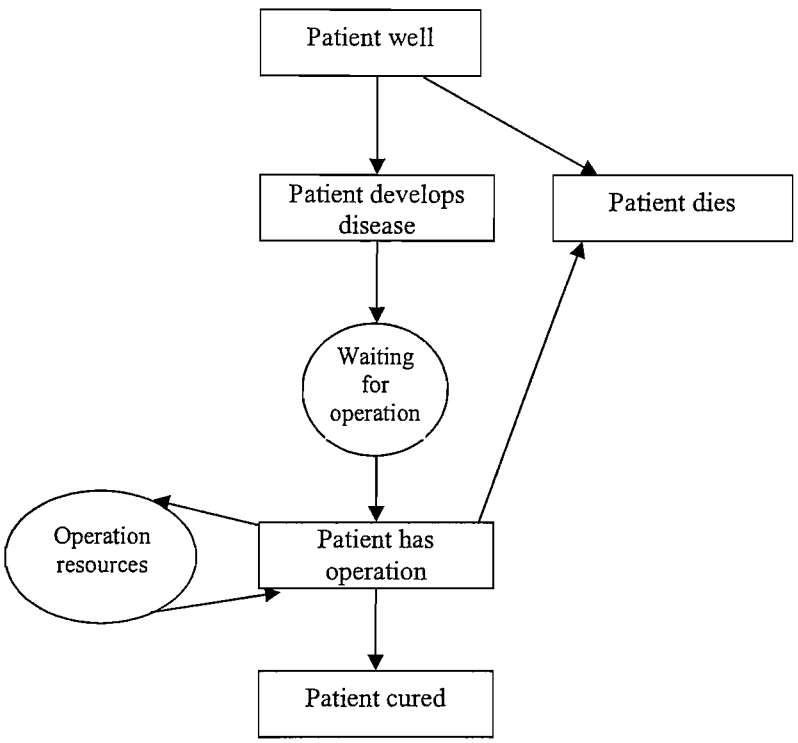

Figure 2.3.6 Discrete event simulation diagram of patient disease and treatment

If the patient develops the disease they are placed in a queue and will wait until the necessary resources are available for the operation to take place. An outcome for the operation is sampled and if it is successful they become well, otherwise they die. If it is successful, a new time is sampled for them to redevelop the disease. Various information can be collected from the simulation, for example expected life time of the patients, time spent waiting for an operation, cost and so on.

In recent years, DES has become more accessible for non specialists by the introduction of commercial visual interactive simulation packages, for example Witness, Simul8.

These have been widely used in industry processes including health studies. In health care systems, they have mainly been used to study resource use, for example planning for bed allocation in hospitals or the timing and optimal use of screening. Jun et al. (2003) provides a good overview of recent simulation studies in this area.

Figure 2.3.7 shows an example from Simul8. Patients (known in simulation as entities) arrive at the Work entry points and are given attributes such as age and disease history. The patients wait in the queue until the Operation Work Centre becomes free and there are available resources for the operation to go ahead. As a result of the operation, a patient may die and leave the simulation. Otherwise the patient will have a new time sampled for the time of the disease recurrence and at this time will join the end of the queue.

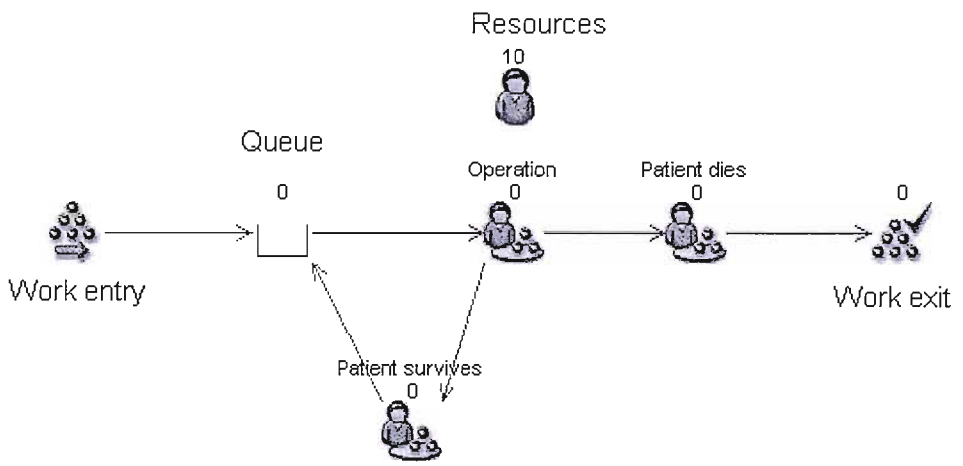

Figure 2.3.7 Simul8 diagram of a discrete event simulation of patient disease and treatment

Simul8 uses non standard terminology, for example: storage areas (queues), work items (entities), labels (attributes), work centres (events). For the purpose of this study the standard terminology is used, shown here in brackets. One of the difficulties of the study of disease progression is that entities may have many future events projected. Some packages have difficulties modelling problems of this type. Indeed, Davies et al. (2003) suggest that these problem are better modelled using software such as POST (Davies and O'Keefe 1988), which must be coded in a high level programming

language, in this case Pascal. A more detailed explanation of DES can be found in Robinson (2003).

2.4 Conclusion

This chapter reviewed the current methodology of modelling health care interventions. It gave a background to the current methods used for modelling health care interventions as a basis for the research in the subsequent chapters. Economic evaluation, such as cost effectiveness analysis, provides a method for comparing health care interventions. These evaluations often use modelling techniques such as decision trees, Markov processes and discrete events simulations. This chapter introduced the concepts of economic evaluation and described each of the modelling techniques.

Chapter 3

Literature Review of Coronary Heart Disease models

Abstract

The aim of this chapter is to provide a contextual background for the subsequent chapters. It reviews the use of models for the treatment of coronary heart disease (CHD). The majority of the models described have been developed to assess the cost effectiveness of different treatment strategies although they have also been used to extrapolate clinical trials, for capacity and resource planning, or to predict the future population with heart disease. In general the models reviewed in this chapter use decision tree models for acute or short term interventions and Markov or state transition models for chronic or long term interventions.

Chapter 3 Literature Review of Coronary Heart Disease models

3.1 Introduction

This chapter reviews the use of models for the treatment of CHD. The majority of the models described have been developed to assess the cost effectiveness of different strategies although they have also been used to extrapolate clinical trials, for capacity and resource planning, or to predict the future population with heart disease. In this chapter firstly short term interventions such as diagnostic tests, thrombolysis and revascularisation are reviewed, then long term interventions such as secondary prevention drugs, finally miscellaneous interventions are reviewed together with generic CHD models.

A systematic, computerised literature search was undertaken of the Medline, Embase and Cochrane databases for studies using decision tree, Markov and simulation models for the treatment of coronary heart disease. Studies were excluded if they used logistic regression methods or similar statistical techniques and more general scoring methods, for example for patient selection for surgery. Those studies evaluating heart failure, arrythmias, and implantable cardioverter defibrillators were also excluded.

3.1.1 Clinical aspects of coronary heart disease

Patients with coronary heart disease usually have coronary arteries which have narrowed due to the build up of fatty materials (atherosclerosis). These narrowings or stenoses influence the patient's survival and may lead to them developing angina pectoris, a heart attack or cardiac arrest.

Angina is a chest pain which is caused by not enough oxygen-containing blood reaching the heart muscle due to the artery stenoses. The anginal pain is exacerbated when the heart is pumping more blood around the body - such as during exercise. Patients with angina are usually given medication to relieve their symptoms such as nitrates, beta

blockers or calcium antagonists. If the symptoms become bad they may be referred for further investigations such as an electrocardiogram (ECG), or angiogram. An ECG is a non invasive test which measures the rhythm and activity of the heart. An angiogram is a type of XRay examination which shows where the arteries are narrowed and how narrow they have become. Often the severity of the heart disease is reported as the number of the major arteries (from zero to three) with significant narrowings. In addition, the patient's health will be significantly worsened if there is narrowing to the left main stem or the left anterior descending arteries (Figure 3.1.1).

If the patient's arteries are sufficiently bad they may be offered surgical treatment such as coronary artery bypass graft (CABG) or percutaneous transluminal coronary angioplasty (PTCA) to improve the blood supply to the heart. CABG is an operation to bypass a narrowed section or sections of coronary arteries using veins or arteries. PTCA is a method for widening the artery using a catheter with a small balloon at its tip. The catheter is passed into the vein and when in place; the balloon is inflated to squash the fatty tissue responsible for the narrowing. Many angioplasties use stents, which are tiny metal cages inserted into the artery to hold it open; these are left in place.

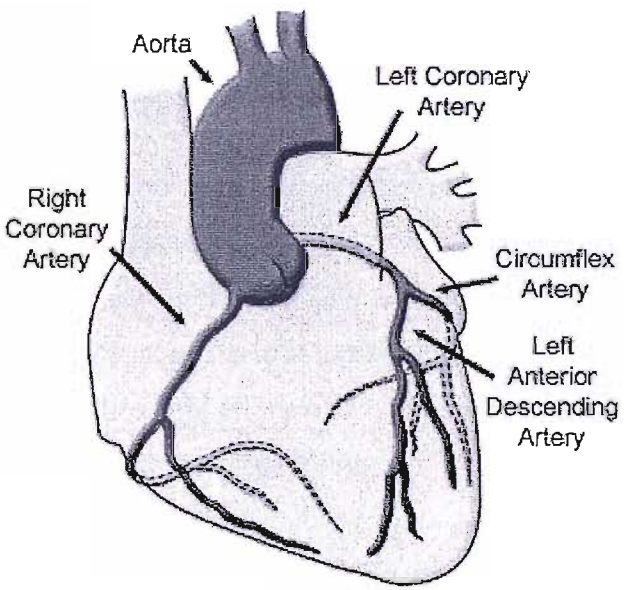

Figure 3.1.1 Anatomy of the coronary arteries in the heart

In unstable angina, chest pain may occur at rest and may increase in severity, frequency, or duration at low levels of activity or for no identifiable reason. Patients with unstable angina are at a high risk of heart attack or even death and should be admitted to hospital

urgently. At hospital they are treated with anti clotting drugs such as aspirin and may be referred for further immediate investigation and surgical treatment.

If one or more of the coronary arteries become blocked a heart attack or cardiac arrest may occur. A heart attack usually causes severe pain in the centre of the chest and may last for many hours. Those who experience heart attack are a high risk of cardiac arrest and immediate death. They are usually admitted to hospital as emergencies and treated as soon as possible with clot busting medication (thrombolysis) and aspirin. They may be referred for further immediate investigation and medical treatment.

Patients with coronary heart disease are increasingly offered secondary prevention medication to reduce the risk of further coronary events. These drugs include aspirin, beta blockers, ACE inhibitors and statins. More information on heart disease can be found on the British Heart Foundation website: www.bhf.org.uk/hearthealth/.

3.1.2 Cost effectiveness and cost utility

The methodology of modelling and economic evaluation is described in chapter 2. Briefly, economic evaluation concerns assessing the costs and benefits of a new technology in terms of a single measure. For different technologies, decision makers are able to decide on the optimal choice according to the technology that is the most cost effective. Those interventions, which are cost saving, are most desirable. These will result in a reduction in cost, and an increase in health benefits. However, the majority of new technologies will require an increase in health care spending. In this case, there will be some cost effectiveness threshold above which the health care provider will be unable or unwilling to accept the new technology.

As a guide, Goldman et al. (1992) stated that a cost effectiveness below $20 000 per QALY gained was '*very attractive*'. Cost effectiveness values of between $20 000 and $40 000 per QALY are consistent with other health funded cost programs such as haemodialysis and hypertension. Values between $60 000 and $100 000 per QALY are '*higher than most currently accepted programs*', whilst values above $100 000 are '*unattractive*'. Evans et al. (2004) discuss the origins and use of cost effectiveness benchmarks in the literature. They state that there may be a generally accepted

benchmark of £30 000 per QALY in the UK. Technologies below this benchmark will be funded by the NHS and those above will not.

It would be attractive to provide an overview of the cost effectiveness results by providing a synthesis of the studies. The US Panel on cost effectiveness in Health recommended a reference case cost effectiveness analysis consisting of a broad standard set of methods to serve as a point of comparison across studies (Russell et al. 1996). However, even if these recommendations are adhered to, there are still many problems in comparing studies. For example they may be conducted in different countries with dissimilar health care systems, use varying fundamental assumptions and methodology, with different datasets, costs, time horizons and durations of treatment. For these reasons, the results between studies of the same intervention have not been synthesised, for example by converting them to the same base year, but have been reported as they appear in the original studies. Indeed the review in this chapter is more concerned with the modelling process than the results of the economic evaluations per se. Nevertheless interested readers can compare cardiovascular interventions studies up to the year 1997 using a 'league table' compiled by Winkelmayer et al. (2003).

3.1.3 Description of the studies

There are several types of models used for health care modelling (Davies 1985). These may be either deterministic where there is no randomness or variability, or stochastic, where natural variability is taken into account by the use of probability distributions. The models most commonly used were the decision tree, Markov, Monte Carlo and simulation models and these are described in more detail in section 2.3. Some of the models described used a decision analytic model, which consisted of a decision tree, and a Markov model used to calculate the life expectancy which is used as a reward at the end of the decision tree (section 2.3.1). In this case the model is categorised as a decision tree if the decision is not directly influenced by the Markov model, for example if the intervention is not modelled within the Markov model. In these cases the life expectancies could as easily been estimated by life tables, a simulation model or other means and results from the model would be similar.

In this study, models are categorised by whether they evaluate short term or long term interventions. Examples of short term interventions are diagnostic tests, thrombolysis and revascularisation and examples of long term interventions are statins and other drugs, and long term generic population models. Examples of resource-constrained interventions are capacity planning models for hospital surgical departments. Of the 57 specific intervention studies reviewed, 28 were considered short term interventions, 26 long term interventions and 3 resource-constrained interventions. The most popular models used were the decision tree model (23) and Markov model (19). However there were a further nine studies that used a state transition model similar to a Markov model. It was unclear from the descriptions in the studies whether these models were Markov. Four studies used the CHD policy model ((Weinstein et al. 1987) although many more studies used the CHD policy model to estimate life expectancies for a decision tree. Only three studies used a discrete event simulation. All the studies reviewed are from North America and Europe. The majority are from the USA (35), followed by the UK (12), and Canada (3). All other studies were from Europe.

Two seminal cost effectiveness works were from Weinstein et al. (1980) and Weinstein and Stason (1977) from Harvard School of Public Health in Boston in United States of America. Weinstein and colleagues studied coronary heart disease in the early 1980s (Weinstein and Stason 1982). Later they developed a computer simulation model in coronary heart disease (CHD policy model) for the United States population (Weinstein et al. 1987). Although this was used mostly to study prevention strategies for coronary heart disease (Hunink et al. 1997; Tosteson et al. 1997; Hatziandreu et al. 1988; Tsevat et al. 1991; Goldman et al. 1989) it has also been used to study the treatment of coronary heart disease. The Harvard School of Public Health has been extremely influential in the field of modelling the treatment of coronary heart disease and nineteen of the studies reviewed in this chapter are from this group.

There has been a rapid increase in the number of cost effectiveness analyses published in the medical literature in recent years (Elixhauser et al. 1993; Elixhauser et al. 1998). Many of those for coronary heart disease (CHD) have been reviewed by Kupersmith (1994; 1995a; 1995b). In additional, systematic reviews of stable angina (Sculpher et al. 1998), diagnostic tests (Mowatt et al. 2004), stenting (Meads et al. 2000; Hill et al. 2004), thrombolysis (Boland et al. 2004), clopidogrel (Main et al. 2004) and statins

(Ebrahim et al. 1999) have previously been undertaken in the form of Health Technology Assessments for NICE. Many of the studies described in this chapter have also been reviewed by the Centre for Reviews and Dissemination at University of York (http://www.york.ac.uk/inst/crd/index.htm).

3.2 Diagnostic strategies for CHD

3.2.1 Initial diagnosis of CHD

The successful diagnosis of coronary heart disease in individuals presenting with chest pain has a significant bearing on their future treatment and prognosis. Many individuals may present with chest pain similar to symptomatic CHD but after diagnostic tests have no evidence of CHD. Conversely, there may be many individuals with no chest pain who have CHD.

Diagnostic tests can be either non invasive, for example exercise electrocardiogram, nuclear scan or echocardiogram, or invasive, for example angiogram. Exercise electrocardiogram (Ex ECG) or treadmill testing records the electrical activity of the heart during exercise. Radionuclide tests (including thallium scans) involve an injection of a small amount of radioactive isotopes into the blood. A scanning machine takes pictures of the gamma rays sent out by the isotope from the heart. The pictures show the blood flow to the heart muscle. Positron Emission Tomography (PET) and single photon emission computed tomography (SPECT) are common nuclear scans. An Echocardiogram (ECHO) uses ultrasound waves to show pictures of the heart muscle. It gives information about the condition of the heart muscle and may be performed during exercise or with a stress-inducing drug. An angiogram consists of a catheter inserted into the leg artery and passed into the heart. A dye is inserted into the catheter, which shows up on special XRays, and any narrowings will be shown. Generally, Ex ECG is a cheaper test, but with a lower specificity and sensitivity than the other tests. Mowatt et al. (136) present a systematic review of the clinical evidence for each of the diagnostic tests.

The cost effectiveness of diagnostic strategies for people with chest pain has been assessed by several studies (Garber et al. 1999; Jacklin et al. 2002; Kuntz et al. 1999; Lieu et al. 1997; Patterson et al. 1995; Kim et al. 1999; Lee et al. 1988; Maddahi and Gambhir 1997; Mowatt et al. 2004), see Table 3.2.1. The studies use similar methods; they use a decision tree to model the initial diagnostic process and then use either life expectancy data (Maddahi and Gambhir 1997; Patterson et al. 1995; Lee et al. 1988) or a Markov model (Garber and Soloman 1999; Kuntz et al. 1999; Kim et al. 1999; Mowatt et al. 2004) to derive the long term prognoses of these patients still alive at the terminal nodes of the decision tree. Quality of life improvements result from the successful treatment of angina pectoris and prevention of coronary events, such as MI or death. They reach similar conclusions, namely that the recommended test strategy is dependent upon the pre-test likelihood of coronary heart disease, with cheaper tests such as exercise ECG for low pre-test probability, ranging to immediate angiography for very high pre-test probability. This probability varied according to age, sex, type of chest pain and a number of other risk factors. Kuntz et al. (12) is described in more detail as an example.

Kuntz et al. (1999) extended earlier work completed by Doubilet et al. (1985). They constructed a decision tree and Markov cycle tree model to evaluate the following strategies 1) no testing, 2) Ex ECHO with angiography if test results are positive, 3) Ex ECHO with angiography if test results are positive, 4) Ex SPECT with angiography if test results are positive, and 5) routine angiography without previous non invasive testing.

The decision tree follows the patients according to choice of diagnostic test, angiography or otherwise. Patients who do not undergo diagnostic testing will not receive revascularisation.
All patients are stratified by vessel disease. Those patients who have a positive result from a diagnostic test will undergo angiography and receive CABG for LMS or 3 vessel disease and PTCA for 1 or 2 vessel disease. Lifetime costs and quality-adjusted life expectancy were estimated for the patients at each of the terminal nodes using Markov models. The model was run with different cohorts corresponding to different age groups (40-70), sex and severity of chest pain.

As mentioned above, this study concludes that Ex ECG or Ex ECHO resulted in reasonable cost-effectiveness ratios for patients at mild to moderate risk for CHD in term of age, sex and type of chest pain. Ex ECG was more cost effective than Ex ECHO and SPECT. Coronary angiography without previous non invasive testing resulted in reasonable cost effectiveness for patients with a high pre-test probability of CHD.

There were slight differences between the studies with respect of the choice of test for low or medium pre-test probability of CHD. Garber and Soloman (1999) and Kim et al. (1999) concluded that Ex Echo was the most cost effective diagnostic test whilst Maddahi and Gambhir (1997) concluded that patients with low pre-test likelihood of CHD should initially undergo Ex ECG and the positive responders would require nuclear cardiology testing while patients with intermediate pre-test likelihood of CHD should have direct referral to nuclear cardiology testing. For low and medium pre-test likelihood of CHD, Patterson et al. (1995) concluded that PET is the most cost effectiveness test, although Garber and Solomon (1999) claim that this is due to several assumptions favouring PET, for example larger prognostic and quality of life benefits from treatment of CHD than found in randomised trials. Mowatt et al. (2004) recommended the use of SPECT based strategies for the diagnosis of CHD in patients with low or medium risk and Ex ECG and CA strategies in those with higher risk.

Many of the differences between the studies can be explained by the choice of data. For example Maddahi and Gambir's preference for nuclear cardiology testing can be explained by the higher values used for sensitivity and specificity of the testing; for example for SPECT sensitivity is 91% compared to 88% and specificity is 89% compared to 77%. Similarly, the choice of cost data and assumptions accounts for much of the differences between Garber and Soloman (1999) and Kuntz et al. (1999), for example Kuntz et al. (1999) assumes an annual cost for patients with angina depending on the severity of their disease, whereas Garber and Soloman (1999) does not.

Table 3.2.1 Models used for analyses for diagnostic tests for CHD (Terminology used: CE cost effectiveness; LYS life years saved; CHD Coronary heart disease; LVEF left ventricular ejection function; CHF Chronic heart failure; Ex exercise; ECG electrocardiogram; Echo Echocardiogram; PET positron emission tomography; SPECT single photon emission computed tomography; CASS Coronary Artery Surgery Study)

Study	Strategy	Data; time horizon	Model used / Risk factors	Results
Garber and Soloman al. 1999 USA	CE of alternative approaches to the diagnosis of CHD compared to angiography.	30 years	Decision tree; age, likelihood of angina	For men with 50% pre-test probability of CHD, CE per QALY compared to Echo was, Ex ECG $8600, thallium $20 700, SPECT $40 300, Angio $55 200, PET $86 300.
Jacklin et al. 2002 UK	CE of preoperative PET before CABG in patients with poor ventricular function	1 year	Decision tree	CE of PET before CABG compared to medical treatment was £77 000 per LYS. PET may be cost effective to select patients with poor left ventricular function for CABG.
Kim et al. 1999 USA	CE of strategies to diagnose CHD in women. Ex ECG vs Ex Thalium vs Ex Echo vs angiogram only.	CASS, 35 years	Decision tree; Likelihood of angina	For 55 year old women with probable angina (pre test probability 0.31), CE per QALY of Ex ECG vs no test was $4300. CE per QALY compared to Ex ECG was Ex Echo ($15 500), Angiogram ($27 000), thallium ($54 000).
Kuntz et al. 1999 USA	CE of using various tests for the diagnosis of CHD in patients with chest pain.	CASS; lifetime	Decision tree; Age (40-70), sex, chest pain characteristics	CE per QALY for 55 year old man: Angiography compared with Ex ECG was $36 400 for typical angina. Ex Echo compared with Ex ECG was $14 900. Ex ECG compared with no testing was $57 700.
Kuntz et al. 1996 USA	CE of routine angiography after MI	GUSTO trial; lifetime	Decision tree + Markov; LVEF, age sex, co-morbidity, CHF, EX	Patient subgroups with severe post infarction angina or a strongly positive Ex ECG had CE between $17 000 and $50 000 per QALY.

			ECG result, previous MI, angina severity.	
Lee et al. 1988 USA	CE of screening for left main coronary artery disease	CASS; lifetime	Decision tree; prevalence of left main vessel disease	Compared with a strategy of observation unless symptoms worsened, initial Ex ECG followed by angiogram in patients with >= 2 mm of ST segment change had CE per LYS of $6500 to 12 400 for 40 to 70 year old patients.
Maddahi and Gambhir 1997 USA	CE of nuclear cardiology testing for diagnosis of CHD and angiography.	Testing period	Decision tree; Severity of chest pain, age, sex	Patients with a low or intermediate pre-test probability of CHD should undergo Ex ECG and SPECT or PET. Patients with high risk of CHD should have angiogram.
Mowatt et al. 2004 UK	CE of SPECT for the diagnosis and management of angina and MI	25 years	Decision tree; prevalence of CHD	For the diagnosis of CHD in a low / medium risk population (<75% prevalence) SPECT based strategies are likely to be cost effective compared to EX ECG. For higher prevalence these strategies are less cost effective than those of Ex ECG and CA.
Patterson et al. 1995 USA	CE of exercise ECG, SPECT, PET and angiography.	10 years	Decision tree; age, sex, likelihood of angina	PET is most suitable for low and medium pretest likelihood of CHD. Angiography is best for high probability.

Lee et al. (1988) evaluated the cost effectiveness of screening strategies for left main coronary heart disease in patients with stable mild chest pain without evidence of left ventricular dysfunction or prior myocardial infarction at different ages. They compared strategies of observation, exercise test or immediate angiography. There were three strategies of exercise testing defined where those with >= 1,2 or 3 mm of ST segment depression undergo coronary angiography. The study showed derived data of the probability of exercise test findings in patients with different severity of CHD and ST segment change. Screening patients with an exercise test is shown to be more cost effective than either angiography or observation. Performing angiography for patients with >=1 or 2 mm of ST segment change is more cost effective than for >= 3 mm and the study recommends >= 2 mm because there will be benefits for other vessel disease not accounted for within the study.

3.2.2 Discussion about diagnostic tests

Most of the studies were unable to perform the diagnostic tests more than once although Mowatt et al. (2004) allowed for patients who had been wrongly diagnosed and assumed that

> '*everyone would be correctly diagnosed over a 10 year period either as a result of an additional scan or as a result of a non fatal MI*'.

Those models that use long term life expectancies assume that the risk associated with the extent of coronary disease persisted long term, ie patients' disease state remains constant over time. Those with long term Markov models were unable to model further revascularisation after the initial decision tree. Kim et al. (1999) cite lack of data on repetitive test referral rates and recurrent angina after CABG or PTCA. In practice, those patients who receive an initial negative chest pain diagnosis may present at a later date with more severe pain. Others who have an initial diagnosis of mild angina may progress to more severe angina and so the assumptions taken within the decision tree may no longer be appropriate. Some or all of these problems may be overcome with the use of more complex techniques, for example DES or Markov cohort models but it is unclear whether the results yielded would be significantly different. In chapter 5 decision trees for short term interventions are considered. It is concluded that decision trees would provide a reasonable estimate of the cost effectiveness of acute interventions even if this intervention happened more than once.

3.2.3 Diagnostic strategies after MI

Kuntz et al. (1996) assessed the cost effectiveness of routine coronary angiography after acute myocardial infarction using a decision tree for the angiography and revascularisation short term pathway and a Markov cycle tree for long term survival. The decision model follows the patients according to whether they have angiography or not for different cohorts of different characteristics. If so and they have anatomically confirmed CHD, they will have CABG or PTCA; otherwise they will be treated medically. They assumed that age, gender, history of prior MI, exercise test result, post infarction angina and left ventricular ejection fraction influenced coronary anatomy and long term survival. The Markov cycle tree model follows the patients' long term survival. They are able to change to different levels of angina, develop congestive heart failure, have subsequent MI or revascularisation or die. The study recommended coronary angiography for patient subgroups with severe post infarction angina, a strongly positive Ex ECG or who had had a prior MI.

3.2.4 Diagnostic strategies for CABG for patients with left ventricular dysfunction

Jacklin et al. (2002) developed a decision tree model to assess the cost effectiveness of diagnostic strategies for patients with left ventricular dysfunction for three strategies: 1) CABG for all patients, 2) using PET to select candidates for CABG, those without hibernating myocardium remaining on medical therapy, and 3) medical therapy for all patients. The model estimated that using PET resulted in lower costs and increased effectiveness compared to using CABG for all patients. The cost effectiveness ratio compared to medical therapy only was £77 000 per life year saved and based on this they considered the treatment cost effective. This seems unlikely to be considered cost effective based on the cost effectiveness ratios discussed in section 3.1.2. However the time horizon chosen for the model was short and given a more appropriate time horizon, the treatment may be cost effective.

3.3 Strategies of reperfusion therapy

Thrombolysis and angioplasty are both effective methods of reperfusion for acute myocardial infarction accompanied by ST segment elevation by re-opening the occluded artery. Tissue plasminogen activator (tPA) and strepokinase (SK) are forms of thrombolysis therapy or clot buster drugs, which are more effective the quicker they are administered (for example GISSI (1986), ISIS-2 (1988), GUSTO (1993), FTT (1994), and Boersma et al. (1996)). These drugs thin the blood and are not suitable for some patients if there is a large risk of bleeding elsewhere. An alternative to thrombolysis is to use primary angioplasty (see section 3.4). A recent health technology assessment (Boland et al. 2004) examined the clinical and cost effectiveness of available drugs for early thrombolysis and concluded that the benefits of the drugs were similar and therefore

> '*streptokinase is the most cost effective drug, judged by virtue of its lower price*'.

Several studies have assessed the cost effectiveness of different aspects of thrombolytic therapy (Krumholz et al. 1992; Fendrick et al. 1994; Lieu et al. 1997; Parmley 1999; Kellett and Clarke 1995; Kalish et al. 1995; Castillo et al. 1997; Laffel et al. 1987; Steinberg et al. 1988), see Table 3.3.1. The studies use similar methods; they use a decision tree to model the initial intervention and then use either data on life expectancy (Kalish et al. 1996; Castillo et al. 1997), life expectancy estimated from the Coronary Heart Disease Policy model (Krumholz et al. 1992; Lieu et al. 1997; Parmley 1999) or a Markov model (Kellett and Clarke 1995) to derive the long term prognoses of these patients still alive at the terminal nodes of the decision tree. Laffel et al. (1987) and Steinberg et al. (1988) both calculated the cost per additional life saved, rather than cost per life year saved, by assessing the lives saved during the first year and the hospital admission respectively.

Table 3.3.1 Models used for analyses for thrombolytic therapy for acute MI.

(Terminology used: CE cost effectiveness; ICER incremental cost effectiveness ratio; LYS life years saved; CHD Coronary heart disease; SK streptokinase; tPA tissue plasminogen activator; ISIS International Study of Infarct Survival trial; GUSTO Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries trial; GISSI Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico; FTT Fibrinolytic therapy trial)

Study	Strategy	Data sources / time horizon	Model used	Results
Castillo et al. 1997 USA	CE of thrombolysis	Fibrinolytic therapy trial; hospital discharge and 1 year	Decision tree model; age, time to presentation	CE of thrombolytic therapy per LYS was $14 438. For patients treated within 6 hours of MI, CE was $11 788 per LYS.
Fendrick et al. 1994 USA	To quantify population health consequences of increased thrombolytic use in the US.	1 month	Decision tree model; age, time to treatment	4000 additional lives could be saved per year if thrombolysis used for all those for whom it is recommended.
Kalish et al. 1996 USA	CE of SK vs tPA	GUSTO; 1 month, 1 year, lifetime	Decision tree model, age, time to treatment	CE of tpa is $30,300 per additional QALY compared to SK.
Krumholz et al. 1992 USA	CE of thrombolysis with streptokinase in elderly patients	GISSI, ISIS – 2; lifetime	Decision tree model; age	CE of thrombolysis for an 80 year old patient was $21,200. For patients treated within 6 hours, CE was $11 788.
Kellett and Clarke 1995, Ireland	CE of SK vs tPA.	GISSI-2, ISIS-3, GUSTO; lifetime	Decision tree; age, symptoms, CHD history, infarct size	CE of tpa is $5900 per additional QALY compared to SK.
Laffel et al. 1987 USA	CE of thrombolytic and interventional strategies in acute	GISSI; 1 year	Decision tree model; time to treatment, infarct	Thrombolysis adminstration more CE for intravenous than intracoronary. Thrombolysis

	MI		size	for large infarcts much more CE than small infarcts.
Lieu et al. 1997 USA Parmley, 1999 USA	CE of primary angioplasty for acute MI vs thrombolysis	GISSI-2,3, ISIS-3,4, GUSTO, FTT; lifetime	Decision tree model; patient (in)eligibility for thrombolysis	Primary PTCA saved money compared with thrombolysis and CE of $12 000 / QALY compared with no intervention. CE increased sharply if < 150 patients with MI per centre.
Steinberg et al. 1988 USA	CE of rt-PA or SK vs no thrombolysis in acute MI	GISSI, hospital discharge	Decision tree model	CE per life saved was $52,800 for SK and $56,900 for tpa versus no thrombolysis

Laffel et al. (1987) and Steinberg et al. (1988) were completed before the widespread use of thrombolytic therapy and much of the cost and efficacy data has now changed. Laffel et al. (1987) compared intravenous and intracoronary thrombolytic therapy with standard non thrombolytic therapy and concluded thrombolysis was cost effective and that intravenous thrombolysis was more cost effective than intracoronary thrombolysis. Steinberg et al. (1988) estimated the number of additional angioplasty and CABG procedures needed due to the increased use of thrombolysis, assuming its adoption. They also concluded thrombolysis was cost effective. Castillo et al. (1997) compared thrombolytic therapy with 'standard non thrombolytic therapy' (*therapy given not described*) and concluded that thrombolysis was significantly more cost effective, especially if treated quickly. Krumholz et al. (1992) showed that thrombolysis remained cost effective in elderly patients. Fendrick et al. (1994) estimated the lives saved from increased thrombolysis for the US. Kellet and Clarke (1995) and Kalish et al. (1996) compared the cost effectiveness of tPA with SK. Both studies found SK to be more cost effective. Lieu et al. (1997) compared primary angioplasty with thrombolysis. They concluded that primary angioplasty was more cost effective than thrombolysis if provided by hospitals that already have fully supported cardiac catheterisation laboratories but was cost ineffective otherwise. Kalish et al. (1996) is presented in more detail.

Kalish et al. (1996) used a decision tree to assess the cost effectiveness of tPA vs SK. tPA is more expensive than SK but also more beneficial both for 30 day and 1 year survival (GUSTO 1993). In the model, patients presenting within six hours after onset of symptoms may be treated with tPA or SK. Patients initially have a certain probability of death or disabling stroke. If patients neither die, nor suffer disabling stroke, they may suffer any combination of the following: non disabling stroke, re-infarction, severe hypotension and anaphylactic reaction to thrombolytic therapy, or have a CABG, and the probabilities of these events are assumed to be independent of each other. Each of these short term complications has a cost and quality of life utility attached. A patient is assumed to be exposed to the risk of these complications only once. Life expectancies were calculated for those patients who survived for one year according to whether the patients had suffered a stroke or not using the Declining Exponential Approximation of Life Expectancy (DEALE) method (Beck et al. 1982). The study estimates that for the baseline cohort, tPA has an incremental cost effectiveness of $27,400 per QALY

compared to SK. Sensitivity analyses showed that the cost effectiveness improved for younger patients.

Kellett and Clarke (1995) found tpa to be relatively more beneficial, compared to SK, than Kalish et al. (1996). They incorporated a risk for congestive heart disease into their model which was higher for SK than for tpa. Those patients with congestive heart disease were more likely to die. In addition they assumed that the risk reduction of tpa over SK was greater than Kalish et al (1996).

3.3.1 Discussion about thrombolysis studies

Each of the studies is unable to assess the impact of repeated thrombolytic procedures for subsequent MI. For example, thrombolysis may have additional benefit on each of a patient's subsequent MI. As mentioned above, some or all of these problems may be overcome with the use of more complex techniques, for example DES or Markov cycle tree but it is unclear whether the results yielded would be significantly different. In chapter 5 decision trees for short term interventions are considered. It is concluded that decision trees would provide a reasonable estimate of the cost effectiveness of acute interventions even if this intervention happened more than once.

3.4 Revascularisation

A coronary artery bypass graft (CABG) is an operation that bypasses blockages in the heart arteries with veins removed from the leg or chest. Percutaneous transluminal coronary angioplasty (PTCA) is a method of using a balloon to reduce the arterial narrowings (stenoses). An artery is inserted into the artery at the top of the leg and directed into the coronary artery using XRay control. Once the balloon catheter is in position the balloon is blown up. Often a metal mesh cage, called a stent, is embedded into the artery wall and holds the artery open. Drug eluting stents are stents coated in a drug which is slowly released into the blood and protects the arteries from restenosis.

Several studies have looked at the benefits and cost effectiveness of revascularisation (Cohen et al. 1994; Wong et al. 1990; Schwicker and Banz 1997; Cleland and Walker

1997; Kwok et al. 2001; Cleland and Walker 1998; Williams 1985; Weinstein et al. 1982; Yock et al. 2003), see Table 3.4.1. Several of the studies were before large scale trials had been completed, (Williams 1985; Wong et al. 1990; Weinstein and Stason 1982) and the results may have to be treated with caution. The studies for CABG used a decision tree combined with long term life expectancy (Weinstein and Stason 1982), a Markov model (Kwok et al. 2001), state transition model (Cleland and Walker 1997; Cleland and Walker 1998) and simple calculation methods (William 1985) and the studies for angioplasty and stenting used a Markov cycle model (Wong et al. 1990; Yock et al. 2003) or a decision tree with a Markov model (Cohen et al. 1994; Schwicker and Banz 1997). The studies found that CABG was suitable for patients with more severe symptomatic and anatomical disease whilst angioplasty was more suitable for less severe indications. Stents were a reasonably cost effective alternative to balloon angioplasty.

3.4.1 Coronary artery bypass graft

Weinstein and Stason (1982) evaluated the cost effectiveness of CABG surgery versus medical treatment for 55 year old males with varying severity of CHD. They used operative mortality rates and pooled long term mortality rates from trials to estimate the survival after 6 years for 1, 2, 3 vessel disease and left main stem for patients operated for CABG and those treated medically. They then estimated the life expectancies of the two groups using the life table method. They assumed that the mortality rates for medical and surgical treatment are identical after 6 years and that they are the same as those obtained from United States life tables for males. Their analyses showed that for patients with severe angina, surgery was cost effective for left main stem and 3 vessel disease but less so for 1 or 2 vessel disease.

Table 3.4.1 Models used for analyses for revascularisation and medical therapy, and other miscellaneous studies

(Terminology used: CE cost effectiveness; ICER incremental cost effectiveness ratio; LYS life years saved; CHD Coronary heart disease; CASS Coronary Artery Surgery Study; SAPAT Swedish Angina Pectoris Aspirin Trial; 4S Scandinavian Simvastatin Survival Study; Benestent Belgium Netherlands Stent; VACS Veterans Aging Cohort Study; BARI Bypass Angioplasty Revascularisation Investigation; VA Veterans Administration; ECSS European Coronary Surgery Study)

Study	Strategy	Data sources / time horizon	Model used	Results
Cleland and Walker, 1997, 1998 UK	CE of revascularisation vs medical treatment	Yusuf et al (1994) Sapat, 4S, CASS; 10 years	State transition model; severity of angina, LVEF	For patients with severe angina, 3 vessel disease or poor LV function, CE of surgery is £5500 - £6200 per QALY compared with medical treatment and aspirin. For those with mild angina, CE is £11,400 per QALY.
Cohen et al. 1994 USA	CE of PTCA vs primary stenting in symptomatic 1 vessel disease	BENESTENT I, STRESS; 6 months, lifetime	Decision tree + Markov model; age, restenosis	CE of stenting compared with angioplasty is $23,600 per QALY.
Kong et al. 2004 USA	Cost of drug eluting stents in a medical centre	5 years	Population disease state model (5 states)	Drug eluting stents will divert >$25M from a medical centre over a five year period. May cause financial crises for many medical centres.
Kwok et al. 2001 USA	Simulated trial of CABG vs medical therapy.	Yusuf et al. (1994) 5, 10 years	Markov model (5 states), age. vessel disease	Advances in the treatment of chronic stable angina have improved outcome for medical and surgical patients.
Schwicker and Banz, 1997	CE of stenting vs PTCA and CABG	Literature review, BENESTENT II	Decision tree / Markov model; age	Cost per event free survival 25-30% lower for stents than PTCA and CABG.

Europe				
Weinstein and Stason, 1982 USA	CE of CABG vs medical therapy	VA Co-op Study, ECSS, CASS; lifetime	Markov (2 states); age, severity of disease	For patients with severe angina, CE of CABG per QALY ranges from $3800 in left main disease to $30 000 in one vessel disease.
Williams, 1985 UK	CE of CABG	Expert opinion; lifetime	Simple calculation; severity of disease	More cost effective for severe angina, three vessel disease and left main stem.
Wong et al. 1990 USA	CE of CABG, angioplasty and medical therapy.	CASS, VACS; lifetime	Markov (73 states), age, gender, symptoms, vessel disease	In patients with severe angina, CE for angioplasty ranged from $6000 to $11 000 per QALY depending on ventricular function and vessel disease. For patients with mild angina, CE are > $41 000 for all patients.
Yock et al. 2003 USA	CE of CABG versus stenting in patients with multi-vessel disease	BARI, lifetime	Decision tree + Markov	Bypass surgery results in better outcomes than angioplasty in patients with multi-vessel disease and at a lower cost.

Williams (1985) assessed the cost effectiveness of CABG for differing severities of angina. They used a simple calculation method based on three cardiologists' opinion to estimate the likely value of QALY lifetime gain from the surgery. Cleland and Walker (1997, 1998) used a spreadsheet state transition model to estimate the costs and benefits of medical treatment versus revascularisation in a hypothetical trial of 100 patients. They compared the treatment arm to the results of the medical arm to include aspirin and statins, assuming that none of the treatment arm would be on these drugs. Kwok et al. (2001) simulated a CABG trial for 5 year and 10 year outcomes using a Markov model to incorporate drugs developed since these trials. They found improved outcomes for both surgically and medically treated patients of similar magnitude and so the fundamental conclusions of the original bypass trials were unchanged.

3.4.2 Percutaneous transluminal coronary angioplasty

Wong et al. (1990) developed a Markov cycle model to compare CABG, PTCA and conservative medical therapy. They grouped patients according to age, gender, coronary anatomy, ventricular function and the presence of mild or severe angina. In the model, each year a cohort of patients could die from cardiac or non cardiac causes or progress to either the *angioplasty, bypass surgery* or *no procedure* sub tree that modelled prognosis for the next year. Patients were assumed to not have had revascularisation before but the model simulated repeat operations due to procedural failure or symptom recurrence. They concluded that the most cost effective form of management depended on the patient's baseline clinical characteristics. They recommended that angioplasty is likely to be more cost effective than CABG as long as complete revascularisation is possible, which may not be feasible in patients with 3 vessel disease. Furthermore, revascularisation was shown not to be cost effective unless symptoms were severe or there were other indications of severe ischaemia or severe multi-vessel disease.

3.4.3 Stents

Cohen et al. (1994) developed a short term decision tree combined with a Markov model for long term outcomes to evaluate the cost effectiveness of stenting as a treatment for symptomatic single vessel coronary disease using SMLTREE. They considered only percutaneous revascularisation techniques as the initial intervention.

The compared the following strategies: 1) angioplasty, 2) stenting, 3) initial angioplasty followed by coronary stenting for symptomatic restenosis (secondary stenting). In the first two strategies they assumed that patients with symptomatic restenosis would be treated by repeat balloon angioplasty. The decision tree follows patients during the six months after the procedure. Patients can either have an abrupt closure of the artery or failure to dilate, in which case they would receive an emergency stent or bypass graft, die from the operation, or have initial success. Those patients who have successful procedures have risk of thrombosis, which could result in a fatal MI or emergency angioplasty or bypass graft, or restenosis, which would require them to have repeat revascularisation. Patients had a maximum of three PTCA attempts before undergoing bypass surgery. Long term outcomes of the patients were evaluated in the *Post Revasc* Markov model. During each 6 month cycle of the model, patients could die, suffer a myocardial infarction, undergo angioplasty or CABG after developing symptomatic restenosis. They concluded that

> '*despite its higher cost, elective coronary stenting may be a reasonable cost effective treatment for selected patients with single vessel coronary disease*'.

The results are very sensitive to the relative stenosis rates and the difference in costs between the procedures.

Schwicker and Banz (1997) developed a similar model to Cohen et al. (1994) to compare the cost effectiveness of stent, balloon angioplasty and bypass surgery for single and multi vessel coronary artery disease study in five European countries over three years. The study uses event free survival (EFS) and cost per EFS as an outcome measure. EFS includes the absence of death, MI and revascularisation procedures. Each of the outcomes have equal weight in the outcome measure. The authors justify the use of EFS by stating that the death and MI rates are '*practically equal*' between strategies. Data for multi vessel disease were based on medical opinion. They concluded that stents had a 25-30% lower cost per EFS for single vessel disease. Yock et al. (2003) developed a Markov model based on the BARI trial to compare the cost effectiveness for stenting for CABG in patients with multi-vessel disease. They used a decision tree for the initial revascularisation and associated in hospital events until the fourth year of follow up. Surviving patients entered a Markov model that ran in 3 monthly cycles. Patients could have repeat revascularisation in the Markov model. The study found that CABG was more effective and less costly than stenting.

3.4.4 Drug eluting stents

Kong et al. (2004) developed a population disease state transition model to investigate the likely impact of drug eluting stents on a typical medical centre over five years. In each year a new cohort of patients presenting at angiography entered the model. In the baseline case there were four treatment options: Medical treatment, CABG, bare metal stenting and balloon angioplasty. In each year patients who had the treatments were either relieved of their symptoms and left the model or developed recurrent symptoms that required additional treatment in later years. Patients were simulated individually. In the scenario, a proportion of patients received drug eluting stents as suggested by a panel of cardiologists. The study concluded that the cost of introduction of these drug eluting stents will be considerable and if current funding is not increased is likely to cause financial difficulties for many of the medical centres.

3.4.5 Discussion about revascularisation studies

We consider revascularisation to be a short term intervention because it happens over a relatively short time period. However in contrast to the studies for diagnostic tests and thrombolysis described above, many of the studies use Markov models. The reason for this is that they have decided to model future revascularisation which would not be feasible with a decision tree model.

3.5 Secondary prevention drugs: Statins

3-Hydroxy-3Methylglutaryl-Coenzyme A (HMG-CoA) Reductase Inhibitors or 'statins' have been shown in several recent trials, for example WOSCOPS (Shepherd et al. 1995), AFCAPS (Downs et al. 1998), 4S (1994), CARE (Sacks et al. 1996), LIPID (1998), to reduce the production of cholesterol in the liver, and so reduce the risk of both initial or primary CHD events and recurrent or secondary CHD events. The most common statins are atorvastatin, fluvastatin, pravastatin, simvastatin, lovastatin and cerivastatin.

The cost effectiveness of statins has been assessed by many studies (Tsevat et al. 2001; Prosser et al. 2000; Russell et al. 2001; Goldman et al. 1991; Huse et al. 1998; Johanesson et al. 1997; Pharoah and Hollingworth 1996; Elliott and Weir 1999; van Hout and Simoons 2001; Muls et al. 1998; Cobos et al. 1999; Maclaine et al. 2001; Ganz et al. 2002; Grover et al. 1998, 1999; Pickin et al. 1999; Ebrahim et al. 1999; Ashraf et al. 1996; Palmer et al. 2003; Scuffham and Chaplin 2004), see Table 3.5.1. Most of these studies use a Markov cohort model (also called the life table method) to estimate the long term or life time prognosis of patients for those on statins compared to those on placebo or no treatment. In contrast Cobos et al. (1999), Maclaine et al. (2001) and Palmer et al. (2003) have used short term models to measure the success of patients reaching desired levels of cholesterol. Most of the studies measured the outcome of life years saved, rather than quality adjusted life years saved. The quality of life of patients on statins was assumed to be not statistically different to those not on statins.

Several of the studies have compared the cost effectiveness of individual statins (Russell et al. 2001; Huse et al. 1998; Elliott and Weir 1999; Cobos et al. 1999; Maclaine et al. 2001; Palmer et al. 2003) with each other (section 3.5.1). Other studies use one statin or other, often according to the statin used in a particular trial, to assess the effectiveness of statins. As mentioned above, statins reduce cholesterol levels and this in turn reduces the risk of CHD events. Some of the studies have calculated the reduction in cholesterol levels and applied survival equations (Russell et al. 2001; Huse et al. 1998; Maclaine et al. 2001; Elliott and Weir 1999; Goldman et al. 1991; Grover et al. 1998, 1999; Johanesson et al. 1997) for example the Framingham equations, while others have used a risk reduction applied to the CHD event rate (Ashraf et al. 1996; Ebrahim et al. 1999; Ganz et al. 2000; Muls et al. 1998; Pharaoh and Hollingworth 1996; Pickin et al. 1999; Tsevat et al. 2001; Van Hout and Simoons 2001). Several studies have simulated and then extended clinical trials, for example the CARE trial (Tsevat et al. 2001; Van Hout and Simoons 2001), PLAC I & II (Ashraf et al. 1996; Muls et al. 1998), 4S (Johannesson et al. 1997; Van Hout and Simoons 2001), LIPID (Van Hout and Simoons 2001), LIPS (Scuffham and Chaplin 2004). All of the studies conclude that statins represent good value and the higher the risk of the patient of CHD events, the more cost effective statins are. Furthermore, the general consensus was that statins should be considered for individuals with coronary heart disease and individuals without CHD but who are at high risk of developing CHD.

Table 3.5.1 Models used for cost effectiveness (CE) analyses for cholesterol lowering strategies and other secondary prevention drug therapies (Terminology used: CE cost effectiveness; ICER incremental cost effectiveness ratio; LYS life years saved; CHD Coronary heart disease; ATV atorvastatin; FLV fluvastatin; CRV cerviastatin; LVA lovastatin; PRV pravastatin; SMV simvastatin; PLAC pravastatin limitation of atherosclerosis in the coronary arteries trial; WOSCOPS West of Scotland Coronary Prevention Study; 4S Scandinavian Simvastatin Survival Study; AFCAPS Air Force/Texas Coronary Atherosclerosis Prevention Study; LIPID Long-Term Intervention with Pravastatin in Ischemic Disease; CARE Cholesterol and Recurrent Events; LIPS Lescol Intervention Prevention Study)

Study	Strategy; drug used	Data sources / time horizon	Model used / Risk factors / no. of health states	Results
Ashraf et al. 1996 USA	CE of pravastatin for secondary prevention of CHD.	PLAC I, PLAC II Framingham; 10 years	Markov (3 states); age, severity of disease	CE for CHD patients treated with pravastatin varied from $7,124 to $12,665 per LYS (for 1 to 3 risk factors).
Ebrahim et al. HTA 1999 UK	CE of statins in preventing CHD at different CHD risk levels	WOSCOPS, AFCAPS, 4S, CARE, LIPID; lifetime	Life table method (2 states); CHD event risk, age	CE (£/LYS) at annual total mortality rate of 1.5% 7240, 3% 4730, 6% 2480. For 3% annual mortality, atorvastatin (10 mg) 2188, simvastatin (27mg) 6096, pravastatin (40mg) 7721.
Ganz et al. 2000 USA	CE of statins in older patients with MI, pravastatin (40 mg)	CARE; Lifetime	Markov model (six states); age,	CE of statin therapy of patients of age 75-84 with previous MI was $18,800 per QALY
Goldman et al. 1991 USA	CE of statins for secondary prevention of CHD	Framingham heart study; Lifetime	CHD policy model; cholesterol level, age, drug dosage, blood pressure, smoking, weight	CE of lovastatin (40 mg), Men $8600 - $38 000 per LYS; Women $29 000 - $49 000 per LYS
Grover et al.	CE of statins in patients with	4S, Framingham	Markov model; age, sex,	CE of statin ranged from $4487 to $8532 per LYS

1999 Canada	CVD disease, simvastatin (27.2 mg)	Study, Lipid Research Clinics Program; Lifetime	cholesterol level	in high risk men and $5138 to $8389 for women.
Grover et al. 1998 Canada				
Johannesson et al. 1997 Sweden	CE of simvastatin treatment to lower cholesterol level for patients with CHD. simvastatin (27.2mg)	4S; Lifetime	Markov model (4 states); age, sex and cholesterol level	CE ranged from $3800 per LYS for an 70 year old man to $27,400 per LYS for a 35 year old woman, with only direct costs.
Muls et al. 1998 Belgium	CE of pravastatin for secondary prevention of CHD for Belgium.	Uses model as in Ashraf et al; 10 years		CE for CHD patient treated with pravastatin varied from $13,274 (3 risk factors) to $24,359 (1 risk factor).per LYS
Pharaoh and Hollingworth, 1996 UK	CE of statins in lowering serum cholesterol concentration in patients at varying risk. simvastatin (27.2mg)	4S, WOSCOPS, population of typical district health authority; 10 years	Life table method (2 states), age, sex, cholesterol level	CE for patients aged 45-64 year old with pre-existing CHD cholesterol concentration > 5.4 mmol/l was £32 000 per LYS.
Pickin et al. 1999 UK	CE of statins in preventing CHD at different CHD risk levels	4S; lifetime	Life table method (2 states); CHD event risk, age	CE (£/LYS) at CHD event risk were 4.5%: £5100; 3%: £8200; 2%: £10,700; 1.5%: £12,500
Prosser et al. 2000 USA	CE of cholesterol lowering therapies including diet according to different risk factors; simvastatin (27.2mg)	4S; 30 years	CHD policy model, blood pressure, smoking, age, cholesterol level	CE per QALY ranged for male from $1800 for 45 to 54 years of age to $9900 for 75 to 84 years of age and for female from $8100 (45-54 years) to $40 000 (35-44 years.
Scuffham and	CE of fluvastatin versus no	LIPS, 10 years	Markov model (six states)	CE per QALY gained was £3207 for fluvastatin

Chaplin 2004 UK	statins for SP of cardiac events following successful PTCA			compared to no statins
Tsevat et al. 2001 USA	CE of pravastatin therapy for survivors of myocardial infarction; pravastatin (40mg)	CARE; Lifetime	Markov models; (2 states; 7 states) age < 60, > 60; LDL level	CE per QALY of $16 000 to $32 000. More favourable for patients > 60 years old and patients with LDL cholesterol levels > 125 mg/dL.
Van Hout and Simoons 2001 Holland	CE of statins in preventing CHD at different CHD risk levels	WOSCOPS, AFCAPS, 4S, CARE, LIPID; lifetime	State transition model (5 states); age, sex	CE per LYS was 9970 Euros (CARE), 8028 Euros (LIPID), 6695 Euros (4S).
Comparison of individual statins				
Cobos et al. 1999 Spain	CE of alternative statins in Spain for patients at different risk levels (FLV, LVA, PRV,SMV)	Catalan Nutritional Survey; 2 years, Delea et al. Kong et al	Stochastic simulation model; age, smoking, hypertension, cholesterol level	CE (pesetas per LYS) were FLV (233,800 ; 266,480), LVA (279,778; 271 400), PRV (270, 900; 369 400); SMV (245 100; 298 400) for Delea et al. and Kong et al. respectively.
Elliott and Weir 1999 USA	CE of different statins (ATV, CRV, FLV, LVA, PRV, SMV)	4S; Lifetime	Markov cohort simulation; age	CE of ($ per LYS) was ATV 5421, FLV 5790, CRV 6158, PRV 8575, SMV 9232, LVA 15073.
Huse et al. 1998 USA Russell et al. 2001 Canada	CE of alternative statins in secondary prevention ATV (10mg), FLV (20mg), LVA (20mg), PRV (20mg), SMV	Framingham Heart Study; Lifetime	Markov model (seven states); age, diabetes, smoking, hypertension	CE of statins ($ per LYS) ranged from 65 yr old with high LDL cholesterol to 45 year old with low LDL cholesterol: ATV (10 600 – 35 900), SMV (13 000 – 43 100), FLV (14 700 – 47 400), PRV

	(10mg)			(15 900 – 51 800), LVA (20 099 – 63 614).
Maclaine et al. 2001 UK	CE of alternative statins to achieve target cholesterol, atorvastatin, SMV, CRV, FLV and PRV	Meta analysis; 1 year	Decision tree; cholesterol level	Mean annual cost per patient to reach target LDL cholesterol was atorvastatin (£383), SMV (£431), CRV (£501), FLV (£820) and PRV (£1213.).
Palmer et al. 2003 UK	CE of rosuvastatin for patients reaching target cholesterol vs other statins	STELLAR, 1 year	Decision tree model; cholesterol level	CE with fluvastatin, incremental cost per additional patient to target for rosuvastatin was £24 using LDL-C and £83 using total cholesterol.

Pickin et al. (1999) examined the cost effectiveness of statin treatment in subgroups of the population at different levels of absolute CHD risk to incorporate both primary and secondary prevention cohorts. The CHD risk was defined as definite and probable fatal and non fatal coronary events. The life table method (often called Markov cohort simulation) was used in cohorts of patients based on the 4S trial for secondary prevention (average age 58 years). The mortality of men on placebo during the 5.4 years of the 4S trial was 1.74 times that of men age 58-64 in the UK general population and that ratio was assumed to remain constant for life. The annual probability of dying in any given cohort treated with simvastatin was calculated by multiplying the annual probability in the placebo by the relative risk of all cause mortality observed for treated men in the 4S trial, ie 0.66, and this was assumed to remain constant for life. For each year, a number of the cohort will die. Health service savings on procedure and admissions were estimated by reducing UK hospital treatment costs in the same proportion as seen in the 4S trial. Pickin et al. (66) estimate that cost per life year saved is £5100 for the secondary prevention cohort who have an annual event risk of 4.5%. Pickin et al. (1999) recommended that all CHD patients and those with a CHD event risk of greater than 3% per year should be treated with statins. However they estimated that the total annual cost would be about £885 million in England and this cost was

> '*equivalent to 25% of the present expenditure on community prescribed medicines*'.

Ebrahim et al. (1999) used the same model as described above in Pickin et al. They pooled data from 23 published RCTs for cholesterol lowering to give a relative risk reduction of CHD mortality of 27%. Pharoah and Hollingworth (1996) used a similar life table model for 10 years to estimate the cost effectiveness for cohorts in a health authority population for a range of ages and risk of fatal CVD disease. They also estimated the likely cost for the health authority population of using statins in different subgroups over 10 years, for example this would be £11.1 million to give statins to patients with CHD aged 45-64 years old. Van Hout and Simoons (2001) simulated each of the major trials over the trial period and then extended them for a further five years and for the cohorts' lifetimes. Ganz et al. (2000) modelled the cost effectiveness of statins for patients aged over 75 years with myocardial infarction. Tsevat et al. (2001) determined the cost effectiveness of pravastatin for survivors of myocardial infarction with average cholesterol levels by constructing two pairs of Markov models based on

recurrent event data, from the CARE trial. Ashraf et al. (1996) and Muls et al. (1998) modelled the cost effectiveness of statins with a Markov model which used the recurrent CHD events reductions from the PLAC I & II trials. Similarly, Johanesson et al. (1997) used a Markov model for patients in the 4S trial. Scuffham and Chaplin (2004) used a Markov model to investigate the cost effectiveness of statin use after successful PTCA procedure using the LIPS trial.

Goldman et al. (1991) and Prosser et al. (2000) both used the CHD Policy Model to evaluate the cost effectiveness of statins according to different risk factors, such as age, pre-treatment cholesterol level, drug dosage, blood pressure, weight and smoking. Grover et al. (1998, 1999) used the Cardiovascular life expectancy model to estimate the benefits of statins based on the 4S trial. The Cardiovascular life expectancy model describes the yearly transitions to secondary CVD end points such as nonfatal MI, congestive heart failure and stroke as well as fatal CVD events using multivariate logistic regression equations from patient's characteristics such as age, sex, blood pressure, smoking and cholesterol levels.

3.5.1 Comparison of individual statins

Several studies have compared the cost effectiveness of individual statins (Table 3.5.2). Huse et al. (1998) developed a Markov model to compare the cost effectiveness of different statins. Different doses of each of the drugs were allocated which in turn reduced the cholesterol level of the cohort. Elliott and Weir (1999) used a Markov model for a cohort of 60 years of age and simulated them with annual cycles until age 85 or they died. They used doses for each of the drugs necessary to provide a 35.57% reduction in LDL cholesterol as in the 4S trial or the maximum possible dosage if the reduction was not possible.

Maclaine et al. (2001) and Palmer et al. (2003) used decision tree models to estimate the relative cost effectiveness of the statins to achieve a target LDL-C level during a year. The model aims to represent the drug management process of a hypothetical cohort. Patients with initial high cholesterol are assigned to initiate treatment and reviewed after 12 weeks. If they have met their target they stay on this dosage and will not be reviewed again, if not they receive a higher dosage. They are reviewed several more times during

the year. The models assume that patients are always started on the lowest dose of the drug.

Cobos et al. (1999) used a stochastic simulation model to estimate all the patients' percentage reduction in their cholesterol during a two year period using different doses and drugs. They used two different statin effectiveness trials which gave different ordering for the cost effectiveness of the statins (Table 3.5.2).

Table 3.5.2 Relative cost effectiveness of statins

Drug ranking	**Huse et al. (1998)**	**Russell et al. (2001)**	**Elliott and Weir (1999)**	**Maclaine et al. (2001)**	**Cobos et al. (1)**	**Cobos (2) (1999)**	**Palmer et al. (2003)**
1st	Atorva.	Atorva.	Atorva.	Atorva.	Fluva.	Fluva.	Rosuva.
2nd	Simva.	Lova.	Fluva.	Simva.	Simva.	Lova.	Atorva.
3rd	Fluva.	Simva.	Ceriva.	Ceriva.	Prava.	Prava.	Simva.
4th	Prava.	Fluva.	Prava.	Fluva.	Lova.	Simva.	Fluva.
5th	Lova.	Prava.	Simva.	Prava.			Prava.
6th			Lova.				

Cobos (1) uses Delea et al. Cobos (2) uses Kong et al

3.6 Secondary prevention drugs: Other therapeutic drugs

In addition to statins, several other drugs have been shown to have beneficial effect for either symptom relief or prognostic gain for coronary heart disease patients. Beta blockers act to slow the heart rate and lower blood pressure by blocking the effects of adrenaline. Calcium antagonists (also called calcium channel blockers), such as Amlodipine, act to expand the arteries, making it easier for the blood to flow. Angiotensin converting enzyme (ACE) inhibitors block an enzyme normally present in the body and so cause the blood vessels to relax. Antiplatelet drugs, such as aspirin and clopidogrel, help to stop the blood clotting by reducing its viscosity.

The cost effectiveness of medical therapies have been assessed by several studies (Phillips et al. 2000; Doyle et al. 2002; Gaspoz et al. 2002; Lindgren et al. 2004; Tsevat et al. 1997; Thaulow et al. 2002), see Table 3.6.1. Philips et al. (2000) and Gaspoz et al. (2002) both used the Coronary Heart Disease Policy model to evaluate beta blocker use after MI, and aspirin and clopidogrel respectively. Lindgren et al. (2004) used a Markov model and Main et al. (2004) used a decision tree to evaluate clopidogrel for patients with acute coronary syndromes. Tsevat et al. (1997) used a Markov model to evaluate captopril therapy after myocardial infarction. Doyle et al. (2002) used a Markov model to evaluate the use of amlodipine. Thaulow et al. (2002) used a decision tree to evaluate amlodipine in patients undergoing angioplasty procedures.

3.6.1 Beta blockers

Philips et al. (2000) investigated two strategies: one cohort of MI survivors in 2000 followed up for 20 years (*single cohort*) and 20 successive annual cohorts of all first MI survivors in 2000-2020 (*multi cohort*). They assumed that the beta blockers would have the maximum relative risk reduction for coronary events for the first three years compared to those not taking the drug, declining to a 7% risk reduction for the next three years, followed by a 1% risk reduction in the remaining 14 years. The single cohort had a cost per QALY gained of $4500 and the multi cohort was cost saving.

3.6.2 Aspirin and clodipogrel

Three studies have assessed the use of clopidogrel for patients with acute coronary syndromes such as unstable angina or MI. Gaspoz et al. (2002) assessed four strategies: i) aspirin for all eligible patients, ii) aspirin for all eligible patients and clopidogrel for those ineligible, iii) clopidogrel for all patients, iv) aspirin for all eligible and clopidogrel for all patients. The authors found that aspirin was a cost effective treatment but because of its higher cost, clopidogrel had an unattractive cost effectiveness ratio, unless its use is restricted to patients who are ineligible for aspirin. It is interesting that beta blockers were found to be more cost effective than aspirin even though aspirin is much cheaper than beta blocker and yet they have similar risk reductions in coronary

events, and the benefit for beta blocker lasted only short term. One of the reasons for this is that Gaspoz et al. (2002) includes health costs for non coronary heart disease.

Lindgren et al. (2004) and Main et al. (2004) evaluated clopidogrel used in combination with aspirin in comparison with aspirin only. They assumed that clopidogrel would only be used for 12 months. Lindgren et al. used a Markov model and Main et al. used a decision tree model for the first year and a Markov model with four states thereafter. In contrast to Gaspoz et al.(2002) both studies found clopidogrel to be cost effective. As Lindgren et al. notes, Gaspoz et al. assumes 25 years of treatment with clopidogrel which leads to less favourable outcomes.

3.6.3 ACE inhibitors

Tsevat et al. (1997) used the actual all cause mortality data for years 1 to 4 from the SAVE trial stratified by age group to evaluate captopril therapy after MI with low ejection fraction. Survival beyond the fourth year was simulated in a Markov model, which distinguished between coronary heart disease related mortality and other cause mortality. For each age group, they developed a '*limited benefit*' model (ie benefits of captopril only lasts 4 years) and a '*persistent benefit*' model (ie benefits persists). The cost effectiveness of captopril ranged from $3600 per QALY gained for 80 year old patients to $60,800 per QALY gained for 50 year old patients using the limited benefit model. In the persistent benefits model, the cost effectiveness ranged from $3700 to $10,400 per QALY depending on age.

Table 3.6.1 Models used for cost effectiveness (CE) analyses for other secondary prevention drug therapies (not statins)
(Terminology used: CE cost effectiveness; ICER incremental cost effectiveness ratio; LYS life years saved; CHD Coronary heart disease; PREVENT Prospective Evaluation of the Vascular Effects of Norvasc Trial; CURE Clopidogrel in Unstable Angina to Prevent Recurrent Events; CAPARES Coronary Angioplasty Amlodipine Restenosis Study; SAVE Survival and Ventricular Enlargement Trial)

Study	Strategy	Data sources / time horizon	Model used	Results
Doyle et al. 2002 Sweden	CE of treating patients undergoing PTCA with amlodipine	PREVENT; 3 years	Markov (eight states), age	Use of amlodipine resulted in fewer hospitalisations and invasive surgery in the short and long term and is a cost saving therapeutic strategy (SEK 800 per patient over 3 years).
Gaspoz et al. 2002 USA	CE of aspirin, clopidogrel for secondary prevention of CHD	Framingham heart study; lifetime	CHD Policy model; cholesterol level, age, blood pressure, smoking, weight	Increased aspirin use has CE of $11 000 per QALY gained. Use of clopidogrel for ineligible (for aspirin) patients cost $31 000 per QALY.
Lindgren et al. 2004 Sweden	CE of clopidogrel in patients with acute coronary syndromes	CURE trial, Lifetime	Markov (six states), age, sex	CE per QALY gained for clopidogrel (for 1 year) and aspirin compared with aspirin only was €1365.
Main et al. 2004 UK	CE of clopidogrel in patients with acute coronary syndromes	Lifetime	Decision tree	CE per QALY gained for clopidogrel (for 1 year) and aspirin compared with aspirin only was £6078.
Phillips et al. 2000	CE of beta blocker use after	National Co-	CHD Policy model;	CE per QALY gained for beta blocker use after MI is

USA	MI	operative Cardiovascular Project; lifetime	Age (> 65; <65 yrs) cholesterol level, age, blood pressure, smoking, weight	$4,500. Increased use of beta blockers after MI would lead to cost savings and impressive gains in health.
Thaulow et al. 2002 Norway, Canada	CE of using amlodipine in patients undergoing PTCA.	CAPARES trial; 4 months	Decision tree model; age	Amlodipine was cost saving over a 4 month period, resulting from improved clinical outcomes.
Tsevat et al. 1997 USA	CE of captopril therapy after MI.	SAVE; lifetime	Markov (3 states); age	CE of captopril ranged from $3,600 to $60,800 per QALY depending on age in the limited benefit analyses and $3,700 - $10,400 in the persistent benefit analyses.

Table 3.7.1 Models used for analyses for other miscellaneous studies

(Terminology used: CE cost effectiveness; ICER incremental cost effectiveness ratio; LYS life years saved; CHD Coronary heart disease)

Study	Strategy	Data sources / population	Model used	Results
Davies et al. 1994 UK	Planning services for CHD patients in a hospital department	5 years	Discrete event simulation	With the hospital specific lengths of stay and demand for treatment, the resource bottlenecks were found to be the number of cardiology beds.
Groothius et al. 2000 Holland	Capacity planning for catheterisation in a hospital department	1 day	Discrete event simulation	The results of the simulation experiments give valuable information how to optimise the use of the catheterisation room.
Harper et al. 2004. UK	Planning services by geographical location for increased revascularisation	1 year	Discrete event simulation	The model helped health care planners evaluate the consequences of different geographical distributions and organisations of their services.
Krumholz et al. 1993 USA	CE of smoking cessation after MI	Lifetime	Decision tree; age	A nurse-managed smoking cessation program after acute myocardial infarction has CE of $220 per LYS.
Lowensteyn et al. 2000 USA	CE of exercise training for primary and secondary prevention	Lifetime	Cardiovascular disease life expectancy model, age, sex	CE of exercise training for CHD patient ranges from $341 for 55-64 year old male (unsupervised) to $42,367 for 35-54 year old female (supervised).
Nichol et al. 1998 USA	CE of public access defibrillation	Medical literature; lifetime	Decision tree	CE of public access defibrillation was $44 000 per QALY by lay responders and $27 200 per QALY by police.

Tosteson et al. 1996 USA	CE of coronary care unit for emergency department patients with chest pain.	Multicenter Chest Pain Study; lifetime	Decision tree	CCU had CE of < $50 000 per QALY if probability of MI was > 29%. .

3.6.4 Amlodipine

Thaulow et al. (2002) used a decision tree model to find the total expected cost per patient for a 4 month period following an initial angioplasty for those treated with amlodipine or placebo. The model used clinical data from CAPARES and clinical experts were used to quantify health care resources used for each clinical outcome. The use of amlodipine decreased the rates of MI and revascularisation. The study did not calculate cost per life year or QALY saved but surmises that the placebo group had a higher total cost than the treated group, thus the amolodipine as an adjunct to PTCA was found to be cost saving. Doyle et al. (2002) constructed a Markov cohort model over 3 years with six month cycles. Patient level data from PREVENT was used to populate the model. They commented that

> '*the constantly changing health status of the subjects observed during PREVENT was ideally suited for analysis using Markov modelling techniques due to the ability to incorporate time dependency into the transitional probability of entering any given health state.*'

They found no significant improvement in health but fewer hospitalisations which resulted in a slight cost saving for those treated with amlodipine.

3.6.5 Discussion about studies for drug interventions

One of the difficulties with extrapolating beyond the end of a trial is that it is not possible to exactly predict the benefit of the treatment after the end of a trial. It may be there is no continuing benefit of the treatment after the trial, or that the benefit continues after the trial with a continual separation of the survival curves beyond the trial period, or indeed something between these extremes (eg Philips et al. 2000). The studies discussed in this section make varying assumptions with regard to the continuing effect of treatment. Several of them assume that there will be no continued benefit after the trial end point or a coronary event, for example Tsevat et al. (2001), Johanesson et al. (1997), Muls et al. (1998), Ashraf et al. (1996). Others assume that treatment benefits will continue indefinitely (Pharaoh and Hollingworth 1996; Van Hout and Simoons 2001; Ganz et al. 2000; Pickin et al. 1999; Ebrahim et al. 1999). One solution is to provide results on both possible extremes, for example Tsevat (1995).

Several of the studies attempted to simulate clinical trials and this may lead to biases due to the trial, for example the CARE and PLAC I trial did not result in a statistically significant difference in mortality whereas the 4S and LIPID trial did, but on the other hand they avoid assumptions about the generalisability of the trial to different populations. Several of the models, for example Pharaoh and Hollingworth (1996), Pickin et al. (1999), Ebrahim et al. (1999), assume that non fatal events and health cost savings are proportional to the mortality benefit seen. As mentioned above, most of the studies measured the outcome of life years saved, rather than quality adjusted life years saved. This is likely to result in worse cost effectiveness values than calculating cost per QALY. Only two authors justified the modelling technique used. Scuffham and Chaplin (2004) commented,

> '*A Markov model was chosen because the differential timing of events can be modelled explicitly*'

As shown in Table 3.5.1, most of the Markov models have fewer than seven health states and based on the work in this thesis the Markov model is likely to be the optimal model for these studies.

3.7 Miscellaneous studies

3.7.1 Coronary care units

Tosteson et al. (1996) assessed the cost effectiveness of coronary care units (CCU) compared to an intermediate care unit (ICU) using a decision tree for the first 48 hours after arrival and combined this with an estimate of their life expectancy (Table 3.7.1). Within the first 48 hours, patients could either have a diagnosed MI or not, die or survive. The probability of death in first 48 hours depends on whether they have a MI and whether they are referred to ICU or CCU. Those with MI who are referred to ICU instead of CCU have a 15% increase in mortality. Patients who survive 48 hours are classified according to the level of disease severity. During the remainder of the hospitalisation, patients remain at risk of developing complications or dying and these events are assume to depend on their initial survival, myocardial infarction status, initial triage site and worst complication during the hospitalisation. The study concluded the

CCU should be used for patients with a moderate (> 21%, depending on age) probability of MI, ie patients with ECG changes of ischaemia or recent infarction.

3.7.2 Smoking cessation

Krumholz et al. (1993) assessed the cost effectiveness of a nurse-managed smoking cessation program after myocardial infarction using a decision tree combined with patient life expectancies. The study estimated a cost effectiveness of $220 per year of life saved.

3.7.3 Public defibrillators

Nichol et al. (1998) assessed the cost effectiveness of public access defibrillation using a decision tree combined with life expectancy data. A patient who experienced a sudden cardiac arrest either died before hospital, died in hospital or lived to discharge. If the emergency medical system was supplemented by public access defibrillation by lay responders then patients who experience sudden cardiac arrest in a public place potentially benefited from enhanced defibrillation. The authors concluded that public access defibrillation was potentially cost effective and recommended a trial.

3.7.4 Exercise training

Lowensteyn et al. (2000) assessed the cost effectiveness of exercise training using the Cardiovascular Disease Life Expectancy model (Grover et al. 1998). They used randomised controlled trials to provide estimates for the reduction of CHD risk factors of individuals assigned to exercise training. The model followed cohorts over their lifetime. Adherence to the exercise program was estimated to be 50% for the first year, and 30% for all remaining years. They assumed individuals who stopped exercise stopped accruing benefits and their risk factors reverted back to the original values. They assessed supervised and unsupervised programmes and found that exercise training for both was found to be highly cost effective for men with CVD. Exercise training was less cost effective in women.

3.7.5 Capacity planning

Davies (1994) developed a discrete event simulation (DES) to predict the resource use and costs for patients with CHD in a hospital department. Patients arrived into the model, according to a specified demand, if they are referred for angiography. After angiogram, they are referred to angioplasty, bypass surgery or medical treatment, and patients will join treatment queues if appropriate. The simulation dynamically models the use of beds, catheter labs and theatres. The level of demand and resources were varied to assess the bottlenecks in the system.

Groothius et al. (2001) developed a DES to optimise the use of catheterisation capacity in a hospital department. Their simulation is similar to Davies et al. (1994) although it does not model the survival of patients after procedures or the effect of different strategies on the treatment waiting lists, instead looking at the effects of different scheduling procedures on throughput and efficiency of the resources. Harper et al. (2004,2005) developed a discrete-event geographical location-allocation simulation model for evaluating various options for the provision of cardiac services within the Eastern region of the UK. In particular they modelled patient travel times to a variety of possible health care centres in order to increase existing revascularisation services.

3.8 Generic models

Several studies have constructed generic or system models for CHD (Bonneux et al. 1994; Weinstein et al. 1987; Bensley et al. 1995; Cooper et al. 2002) (See Table 3.8.1). These models model the wider CHD disease process, not only that specific to a particular intervention.

Hunink et al. (1990) describe the CHD Health Policy model as a computer simulation state transition model of CHD in US residents aged 35 through 84 years without coronary heart disease. The model projects the future CHD incidence, prevalence, mortality and resource costs under alternative assumptions about preventative and therapeutic interventions. Relative risk coefficients and CHD incident rates were based on data from the Framington Heart Study. The model has been used extensively to study

strategies for primary prevention (Goldman et al. 2001; Tsevat et al. 1991; Edelson et al. 1990; Goldman et al. 1989; Tsevat 1992) and treatment strategies of CHD, for example use of statins (Prosser et al. 2000, Goldman 1991), aspirin (Gaspoz et al. 2002) and beta blocker (Philips et al 2000). It has also been used to provide estimates of life expectancy for other decision analytic models, for example for statins (Tsevat 2001), thrombolysis, (Krumholz et al. 1992; Lieu et al.1997; Parmley 1999), stents (Cohen et al. 1994), angiography (Kuntz et al. 1996), and ACE inhibitors (Tsevat et al. 1997).

The model includes risk factors for age, sex, smoking status, diastolic blood pressure, serum cholesterol and relative weight. The model consists of three integrated sub models: the demographic-epidemiologic, the bridge and disease history sub models (Figure 3.8.1).

The demographic epidemiologic model predicts CHD incidence and non-CHD mortality among subjects without CHD stratified by age, sex, blood pressure, smoking status, cholesterol. After development of CHD, the bridge sub model characterises the initial CHD event and the subsequent events in the next 30 day period. The Disease History model predicts the subsequent CHD events, revascularisation procedures, CHD mortality and non-CHD mortality among patients with CHD and history of myocardial infarction, cardiac arrest and CABG and PTCA. The patients move between the twelve states at the end of each model year according to any events that have occurred in that year. For modelling interventions, risk factors are adjusted by a relative amount (eg, 10% reduction in cholesterol) or absolute amount (eg a 5 mm HG decrease in diastolic blood pressure) or the mean value is redefined (eg change the mean number of cigarettes smoked per day from 12 to zero) for any or all cells. Secondary prevention is simulated by reducing the DH probabilities.

Table 3.8.1 Generic policy models

(Terminology used: CE cost effectiveness; ICER incremental cost effectiveness ratio; LYS life years saved; CHD Coronary heart disease; GPRD General Practitioners Research Database; UKHAS United Kingdom Heart Attack Study)

Study	Strategy	Data sources / time horizon	Model used / Risk factors	Results
Bensley et al. 1995 UK	Prediction of resource use and CHD population	1 year	Spreadsheet deterministic model	Estimate of likely resource use for different referral rates and event rates.
Bonneux et al. 1994 The Netherlands	Prediction of CHD population including congestive heart failure	Framingham heart study; lifetime	Markov simulation model; cholesterol level, age, drug dosage, blood pressure, smoking, weight	Declining mortality and incidence and increase in health care demands is shown to be consistent by the model.
Cooper et al. 2002 UK	Prediction of CHD population	GPRD, UKHAS, Until age 85.	Discrete event simulation; vessel disease, age, sex	Predicts national CHD morbidity and mortality levels as a result of different interventions.
Weinstein et al. 1988 USA	Prediction of CHD population, various cost effectiveness analyses	Framingham heart study; lifetime	Markov simulation model; cholesterol level, age, drug dosage, blood pressure, smoking, weight	Has been used to calculate cost effectiveness of various prevention and treatment interventions and predict realistic target levels of mortality and morbitity as a result of these interventions.

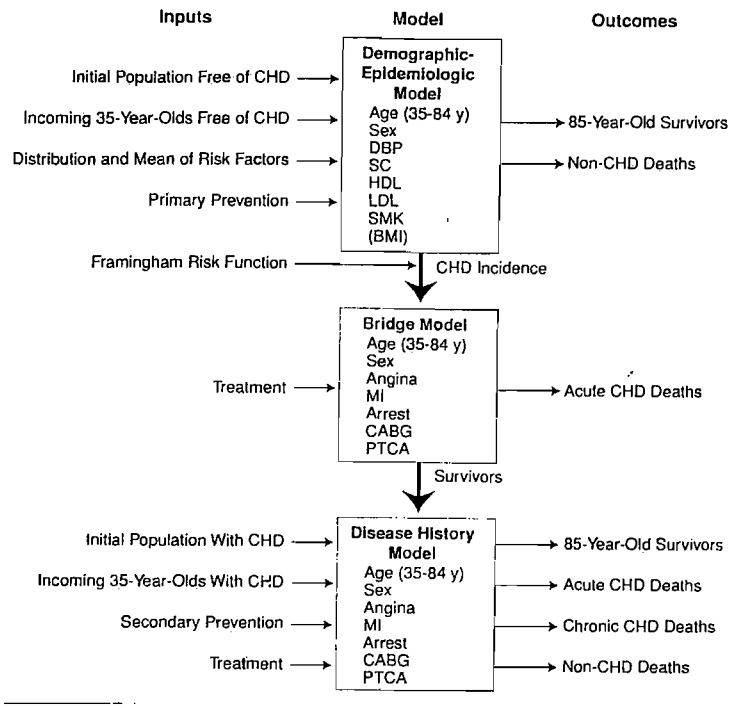

Figure 3.8.1 Overview of the coronary heart disease (CHD) policy model by Hunink et al. (1990).

The model was written in FORTRAN. It is based on a derivation of the Framingham risk equations (Anderson et al. 1991) for the US population and uses data obtained from a literature review, hospital discharge data, US nation-wide health surveys and ongoing clinical trials. The model is inflexible with restrictive assumptions about transitions between states. The model assumes, for example, that the progress of any patient in any state is independent of how they arrived there (Markov assumption). This approach causes the number of strata to be very large (5400 strata in DE model, 1200 in DH model). Risk factors have to be independently distributed in the population, rather than correlated. In addition the model does not consider congestive heart failure or PTCA. Nevertheless, the model achieves its aim in forecasting CHD and led to a number of studies using the model. In addition it has been largely replicated (with one or two alterations) by Bonneux (1994).

Bonneux et al. (1994) attempt to '*forecast the plausible evolution of heart disease morbidity*' using a state transition model with a similar structure to that of the Coronary Heart Disease Model as described by Weinstein et al. (1987). The model excludes

cardiac arrest as a prevalent state and includes congestive heart failure. Most of the limitations of the Weinstein model also apply to Bonneux. The model projects heart disease from 1985 – 2010 for different levels of decrease in incidence. The model predicts that morbidity will decrease among the young and middle aged but increase among the elderly.

Bensley et al. (1995) constructed a simple spreadsheet flow model of the need for cardiology services. The spreadsheet model is deterministic and can be seen to be similar to an arithmetical bookkeeping exercise. The population is aged 35-74 and starts from a state of health with a risk of angina and acute coronary events. Patients' progress is then modelled through diagnostic tests (exercise tests and angiogram), surgical (CABG and PTCA) and medical treatment (Aspirin, thrombolysis, beta blocker). At each stage of the model the total population is subdivided into smaller populations to reflect the number of people using the associated resources. The model includes no risk factors, not even age or sex, no demographic change, and no specific risk factors. The model can be used to predict the likely number of CABG, PTCA, angiogram and deaths for different event and referral rates.

A discrete event simulation model for CHD treatment in the UK was developed (Cooper et al. 2002). It modelled patients who have had a coronary event, through their treatment pathways and subsequent coronary events. The main interventions modelled were CABG and PTCA, ambulance and thrombolysis response times, cardiac rehabilitation, and secondary prevention drugs such as statins, beta blockers, ACE inhibitors and aspirin (Davies et al. 2003). The main risk factors in the model are age, sex, history of previous events and the extent of the coronary vessel disease. By modelling using discrete event simulation, we were able to avoid many of the limitations imposed by the Markov assumption in the Weinstein model (see section 9.6).

3.9 Discussion

Many of the studies that model a specific intervention have not estimated the overall cost effectiveness of a population for that intervention, instead concentrating on a base

case cohort with sensitivity analyses for other cohorts with different risk factors. Although the range of cost effectiveness for different risk cohorts is interesting, the policy maker may also be interested in the absolute impact (ie costs and benefits) of the intervention to a population. For example, Pickin et al. (1999) conclude that the statins are a very cost effective drug but if they were to be prescribed to all individuals with CHD or a greater than 3% annual risk of coronary events, this will entail treating 8% of the adult UK population at a cost equivalent to 25% of the present expenditure on community prescribed medicines! Clearly the decision to implement the intervention in this case would be largely influenced by the expenditure available.

Very few of the studies reviewed had been validated in a tangible form and relied instead upon 'face validity'. Part of the difficulty in validating the models may be that studies normally use a single incident cohort of patients through the model, rather than repopulating the model each year according to recurrent events from a prevalent population (Davies et al. 2003).

Based on the literature review in this chapter, the reporting in many of the studies of the modelling was of a poor standard. The quality of economic evaluation reports is discussed in more detail in section 4.2. Clearly there is limited space for description of the model in journal articles but in many cases the authors did not include diagrams of the models and the modelling methodology described was unclear. The description of the models should be sufficient for a competent modeller to reproduce the models and all too often this would not have been possible.

3.10 Conclusions

A literature review of Coronary Heart Disease treatment models has been conducted to provide a contextual background for the subsequent chapters. The majority of the models described have been developed to assess the cost effectiveness of different treatment strategies. The most commonly used models were decision tree models for short term interventions and Markov or state transition models for chronic or long term interventions. Virtually all studies used cohort based models rather than population based models and so few estimate the likely total costs and benefits for a population.

Chapter 4

Methodology Issues for Modelling Health care Interventions

Abstract

There has been much debate in the recent health economic literature concerning the quality of health economic modelling studies and a summary of the recommendations for best practice for building models is presented. The optimal choice of modelling technique is investigated, according to the characteristics of the health care intervention. Several guidelines are identified from a review of the modelling literature and others are presented as hypotheses which will be explored in later chapters.

It is concluded that the optimal model will be the simplest that adequately captures the disease condition or health care system. The use of population-based models and the provision of health care outcomes for the likely cost, health benefits and cost effectiveness of the intervention is recommended. The choice of the preferred model will depend on the likely ease and speed of development, the complexity of the model in terms of the number of states, and the interconnectedness of the system. The modeller will need to judge whether interactions between individuals is a significant issue in the health care system and whether queuing for resources and resource constraints are relevant to the research question.

Chapter 4 Methodology Issues for Modelling Health care Interventions

4.1 Introduction

Economic evaluation attempts to compare health care interventions as a basis for Health service decision makers. An overview of economic evaluation and some of the modelling techniques used has been presented in Chapter 2.

There has been much debate in the recent health economic literature concerning the quality of health economic modelling studies and a summary of the recommendations for best practice for building models is presented. The optimal choice of modelling technique is investigated, according to the characteristics of the health care intervention. Several guidelines are identified from a review of the modelling literature and others are presented as hypotheses which will be explored in later chapters.

4.2 Quality of models

In recent years, economic analyses have become increasingly common in the medical literature. Elixhauser et al. (1993, 1998) estimate that 1897 cost benefit analyses or cost effectiveness analyses have been reported between 1979 – 1990, rising to 2274 between 1991 and 1996. This increase in the number of economic evaluations has led to a greater willingness to use the results as a basis for allocating scarce resources.

However, there has been much doubt concerning the validation, quality and comparability of cost-effectiveness studies (Udvarhelyi et al. 1992; Gerard et al. 2000; Adams et al. 1992; Jefferson and Demichelli 1994; Evans et al. 1995; Neumann et al. 1997; Luce et al. 1996; Jefferson et al. 2002; Neumann et al. 2000). Indeed an editorial in BMJ (Drummond and Jefferson 1996) states:

> *'although coverage of economic evaluation has been limited and the tools used for quality assessment have varied, the overall conclusions show that*

there is a long way to go before economic evaluations can be regarded as good enough to justify their use in decision making'.

Neumann et al. (2000) evaluated the quality of 228 cost utility analyses. They concluded that reporting practices in cost-utility analyses have varied considerably. They noted that the quality of published analyses improved slightly over time and was higher in general clinical journals and in journals that published more of these studies. Many other reviews have also shown similar methodological flaws (Udvarhelyi et al. 1992; Gerard et al. 1999; Adams et al. 1992; Neumann et al. 1997; Briggs and Sculpher 1995)

Kaissirer and Angell (1994) writing in an editorial of the New England Journal of Medicine (NEJM) argued that

'because of the discretionary nature of the methods used to analyse cost effectiveness and the increasing importance of such analyses, it is incumbent on the authors, journal editors and the funders of these studies to minimise any source of bias'.

Russell et al. (1996) cite similar concerns:

'studies vary widely in the health effects and costs included and in the way these are valued and combined, so that studies of the same intervention can produce very different cost effectiveness ratios; potential users may be confused and suspicious that cost effectiveness analyses can be manipulated to support any conclusion.'

Sheldon (1996) cites many examples of technical error and biased results, as well as poor practice in eliciting expert opinion and, in the analysis of uncertainty, to construct an almost irrefutable case for the poverty of current practice in cost effectiveness modelling. One of his main conclusions is that

'until a clear structure for critically appraising decision models is developed, models which produce unrealistic and biased results will continue to be published'.

In answer to these criticisms there have been efforts from the research community to improve the quality of submitted and published economic articles by setting guidelines for economic evaluation and defining 'best practice'. The British Medical Journal set up a working party to study economic evaluation, which subsequently published guidelines for economic evaluation which could be understood by specialist and non specialist readers, and 32 point checklists for use by referees, authors and editors (Drummond and Jefferson 1996).

In 1993, The US Public Health Service convened the Panel on Cost Effectiveness in Health and Medicine to develop recommendations to improve the quality and comparability of studies. They subsequently published recommendations for the use of the reference case and the reporting of cost effective analyses (Weinstein et al. 1996; Siegel et al. 1996; Russell et al. 1996). In the late 1990s, the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) set up a task force made up of '*experienced developers or users of models who worked in academia and industry, and came from several countries in North America and Europe*'. The task force subsequently published their findings on the criteria for assessing the quality of health care models (Weinstein et al. 2003). A recent Health Technology Assessment has reviewed these guidelines and produced a synthesised guidance for good practice (Philips et al. 2004). It is likely that these guidelines will be used by referees to judge the quality of economic evaluation modelling studies submitted to journals although the authors emphasise that these guidelines are

> '*specific to decision-analytic modelling in economic evaluation and do not cover more general attributes of good practice in economic evaluation*'.

This section presents a summary of recommendations for best practice for building models for economic evaluation as developed by Halpern et al. (1998), Davies et al. (2003), Sculpher et al. (2000), Weinstein et al. (2003) and others (Sonnenberg et al. 1994; McCabe and Dixon 2000; Brennan and Akehurst 2000; Weinstein et al. 1996; Siegel et al. 1996; Russell et al. 1996; Eddy 1990), and some of the more common errors to avoid (Sonnenberg et al. 1994; Buxton et al. 1997).

4.2.1 What makes a 'good' model?

In an article which attempted to establish some major principles of good modelling practice for health care modelling, Sculpher et al. (2000) proposes that

> *'the purpose of decision models is to inform decision making at a particular point in time'.*

They suggest that a better decision will be made using the model at a point in time than not using a model. Furthermore, the model could be tested, by

> *'randomly allocating decision makers to use and not use the model'.*

In this test, the model is deemed useful or valid if the group using the model made the better decisions. This view is shared by Sonnenberg et al. (1994) who comment,

> *'validity refers to the ability of a decision model to recommend optimal decisions'.*

They go on to point out the obvious difficulties with this,

> *'short of a clinical trial of a decision model, validity of a recommended decision cannot be assessed because there is no gold standard for the quality of a decision'.*

However comparisons between the model and clinical trials, observational studies and other models is still a useful process (Sculpher et al. 2000). They conclude that the accuracy of the model to portray reality is somewhat less important than its ability to improve decision making. All models are 'wrong' in term of their predictions but the level of use of the models may be a more appropriate test of their validity. However there are various techniques used to validate the model and these are discussed in more detail later.

> *'Describing what is a 'good model' is a difficult undertaking*', Sculpher et al. (2000)

acknowledges,

> *'Such a description needs to be sufficiently generic to apply across diseases, interventions and model types but to avoid being too general and hence of little value in any given context'.*

They stress the importance that the analyst adequately describes the model and provides a

> *'clear and honest justification'*

for their approach. This will enable users to make a more informed judgement about whether the results are credible or informative.

Dallenbach (1994) gives an overview of operational research / management science methodology for developing and implementing models. Simon (1982) describes the process of modelling. Halpern et al. (1998) and Weinstein et al. (2003) propose a list of recommendations for 'good practice' to help model designers and reviewers to focus on the key criteria during the development / evaluation process in health outcomes research. These recommendations are described below together with complementary views from other authors. Although the recommendations are directed toward health care modelling, the principles described hold true for different modelling applications.

4.2.2 General guidelines

Little (1970) describes in general terms that for a mathematical model to be useful it should be

i. *Simple - easily understood by the decision maker*
ii. *Complete - all significant aspects of the problem that affect the measure of effectiveness should be included*
iii. *Easy to manipulate - possible to obtain answers from the model with a reasonable amount of computational effort.*
iv. *Adaptive - reasonable changes in the structure of the problem situation do not completely invalidate the model*
v. *Easy to communicate with - easy for the analyst and / or user to prepare, update and change inputs and get answers quickly*
vi. *Appropriate for the situation studied - model produces relevant outputs at the lowest possible cost and within the time required for effective decision making*
vii. *Relevant - able to produce information that is relevant and appropriate for decision making*

In addition Akehurst et al. (2000) state further properties including internal consistency, reproducibility and exploration of uncertainty. Davies et al. (2003) suggest that a model may have all or many of the above characteristics and still provide poor predictions.

4.2.3 Study question

Before development of a model begins, there should be a clear definition of the purpose of the model (Sculpher 2000; McCabe and Dixon 2000; Halpern et al. 1998; Nuijten et al. 1998; Soto 2002). According to Halpern et al. (1998), this 'study question' includes the disease or condition, interventions, populations and the perspectives of the study. Furthermore they state that the study question should be examined for reasonableness, for example is it clinically relevant and feasible, and is modelling the most appropriate approach? This assessment of clinical relevance may require the involvement of clinicians and policy makers. The study question may be better answered by using available retrospective data or in a prospective clinical trial or observational study.

Buxton et al. (1997) suggest that modelling is most appropriate for the following purposes:

- *Extrapolating beyond the data observed in a trial*
- *Linking intermediate clinical endpoints to final outcomes*
- *Generalising to other settings*
- *Synthesizing head to head comparisons where relevant trials do not exist*
- *Informing decisions in the absence of hard data*

Halpern et al. (1998) also suggests modelling may be appropriate in some cases where it can provide a cheaper and quicker alternative to other methodologies.

4.2.4 Design of model

After deciding to use a model the next step is to conceptualise the study question in a theoretical structure (Sculpher et al. 2000). They state that this structure should include

'all clinically and economically relevant events'.

Furthermore, they state, in order for the model to be manageable and comprehensive to the user, constraints and model boundaries need to be specified. The analyst should be able to justify the assumptions made to incorporate these constraints. Weinstein et al. (2003) urges that the structure of the model be as simple as possible while still

'capturing underlying essentials of the disease process and interventions'.

4.2.5 Model boundaries

The model boundaries need to be determined at the onset of the study (Akehurst et al. 2000). The analyst needs to decide '*what to include and what to exclude*' (Davies et al. 2003). These include the

> '*time frame, population / sub-populations, perspective, comparators, setting, country or region, payment system, index patients or disease characteristics and other factors that will determine the type and extent of costs and events to include in the model*' (Halpern et al. 1998).

The boundaries of the model will depend on the disease or condition and intervention under study (Sonnenberg et al. 1994). Model perspective also needs to be determined and clearly stated. Many believe that a societal perspective should be used (Gold et al. 1996), however the perspective should agree with the purpose of the model. The Washington Panel makes recommendations for many of these boundaries (Weinstein et al. 1996; Russell et al. 1996; Siegel et al. 1996).

4.2.6 Complexity of model

The analyst should aim to produce a model that is as simple as possible (Sculpher et al. 2000, Akehurst et al. 2000; Weinstein et al. 2003; Halpern et al. 1998; Buxton et al. 1997). However the model should include the underlying essentials of the disease process and interventions (Weinstein et al. 2003). Weinstein comments further,

> '*it is not necessary to model the full complexity of a disease if the decision can be informed by a more aggregated structure, in terms of disease states or population subgroup*'.

The simplifications that are made should be justified by the analyst who should explain how these assumptions are unlikely to have a

> '*material impact upon the results of the model*' (McCabe and Dixon 2000).

4.2.7 Transparency

Several authors (Sculpher et al. 2000; Akehurst et al. 2000; Buxton et al. 1997; McCabe and Dixon 2000; Halpern et al. 1998; Weinstein 2003) urge transparency in the

reporting on the data use and the structure of the model. Halpern et al. (1998) recommends that information be available for a review process. They state this information should be presented in a

'clear and easy to understand fashion'.

For published articles, limited in length by the journals, they recommend the use of technical appendices for additional information such as data sources, assumptions, event probabilities, health care resource utilisation, utilities and costs and perspective. Siegel et al. (1996) recommends including a diagram of the event pathways of the model to aid understanding. The model should be reproducible from the information available, ie an independent competent analyst should be able to obtain the same results by replicating the model (Akehurst et al. 2000).

4.2.8 Data sources

Models are often built where the 'best' available data is less than ideal, but this does not invalidate the model (Weinstein 2003; Sculpher et al. 2000). Weinstein et al. (2003) recommend that a systematic review should be conducted of the literature on the key model inputs. Often the data needs be manipulated to obtain estimates of effectiveness, cost and preferences and the methods used for this should be given (Siegel et al. 1996). Sources of data used for model parameters include event probabilities, health care resource utilisation, utilities and costs.

Clearly, the model should use the 'best' data available. Halpern et al. (1998) recommends the use of epidemiologic studies, randomised controlled trials (RCTs), or observational studies. Retrospective data and expert opinion are also often used in models. Each of the sources of data has potential biases. The quality and relevance of the data should be evaluated and inclusion should be justified (Halpern et al. 1998). They state that the evaluation of prospective data quality should include importance of study, sample size, year, length and degree of patient follow up and methods of data collection (eg doctor diagnosis, patient self reported). However Davies et al. (2003) highlight that although the data may be of good quality and internally consistent, the limitations of this type of data should be recognised. For example, data may not be available for all the categories required by the model and it may be necessary to make extrapolations from data from other, less appropriate studies. In addition, randomised

trials and observational studies may exclude particular categories of patients, such as the elderly or those at risk of complications of an intervention.

4.2.9 Costs

By definition, all economic models include costs or charges. The costs used in the model will depend upon the perspective adopted, eg patient, society or hospital. Russell et al. (1996) recommend the societal perspective should be used for cost effectiveness analyses, in order to facilitate comparison between interventions and patient. Costs from different sources should be standardised by updating to a particular year. For long term projections, results should be discounted (see section 2.2.5).

4.2.10 Assumptions

The validity of models often depends on the reasonableness of their assumptions (Gold et al. 1996) and the discrepancy observed between models is often due to differences in assumptions. As such, model assumptions require a high degree of transparency and need to be stated clearly (Akehurst et al. 2000; Nuijten et al. 1998; Soto 2002). Assumptions having even minor impact on model parameters may have substantial effects on projected outcomes.

4.2.11 Treatment of intervention strategies and outcomes

When designing the model, the analyst should take care not to exclude important treatment or intervention strategies (Halpern et al. 1998). This should be based on a review of published literature and clinical trials as well as on expert consultation.

Similarly models should include all relevant outcomes,

> '*including negative consequences of health care interventions*' (Halpern et al. 1998).

They suggest the following outcomes may be included: initial success and failure of an intervention, relapse, adverse events, discontinuation or non compliance or death. They note that a failure to include all relevant outcomes could result in

> '*incomplete evaluation of treatment strategies, producing biased results*'.

Halpern et al. (1998) stress the need for models to provide outcomes, which will be comparable to other treatments or interventions. They state that,

'*intermediate outcomes often do not provide sufficient information*'

to be able to make these comparisons. For example a model evaluating strategies for the reduction of cholesterol associated coronary heart disease is less interested in the short term change in serum cholesterol rather than the incidence of coronary heart disease. Halpern et al. (1998) recommends that

'*models generally include long term or final outcomes*'.

4.2.12 Internal consistency

The model should have internal consistency, or mathematical correctness (Akehurst et al. 2000). Sculpher et al. (2000) recommend that the model be regularly checked using internal tests (or 'debugging') by the analyst to reveal errors with model code or the use of data. Weinstein et al. (2003) and Sculpher et al. (2002) recommend that the analyst provide evidence that the model has been tested in this way. The best method for checking mathematical correctness is by numerically checking the results by hand for a sufficiently wide range of inputs (Daellanbach 1994). The correctness of all numerical constants should be verified.

Other techniques to test for internal consistency include movement of results in sensitivity analysis (including analysis of extreme values) to see if they follow expectations or checking that all probabilities range between 0 and 1. The model can be run under simplifying assumptions for which true characteristics are known or can be easily computed (Davies and Davies 1986).

Halpern et al. (1998) state that all steps in a Markov model should be feasible. They also say,

> '*the model should be symmetric in that the modelled prognosis must be the same for the same condition / treatment combinations in different sections of the model*'.

The model can also be tested for internal consistency by building another model using the same data but within a different software package (Sculpher et al.2002).

4.2.13 Sensitivity analysis

According to Weinstein et al. (2003),

> *'all modelling studies should include extensive sensitivity analyses of key parameters'.*

Sensitivity analysis involves running the model with a range of values for the model parameters and evaluating the impact on the model output (Halpern et al. 1998).

The simplest form of sensitivity analysis is uni-dimensional where one variable is altered at a time. However multi-dimensional analysis permits greater exploration of the variability of the parameters and their interaction. Results of multi-dimensional sensitivity analysis are harder to derive and interpret and may require specialist software packages (Halpern et al. 1998). They state that

> *'where the number of parameters is large, an infeasible number of iterations may be required'.*

They suggest reducing the number of iterations by varying only correlated parameters. In all cases, an explanation of selected sensitivity parameter values should be provided.

Recently there has been much research into the best practice for sensitivity analysis for economic evaluation. For example, researchers have attempted to develop an indication of the confidence of the cost effectiveness results in a similar way to confidence intervals for trials. This has led to the introduction of cost effectiveness acceptability curves which represent the probability that the cost effectiveness will be within a certain range. Sensitivity analysis and uncertainty has been described in more detail elsewhere, for example Briggs (1994), Briggs and Sculpher (1994). These analyses often require the use of Bayesian methods (Briggs 2000).

4.2.14 Verification and validation

Weinstein et al. (2001) defines verification as demonstrating that the model's inputs and outputs are

> *'consistent with known facts and that it is functioning properly in a technical sense'.*

In other words, the results should seem realistic for the study question (McCabe and Dixon 2000; Weinstein et al. 2003, Soto 2002; Halpern et al. 1998). Several methods of verification have been discussed in section 4.2.12.

Often the model will need to be calibrated against real data to make the results of the model more realistic. Weinstein et al. (2003) recommend the model is calibrated, where possible, using a data source

> '*independent of the data used to estimate input parameters in the model*'.

A description of the calibration process should be included in any report about a model conveyed to decision makers.

Validation involves assessing whether the model projections represent real-world outcomes. Pidd (1996) suggests that validation is best regarded as

> '*an ideal towards which we must strive whilst recognising that it may be limited*'.

The validation can be completed on two levels: as a black box validation and open box validation (Law and Kelton 1991).

According to Pidd (1996), black box validation is where the outputs of the model are compared with the reference system without looking at the internal construction. He states,

> '*the aim is to test whether the two sets of observations are close enough to be confident that the model has adequate validity*'.

Smith et al. (1993) states,

> *'what is or is not a close enough approximation is largely a question of judgement*'.

The answer may depend on the purpose of the model and the intended use of its solution.

According to Pidd (1996), open box validation concerns the detailed internal comparison of the model with the reference system. He states,

> *'this may present difficulties because the reason for building the model may be to help understand the structure of the reference system*'.

Nevertheless it is possible to check a number of key features. If any probability distributions are employed are they reasonable, given the phenomena being modelled? Does the model apply what is believed to be the appropriate theory? A more detailed description of issues related to validation and validity can be found in Zeigler (1976)

Halpern et al. (1998) point out that there are likely to be difficulties with comparing model outcomes with actual events at the time of the model development. However the model may be compared to a previous time period by altering some of the parameters. It is often difficult to get good historical data (Davies et al. 2003). They suggest that when the validation process produces a poor match with the reference system,

'it may not be clear why this has happened and how to address it'.

4.2.15 Common modelling errors

Eddy (1990) identifies the following key limitations in modelling. First it does not provide new observations. If based on incorrect clinical judgement, modelling will perpetuate any of these errors (rubbish in – rubbish out). Models can be poorly designed. For example oversimplification by omitting important variables, squeezing the problem into a familiar or convenient mathematical form or assuming the outcomes assessed by the model are the only ones of interest. Finally results can be misinterpreted and decision makers may fail to appreciate the degree of uncertainty in the results. Buxton et al. (1997) and Sheldon (1996) raise several similar concerns about modelling. They warn against the incorrect use of clinical and observational data, which may produce unrealistic results. They also note the difficulties from extrapolating from data and potential biases, which may be hidden within the models because of lack of transparency.

Sonnenberg et al. (1994) listed the following common errors in model construction that reviewers should look for:

– *Invalid model syntax*, eg probabilities of the branches of a chance node of a decision tree not summing to one.

– *Conditioning of action on unobservable states*, ie modelling the presence of a disease before a diagnostic test has been undertaken.

– *Violations of symmetry* in modelling disease prognosis

– *Failure to link variables* that are inherently related

– *Failure to apply consistent bias*, ie making assumptions which favour one strategy over another

– *Incorrectly modelling a treatment*

4.3 Choice of modelling technique

In this section the choice of the modelling technique is examined. This question has been addressed, in particular, by Karnon and Brown (1998) and Barton et al. (2004). Based on their and other authors' work assumptions (A1-A4) and hypotheses (H1-H6) concerning the choice of modelling technique are developed which will be examined in more detail in subsequent chapters.

The choice of modelling technique used will depend on the particular expertise, background and preferences of the modeller, data available, funding and the structure and complexity of the disease and health care intervention to be studied. In turn, the model chosen will

> '*influence the assumptions that can be made and hence may impact on the output*'. (Davies et al. 2003).

According to Sculpher et al. (2000), the analyst should select

> '*the simplest format possible that adequately reflects the disease*'.

Halpern et al. (1998) recommends the use of deterministic models in most circumstances as

> '*the additional time, expense, and complexity involved in stochastic modelling are not worth the gain in precision*'.

The analyst should ensure that this simplicity does not restrict the model by making unreasonable simplifying assumptions (Sculpher et al. 2000). According to Karnon and Brown (1998)

> '*the trade-off between the simplicity of use of a methodology and the necessary accuracy of the portrayal of reality is subjective*'.

They also suggest that

> *'the choice of the decision model should be based on an assessment of the incremental benefits, in terms of increased confidence in the model, which are gained at the expense of the incremental costs of moving to a more complicated modelling methodology'.*

In section 2.2.6, the use of population and cohort models was discussed. It was concluded that

A1) A population analysis provides a more comprehensive summary of the value of the intervention for the health care planner than a cohort analysis.

A2) The cost and health benefit outcomes of an intervention are as important an output as cost effectiveness.

4.3.1 Acceptance by model users

Olson et al. (2003) conducted a survey of the perceived value and understanding of Pharmacoeconomic models among decision makers in the USA by interviewing 20 Pharmacoeconomic research scientists from various pharmaceutical and biotechnological companies. They identified factors that determine whether a model is well received by decision makers.

> *'The most frequently mentioned factor was (1) ease of understanding (ie model simplicity and transparency) (19 of 20)'.*

There was no consensus to which modelling format was most effective, with a variety of methods mentioned including regression models and spreadsheet models.

> *'However, two participants specifically mentioned that Markov models were not well received because of the lack of understanding associated with this modelling technique'.*

Model acceptance is often very important in determining whether a model is widely used after development or not. Anecdotal evidence suggests that spreadsheet models are more readily accepted than simulation models because of familiarity of the software. Furthermore simulation models may appear to be 'black box' and their results may not be readily trusted.

Melao and Pidd (2003) conducted a survey among potential business process simulation users to investigate the usage of simulation. These people were engaged in modelling activities and were the people

> '*most knowledgeable about the realities of modelling and simulation of business processes*'.

They concluded that the number of simulation users was low even within a group who might be expected to be favourable disposed to simulation. Process mapping and spreadsheet modelling were much more popular and when asked why they stressed factors such as simplicity, ease of use, quick development and ease of communication. This low usage of simulation has also been reflected by other studies of simulation application areas, for example Hollocks (1992).

Stanbridge (1999) discusses some ideas that may help overcoming barriers to the acceptance of the use of simulation in health care delivery application. He suggests,

> '*Make sure that the information provided by the simulation model has more value than the information provided by an expected value analysis that can be implemented on a spreadsheet*'.

4.3.2 Ease and speed of model development

Karnon (2003) constructed Markov and DES models for the evaluation of the alternative adjuvant therapies for early breast cancer in the context of a stochastic evaluation, which described probability distributions around the outputs of the models. He constructed the Markov process using Excel using a risk analysis programme add-in (Crystal Ball), and the DES using Simul8.

He constructed the models as cohort analyses. There were minor structural differences between the two models but the pathways of the two models were identical. He commented that the DES model was able to

> '*represent the available data in a more intuitive manner.*

He used a cycle length of one month for the Markov model and a minimum time period of one month for the DES model. The cohort consisted of patients aged between 50 and 59 years on entry for the model and the model was run until all patients had died or were aged 100 years old.

The cost and effectiveness outputs from the DES model had higher values than the Markov model. The cost outputs varied by less than 6%, and the QALYs and life years saved varied by less than 2%. Furthermore the cost effectiveness estimates were 3% higher for the DES than the Markov model. He commented that

> *'it would appear to be good fortune that the divergences between the models acted in opposite directions that almost cancelled each other out'.*

He concluded that both model results would lead to the same resource allocation decision.

Karnon (2003) noted that the DES provided the more precise results because it handles time to event in a more flexible way and parameter values were linked to time spent in a state in a more accurate way. However in this case, these advantages of DES do not outweigh

> *'the far greater time to develop and evaluate the DES model'*,

and he concluded that the Markov model would be the more appropriate technique.

In general DES models are more difficult and take longer to develop than Markov and decision trees. Karnon and Brown (1998) and Davies et al. (2003) comment that because of the complexity of DES, they require specialist expertise to develop. Often the development of a DES must be coded in a high level language rather than using an off the shelf package, requiring computer programming skills. Karnon and Brown (1998) state

> *'DES increases the demand for time and finance. Time refers to the time required to develop the model, rather than running time, which is limited to the speed of modern computers'.*

They developed Markov process and DES models for breast cancer. They found that

> *'the final analysis of the two models took one hour and three days for the Markov process and simulation model. However the time to analyse not only includes the final correct experimentation with the models but the whole process of verification and validation which required significantly more time than the final experimentation phase (weeks in the case of the DES model, days for the Markov process)'.*

Barton et al. (2004) also concludes that the running time of the DES will be longer than for the Markov models because the modeller will need to run many replications of the model to ensure statistical significance in the results.

On the basis of the literature reviewed in this section it is concluded:

A3) DES models are more difficult and take longer to develop than Markov and decision trees.

4.3.3 Data requirements

Robinson (2003) provides a good overview of simulation modelling. He comments

> '*most simulations require a significant amount of data. This is not always immediately available and where it is much analysis may be required to put it in a form suitable for the simulation*'.

Davies et al. (2003) agrees, stating,

> '*in general, a simpler model requires more aggregated data and is thus easier to populate and use, but it must on the other hand, make more extensive assumptions about how the system works*'.

On the basis of the literature reviewed in this section it is concluded:

A4) DES requires more data than other models.

4.3.4 The use of time in models

Sonnenberg et al. (1994) suggest that the model should

> *'reflect the time dependence of events being modelled'*.

Decision trees are most suitable for modelling scenarios where events occur over a short time period or do not occur more than once (Karnon and Brown 1998; Sonnenberg et al. 1994) or evaluations which use an intermediate outcome measure (Karnon and Brown 1998). Markov process models allow longer time periods to be modelled, in which risk of events is continuous, and the timing of the events are uncertain (Sonnenberg and Beck 1993).

The following hypotheses are presented based on the modelling literature. In chapter 5, the use of decision trees, Markov and simulation models is investigated in more detail and the following hypotheses are examined:

H1) If the system modelled involves time related transitions between health states, DES will most accurately model these transitions.

H2) If short term interventions are modelled, and this intervention happens only once in a patient's lifetime decision trees would be an appropriate modelling technique.

H3) If short term interventions are modelled, and this intervention happens more than once in a patient's lifetime, decision trees will underestimate the total costs and health benefits incurred.

H4) Decision trees are an inappropriate choice of modelling technique for long term or chronic interventions.

4.3.5 Complex and dynamic systems

Sonnenberg et al. (1994) recommend the use of simulation for models where the system is too complex for a Markov model, for example

> '*where the action of one patient affects another,* or *in problems where specific resource 'bottlenecks' may exist in the treatment of a disease'.*

Karnon and Brown (1998) states that

> '*the biggest advantage of DES is that it allows more complex and dynamic systems to be modelled, as well as permitting experimentation that might not be feasible otherwise, or that can not be predicted'.*

In addition, simulation represents a stochastic system and can thus reflect the effects of variability in demand and provision (Davies et al. 2003). These views are summarised by Robinson (2003) who states

> '*because it is difficult to predict the performance of systems that are subject to any one of variability, interconnectedness and complexity, it is difficult, if not impossible, to predict the performance of operations systems that are potentially subject to all three. Simulation models, however are able*

explicitly to represent the variability, interconnectedness and complexity of a system'.

Thus simulation is ideally suited to model more complex and dynamic systems. Some of the features of these complex and dynamic systems are discussed in more detail.

4.3.6 Interconnectedness

Robinson (2003) describes an interconnected system as one in which components of the system affect one another, with a change in one part of the system forcing an often unforeseen change in another part. In a health care system, there are often situations where an individual patient will affect other patients. For example, patients may compete for scarce resources or they may infect other patients with a disease.

Davies (1985) reviewed models describing treatment for kidney patients within renal units. She concluded that a major failing of the Markov and deterministic models were that they were unable to reflect the resource use of the system. In particular they could not constrain resource availability or model in detail the varying extent to which resources are used during different stages of a patient's treatment. She concluded that only discrete event simulation was able to include all the important elements of the system and so be useful for health planners.

DES has been widely used in manufacturing, health care and other industries because of its ability to model queues and the use of resources within a system. For example Jun et al. (1999) review the use of DES in health care clinics where it has been used for patient scheduling and admissions, patient routing and flow schemes, scheduling and availability of resources. Davies and Davies (1994) concludes that

'DES is particularly suitable for problems at an operational level where the use of resources is dependent on decisions about individuals'.

Barton et al. (2004) considered the independence of individuals within health care models. They considered this issue to be fundamental in the choice of modelling technique. They concluded that

> *'in cases where there is a significant interaction between individuals and a need to work at an individual level, a DES approach is the only way to represent the system adequately'.*

On the basis of the review of the literature the following hypothesis is presented which is examined in chapters 5 and 9:

H5) For dynamic systems which involve constraints or where patients compete for resources, DES is the most appropriate technique.

4.3.7 Proliferation of states

As mentioned in section 2.3.2, the Markovian assumption forces the creation of extra states within the Markov model in order to model distinct properties or characteristics of the cohort. For more complex systems, this may involve a huge number of states.

Weinstein et al. developed a state transition model for prevention and treatment of coronary heart disease. The Coronary Heart Disease Policy model, describes coronary heart disease in a population according to their physical and clinical characteristics. The population is stratified into the following categories: 50 ages, 2 sexes, 2 smoking statuses, 3 blood pressure levels, 3 cholesterol levels, 3 relative weights. Thus the model is stratified into a total of 5400 sub groups. The authors comment that the main problem of their model is dimensionality.

> *'Constraints on computing time and costs forced us to restrict the number of risk factors and disease history states and to make numerous independence assumptions. We are currently struggling with the issue of how to incorporate coronary angioplasty into the model without doubling the size of the disease history model'.*

DES is ideal for modelling complex systems of this type as it is able to model individuals who carry an unlimited number of physical and clinical attributes with them. For example a similar model to Weinstein was developed for coronary heart disease prevention by Babad et al. (2002). It consisted of a population described in terms of sex, smoking (3 categories), and a continuous range of age, blood pressure and cholesterol.

As a comparison to Weinstein, suppose that a state transition model modelled the continuous variables to the nearest whole number. Then in order to have a similar accuracy as the simulation model the following categories are needed: Sex (2), age (60), smoking (3), blood pressure (140), cholesterol (12), which consists of over 600,000 sub groups! The prevention model was linked to a treatment model (Cooper et al. 2002) which consisted of a further 60 sub categories.

On the basis of the review of the literature the following hypothesis is presented which is examined in chapter 9:

H6) For complex systems where the Markov assumption forces the creation or proliferation of states, DES should be considered.

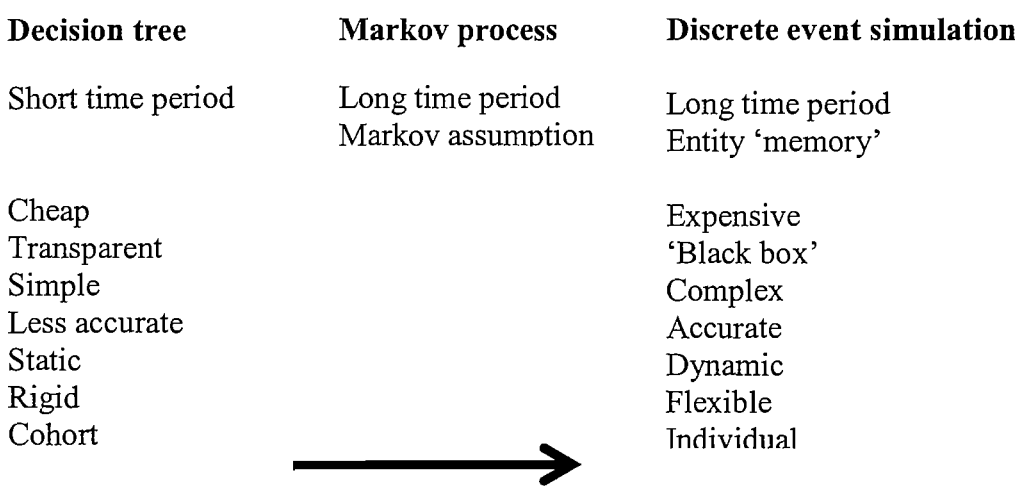

Figure 4.4.1 Differences between the models

4.4 Discussion

In the preceding sections the major strengths and weaknesses of the model techniques have been outlined. These are represented in Figure 4.4.1.

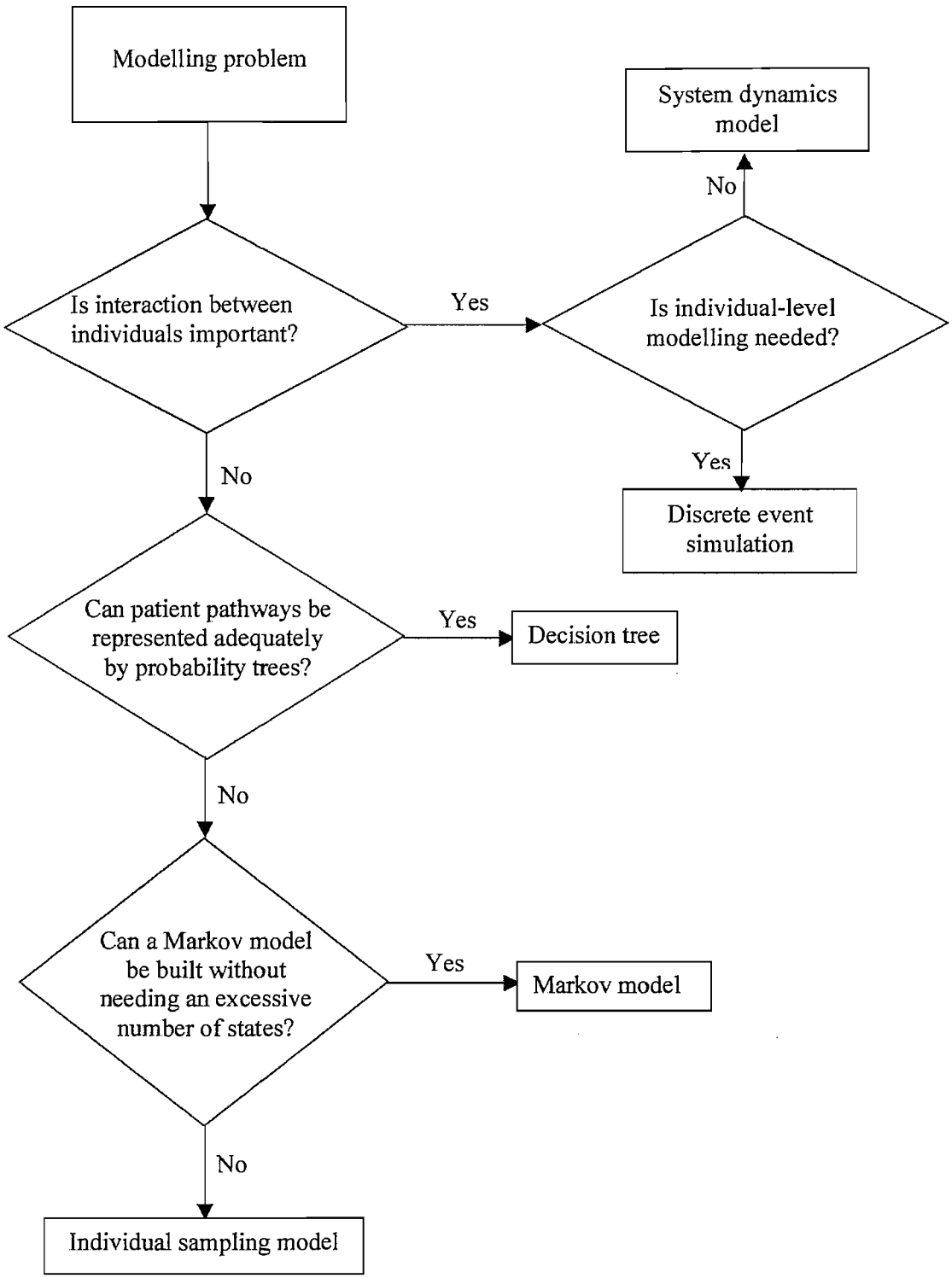

Figure 4.4.2 Selecting an appropriate model type (Barton et al. 2004)

Barton et al. (2004) presented a guide to the choice of the model, Figure 4.4.2. The Figure distinguishes between system dynamics (SD), discrete event simulation, decision

tree, Markov model and individual sampling model. System dynamics models have been described elsewhere (Lane et al. 2000; Dangerfield 1999). Barton et al. (2004) define an individual sampling model as a model

> '*in which the ability to track individuals is an essential part of the model structure, but in which only one individual is modelled at a time'.*

This definition includes the modelling of discrete event simulation or Monte Carlo simulation.

They considered only cohort models and stated that,

> '*the key initial consideration is whether the individuals in the model may be regarded as independent. Where interaction is not thought to be an important issue then the choice is between decision trees, Markov models or individual sampling models. Where interaction is a significant issue in modelling, methods such as DES and SD are required.*'

Based on the review of the literature the most appropriate model to be used is shown in Table 4.4.1. The modeller will need to make a judgement on the complexity of the model, in terms of the number of different states to be included, the significance of interaction between individuals and the necessity to model queues and constraints on the system. If the model is sufficiently complex that the Markov assumption forces the proliferation of states DES should be considered. It is concluded that there is some threshold level above which a DES model becomes the preferred choice and this threshold is examined in more detail in subsequent chapters.

Table 4.4.1 Guidelines for model choice

	Simple		**Complex**
	Acute intervention	**Chronic intervention**	
Population	Markov model	Markov model	DES
Cohort	Decision tree	Markov model	DES

4.4.1 Assumptions and Hypotheses

As part of this chapter on modelling methodology, assumptions and hypotheses concerning the modelling techniques characteristics are outlined as shown below. The assumptions have been concluded from a review of the literature as reported in this chapter and chapter 2. The hypotheses are examined in more detail in subsequent chapters.

A1) A population analysis provides a more comprehensive summary of the value of the intervention for the health care planner than a cohort analysis.

A2) The cost and health benefit outcomes of an intervention are as important an output as cost effectiveness.

A3) DES models are more difficult and take longer to develop than Markov and decision trees.

A4) DES requires more data than other models

H1) If a short term intervention is modelled, and this intervention happens only once in a patient's lifetime decision trees would be an appropriate modelling technique.

H2) If a short term intervention is modelled, and this intervention happens more than once in a patient's lifetime, decision trees will underestimate the total costs and health benefits incurred.

H3) If the system modelled involves time related transitions between health states, DES will most accurately model these transitions.

H4) Decision trees are an inappropriate choice of modelling technique for long term or chronic interventions.

H5) For dynamic systems which involve constraints or where patients compete for resources, DES is the more appropriate technique.

H6) For complex systems where the Markov assumption forces the creation or proliferation of states, DES should be considered.

4.5 Conclusion

In the preceding sections the major strengths and weaknesses of the model techniques have been outlined based on the modelling literature. Based on this information, a series of assumptions and hypotheses concerning the model techniques characteristics have been developed. These hypotheses will be explored in subsequent chapters.

According to the review of the modelling literature, the modeller should strive for simplicity and transparency. The choice of the preferred model will depend on the likely ease and speed of development, the complexity of the model in terms of the number of states, and the interconnectedness of the system. The modeller will need to judge whether interactions between individuals is a significant issue in the health care system and whether queuing for resources and resource constraints are relevant to the research question. Finally, the modeller will need to judge whether the preferred modelling techniques will be most acceptable to the users of the model.

Chapter 5

Comparing Health Care Modelling Techniques: Simple experimental models

Abstract

In this chapter the choice of modelling technique is explored through the construction of simple models. In particular the hypotheses set out in the previous chapter are investigated. Simple decision tree, Markov and simulation models are constructed for short term and long term interventions. The results are compared and the hypotheses are tested empirically. The models use hypothetical data to make the comparison between the models easier to interpret.

It is concluded that for short term interventions, where the intervention happens more than once in a patient's lifetime, decision trees will underestimate the total costs and health benefits incurred compared to the other modelling techniques. When modelled using the same data and assumptions, the Markov and simulation models give similar results which converge as the cycle time of the Markov model decreases. It is shown that the cohort and population-based approaches will yield different results and the population-based approach will give a worse cost effective ratio compared to the cohort-based approach. The appropriate choice of time horizon for the model is critical to the model results and conclusions.

Chapter 5 Comparing Health Care Modelling Techniques: Simple experimental models

5.1 Introduction

In this chapter the choice of modelling technique is explored through the construction of simple models which use hypothetical data. The use of these simple models facilitates interpreting the results from the different modelling methodologies compared with using more realistic models because you can fix all the parameters in an illustrative model and more complex models may have several underlying processes happening. Using these simple models, the hypotheses in the previous chapter are investigated. The conclusions from this chapter will be verified with more complicated and realistic models in chapters 7 through 9. Simple decision tree, Markov and simulation models are constructed for short term and long term interventions. Population and cohort based approaches are discussed. Finally resource-constrained models are investigated.

Unless indicated otherwise, the results for the models are shown in terms of cost (£), effectiveness (years of life saved) and cost effectiveness (incremental cost effectiveness ratio, ICER, £/life years saved). The incremental cost effectiveness ratio is shown as the difference in cost between the intervention scenario and baseline divided by the difference in effectiveness between the intervention scenario and baseline. The model results are compared by assessing whether the 'error' between the results is within an acceptable range.

5.2 Short term interventions: all models

In this section the decision tree, Markov and simulation models are compared for short term interventions. The simple model is in a similar format to the ambulance and thrombolysis model which is developed later in chapter 7.

Individuals are at risk from an unspecified hypothetical disease. Those who have an acute event of this disease have a risk of dying from it. If they survive they will have a chance of further events in the future. They can also die from non related causes. A new intervention is assessed in the treatment scenario which improves their chances of surviving the disease event.

The baseline data used for the simple models is shown in Table 5.2.1. The simple models use an age dependent distribution for the annual probability of an event chosen arbitrarily to be p(event) = $e^{-4.586+0.03x}$, where x is the age of the individual. As is often the case in health care examples, it assumes that older patients are at a greater risk of an event than younger patients and this risk increases exponentially with age. The probability of death from this event is taken to be 0.3 for all ages. The probability of death from other causes is shown in Table 6.4.3. The data used for the treatment scenario is shown in Table 5.2.2. The only change is a reduction in the probability of dying from an event with a cost of £150 for each intervention.

Table 5.2.1 Baseline data used for annual probability of event

Age (years)	**40**	**50**	**60**	**70**	**80**
Annual probability of event ($e^{-4.586+0.03x}$)	0.034	0.046	0.062	0.083	0.112
Probability of dying from event	0.3	0.3	0.3	0.3	0.3
Cost of intervention (£)			£0		

Table 5.2.2 Treatment scenario data used for annual probability of event

Age (years)	**40**	**50**	**60**	**70**	**80**
Annual probability of event ($e^{-4.586+0.03x}$)	0.034	0.046	0.062	0.083	0.112
Probability of dying from event	0.25	0.25	0.25	0.25	0.25
Cost of intervention (£)			£150		

Figures 5.2.1-3 show the decision tree, Markov and simulation models for the simple example. The modelling methodology for these techniques is described in more detail in section 2.3.1-2.3.3.

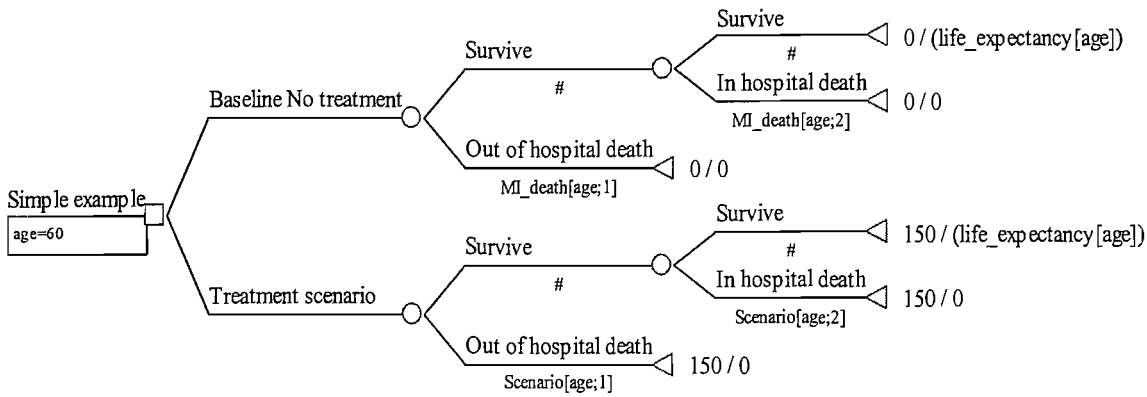

Figure 5.2.1 Decision tree model of short term intervention

The decision tree model is shown in Figure 5.2.1. It uses rewards at the terminal nodes for the cost and life expectancy. The first value is the cost and the second value is the life expectancy which is 0 for those patients that die and life_expectancy[age] for event survivors. This reward is dependent on the starting age of the cohort. These rewards represent the survival time for an individual who had survived the disease event. The parameters Death[age] and Scenario[age] are the probability of dying from the event for the baseline and treatment scenarios which are related to the age of the individual at that time.

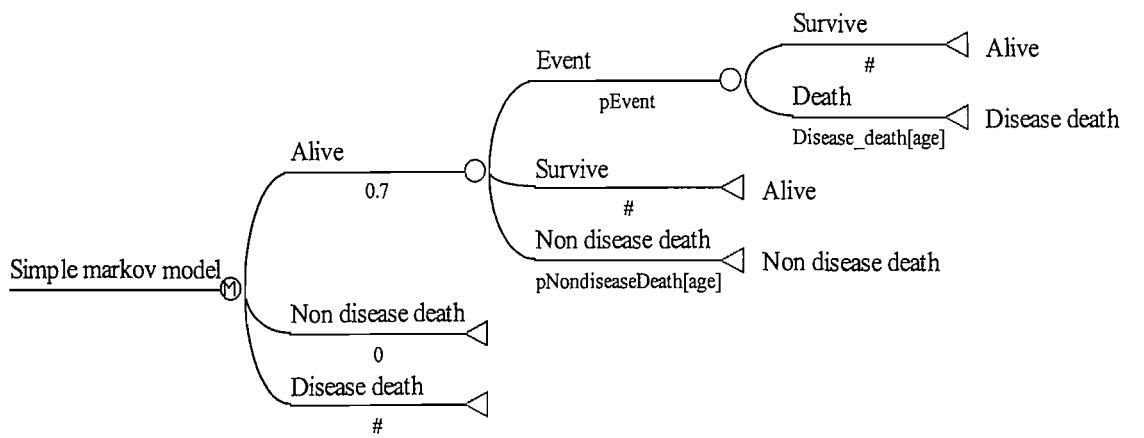

Figure 5.2.2 Markov model of short term intervention

The baseline scenario for the Markov model is shown in Treeage notation in Figure 5.2.2. It consists of three states: *Alive, Non Disease death and Disease death* where *Non Disease death* and *Disease death* are absorbing states. A cohort of individuals is run

with a cycle length of one year until they have all died. The treatment scenario is similar to this but with different values for the Disease_death[age] parameters.

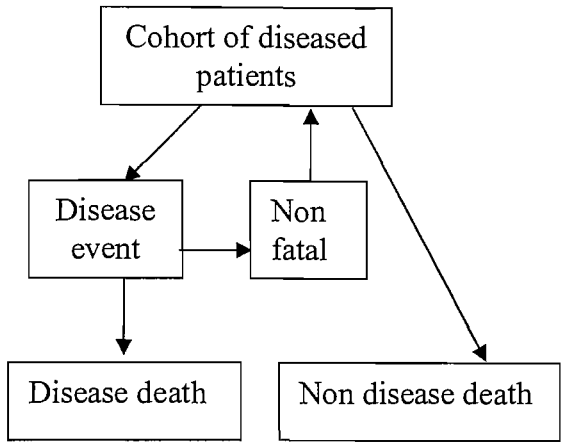

Figure 5.2.3 Simulation model of short term intervention

The simulation samples times to non disease death and acute disease event for each individual in the cohort. For each individual, whichever event happens first will be executed, ie either they will have a disease event or die of non disease cause. If they die, they will have no further events. If they have an event and survive it, a new time will be sampled for their next event. The time to the next disease event is sampled from a Gompertz distribution (Appendix V). The time to the next non disease event is sampled from a cumulative probability distribution of the non disease probability using the inverse transform method.

The simulation models in this thesis are run for enough iterations so that there is sufficient confidence in the accuracy of the output data. The confidence in the accuracy of the output data is calculated using the confidence interval method (Robinson 2004) with a significance level of 95%. In this case, confidence intervals are calculated that give a 95% probability that the value of the true mean (obtained if the model is run for an infinite period) lies within that confidence interval. In this thesis we estimated that a confidence interval that deviated by less than 1% from the mean was acceptable. Often the models are run for more iterations than was necessary to achieve this deviation for even greater accuracy. Finally the model results were checked by running one of the age bands with a much larger numbers of iterations.

The simulation results for this example had confidence intervals that deviated by less than 1% of the mean with 50 iterations and a cohort of 1000 individuals for all age bands. The deviation from the mean varied from 0.8% for the 40 year age band to 1% for the 80 year age band. For even more accuracy, the simulation was run with a cohort of 1000 individuals for 100 iterations.

For comparison purposes it is assumed that the start point in the models is immediately before the acute disease event. However, practically the Markov and simulation model start immediately after the acute event with the proportion who survive the acute event (ie who start in the model).

As mentioned above, the life expectancy rewards at the terminal nodes of the decision tree are the survival times for individuals who have survived the event. These can either be calculated from the Markov or the simulation models by having 100% of the cohort in the Alive state at the start of the run. Table 5.2.3 shows the life expectancy for all survivors of an event from the Markov and simulation models. The life expectancies for the simulation model are slightly longer than those for the Markov model. The reasons for the differences between these life expectancies are discussed later.

Table 5.2.3 Life expectancy (years) for individuals who survive disease event

Age (years)	**40**	**50**	**60**	**70**	**80**
Markov (M)	29.35	22.85	16.82	11.42	7
Simulation (S)	29.35	22.90	16.91	11.53	7.13
Difference in LE (S – M)	0.00	+0.05	+0.09	+0.11	+0.13
'Error' between model results, %	0	+0.2	+0.5	+1.0	+1.8

Table 5.2.3 shows the difference in the results between the simulation and the Markov models and this difference is shown as a percentage 'error'. The error ranges from 0% for the 40 year old cohort to 1.8% for the 80 year old cohort. Over all the age bands there is a mean error of 0.7%. In this dissertation the mean error is used as a measure of the difference between the models' results. In Table 5.2.3 the error was positive for each

of the age cohorts. In the cases where there are both positive and negative errors the mean absolute error is calculated.

Clearly the results from the two models are not identical but are they similar enough for us to accept either set of results? On the other hand are the results significantly different so that we would choose one set of results in preference to the other? In other disciplines such as scientific experimentation, statistical tests such as t-tests are often used to test hypotheses these results. However in these experiments the samples must be independent random samples. Unfortunately the model run results do not meet these requirements and so statistical tests cannot be used. Consequently the discrepancy between model results and its significance must be answered subjectively within the context of modelling for health care interventions.

Generally there is a large potential error involved with modelling health care interventions. Often the data are unreliable or not available and many assumptions have to be made to fit the model. Furthermore many more assumptions need to be made when predicting future treatments, resource use and patients prognoses. As seen later in this chapter the current tendency to use cohort based models rather than population based models may introduce significant errors into the model results. Finally the use of the time horizon is critical to the results and conclusions. If too short or long a time horizon is adopted, the cost effectiveness results may be significantly erroneous.

The following descriptive ranges of model error have been developed as an indication of the extent of the discrepancy between the model results and the consequence of this difference. These ranges are useful because they will be used for all the comparative analyses in this thesis as the basis of deciding how significant the differences in model results are. These ranges are based on the idea of confidence intervals, for example it is possible to choose to accept different confidence intervals (eg 95%, 99%) and the choice of confidence interval may vary between researchers and experiments.

In this context, the following is recommended for the comparison of the model results for life expectancy and cost:

Error < 1 % Results not significantly different

Error < 5% Results different but acceptable error between results so that conclusions from results not materially affected by error

Error > 5% Results significantly different

The following is recommended for the comparison of the model results for cost effectiveness ratio:

Error < 2 % Results not significantly different

Error < 10% Results different but acceptable error between results so that conclusions from results not materially affected by error

Error > 10% Results significantly different

Note that in the above recommendations we refer to results being significantly different but this is not necessarily statistically significantly different according to a statistical test but rather as an indication of how different the results are. A larger error is accepted for cost and effectiveness than for the cost effectiveness ratio for two reasons. Firstly cost and effectiveness are primary outcomes whereas cost effectiveness is a secondary outcome. Secondly cost effectiveness is a less tangible outcome than cost and effectiveness. As discussed in section 3.1.2, the threshold bands for accepting or rejecting treatments on the basis of their cost effectiveness ratio are very wide and often not made public by decision making bodies such as NICE.

Each of the models is run with the baseline and treatment scenario for all different age cohorts. The decision tree model is run with both the life expectancies shown in Table 5.2.3, as calculated by the Markov and simulation models. The results in Table 5.2.4-5.2.7 show the cost and health benefits associated with each of the runs. The increased cost and health benefits for the treatment scenario are calculated and then the cost effectiveness is calculated.

Table 5.2.4 Results from the Markov model for baseline and treatment scenario runs

Age (years)	40	50	60	70	80
Life expectancy Baseline	20.55	15.99	11.77	7.99	4.9
Life expectancy Treatment	23.17	18.02	13.237	8.95	5.457
Increase in LE	2.62	2.03	1.467	0.96	0.557
Cost	376.6	357.6	332.3	300.4	265.4
ICER	144	176	227	313	476

Table 5.2.5 Results from the simulation model for baseline and treatment scenario runs

Age (years)	40	50	60	70	80
Life expectancy Baseline	20.51	15.99	11.81	8.05	4.98
Life expectancy Treatment	23.13	18.04	13.28	9.02	5.53
Increase in LE	2.63	2.05	1.47	0.97	0.55
Cost	375.4	356.1	330.2	297.8	261.4
ICER	143	173	225	307	471

Considering Table 5.2.4 and 5.2.5, the results from the Markov and simulation are not significantly different. The mean absolute error between the Markov and simulation model results for increase in life expectancy, cost and ICER are 0.6%, 0.8% and 1.3% respectively. The differences between these runs are considered in more detail in the next section 5.2.1.

Table 5.2.6 Results from the decision tree model for baseline and treatment scenario runs (with life expectancies from Markov model)

Age (years)	40	50	60	70	80
Life expectancy Baseline	20.55	15.99	11.77	7.99	4.9
Life expectancy Treatment	22.02	17.14	12.62	8.57	5.25
Increase in LE	1.47	1.15	0.85	0.57	0.35
Cost	150	150	150	150	150
ICER	102	131	178	261	429

Table 5.2.7 Results from the decision tree model for baseline and treatment scenario runs (with life expectancies from simulation model)

Age (years)	40	50	60	70	80
Life expectancy Baseline	20.55	16.03	11.837	8.07	4.99
Life expectancy Treatment	22.02	17.18	12.68	8.65	5.35
Increase in LE	1.47	1.15	0.85	0.58	0.36
Cost	150	150	150	150	150
ICER	102	131	178	260	420

Furthermore the results from each of the decision tree runs with the life expectancies estimated from the Markov and simulation models are also similar. However, there is a large difference between the results from the decision tree and the other model techniques. The results from the decision tree model are lower for cost, benefit and cost effectiveness. The mean absolute difference between the simulation model and the decision tree results for increase in life expectancy, cost and ICER are 42%, 53% and 20% respectively. These results are explored in more detail in section 5.3.

5.2.1 Markov versus simulation model

In this section the following hypothesis is considered:

H1) If the system modelled involves time related transitions between health states, DES will most accurately model these transitions.

5.2.1.1 Cycle length

The reasons for the differences are due to the way that each of the models deals with times to event. In particular, only one event is able to happen in the Markov model in any cycle whereas in the simulation model, more than one event may happen in this time period. Thus it is expected that the results from the Markov model will converge to those of the simulation model by reducing the cycle length. This is shown to be the case in Table 5.2.8 which shows the results for a further run of the Markov model with a

cycle length of 6 months. This shows that simulation can be considered the more accurate technique for modelling time related transitions between states.

Table 5.2.8 Life expectancy with all probabilities and each probability separately for the Markov model

Age (years)	40	50	60	70	80
Markov (one year cycle)	20.55	15.99	11.77	7.99	4.9
Markov (half year cycle)	20.52	15.98	11.78	8.02	4.96
Simulation	20.51	15.99	11.81	8.05	4.98

5.2.1.2 'Error' between Markov and simulation model runs

The Markov and simulation models predict events in a slightly different manner. The events in the Markov model will be independent but those from the simulation model will not be.

Consider two fatal events A and B. The Markov model will independently assign a proportion of the cohort to have event A and a further proportion to have event B. On the other hand the simulation model will assign times to the events A and B. In this case, whichever event happens first will occur and the other will not. Thus the occurrence of either event is dependent on whether the other event already happened. Furthermore there will be a difference between the event rates for the two models which is equivalent to the probability of both events occurring. This is demonstrated in the following example.

The probability of fatal events A and B in one cycle are $p(A) = P(B) = 0.05$.
Now $p(A \cap B) = 0.05 * 0.05 = 0.0025$.

Markov model

Events: A = 0.05; B = 0.05. Total Events = 0.1.

Simulation model

When both events are scheduled in the same cycle, ie p(A ∩B) = 0.0025, only the first is scheduled.
Now half the time, A happens first, half the time B happens first.

Events: A = 0.05 – (0.0025/2) = 0.04875; B = 0.04875. Total events = 0.0975.

The difference between the models is 2.5% (ie equal to p(A ∩B).

This simple example demonstrates that there will be a difference between the simulation and Markov models when using the same data. In fact the error occurs because the data has not been parameterised correctly for the simulation model. The data should be adjusted to take into account the dependency of the events. In practice this is often ignored as it is non trivial. In this case, the Markov model will predict more fatal events than the simulation and hence a lower life expectancy. The differences between the models will increase as the event probabilities increase.

5.2.1.3 Discussion

It has been shown in this section that the Markov model gives a good approximation to the simulation model for life expectancy, cost and cost effectiveness for the short term interventions, although these outcomes are underestimated by the decision tree model. Furthermore, by running the Markov model with cycle lengths of six months instead of a year, the Markov model gave estimates for life expectancy within 0.5% of those for the simulation model for all ages. It has been demonstrated that the simulation will most accurately model time related transitions between health states (Hypothesis 1).

5.3 Short term interventions: The decision tree model

In this section the following hypotheses are considered:

H2) If a short term intervention is modelled, and this intervention happens only once in a patient's lifetime decision trees would be an appropriate modelling technique.

H3) If a short term intervention is modelled, and this intervention happens more than once in a patient's lifetime, decision trees will underestimate the total costs and health benefits incurred.

In this section, the decision tree model is examined in more detail. Simplistic data are used as shown in Table 5.3.1 and 5.3.2 and the results for the decision tree are compared to that from a Markov model. The data for these models are similar to shown in Table 5.2.1, with the exception that the annual probability of an event increases linearly with the age of the individual.

Table 5.3.1 Baseline data used for annual probability of event

Age (years)	**40**	**50**	**60**	**70**	**80**
Annual probability of event	0.050	0.100	0.150	0.200	0.250
Probability of dying from event	0.3	0.3	0.3	0.3	0.3
Cost of intervention (£)			0		

Table 5.3.2 Treatment scenario data used for annual probability of event

Age (years)	**40**	**50**	**60**	**70**	**80**
Annual probability of event	0.050	0.100	0.150	0.200	0.250
Probability of dying from event	0.25	0.25	0.25	0.25	0.25
Cost of intervention (£)			£150		

The decision tree model (Figure 5.2.1) uses rewards at the terminal nodes of the life expectancy of event survivors and these are taken from the life expectancies calculated by the Markov model. These rewards represent the survival time for an individual who had survived the disease event (Table 5.3.3).

Table 5.3.3 Life expectancy (years) for all who survive disease event

Age	Life expectancy (years)
40	21.73
50	16.12
60	11.89
70	8.42
80	5.51

5.3.1 Single intervention

In the first experiment, the case where the intervention can happen only once is considered, for example if an individual has an appendix operation. In this case, the Markov and the decision tree models are the same and the results will be the same.

Table 5.3.4 Cohort life expectancy, increase in life expectancy and cost, and cost effectiveness (ICER) for patients of different ages for the decision tree and Markov models

Age (years)	40	50	60	70	80
Life expectancy Baseline	15.21	11.28	8.33	5.89	3.86
Life expectancy Treatment	16.30	12.09	8.92	6.31	4.13
Increase in LE	1.09	0.81	0.59	0.42	0.28
Cost	150	150	150	150	150
ICER	138	186	252	356	544

In the decision tree, a proportion of the cohort will survive the event. This proportion will have a life expectancy as predicted by the Markov model (see Table 5.3.3). In the Markov model, the starting proportion in the Alive state will be the survivors of the event and these survivors will also have a life expectancy as shown in Table 5.3.3. Thus, if short term interventions are modelled, and this intervention happens only once in a patient's lifetime decision trees would be an appropriate modelling technique.

5.3.2 Multiple interventions

The models are now run with no restriction on the number of interventions. This only affects the Markov model, since the decision tree can only model a single intervention. Table 5.3.5-5.3.7 shows the comparative results for the decision tree and Markov models for the baseline and treatment scenario.

Table 5.3.5 Life expectancy for patients of different ages for the decision tree (DT) and Markov (M) models

Age (years)	40	50	60	70	80
Baseline (DT)	15.21	11.28	8.33	5.89	3.86
Baseline (M)	15.21	11.28	8.33	5.89	3.86
Treatment (DT)	16.30	12.09	8.92	6.31	4.13
Treatment (M)	17.71	13.25	9.78	6.87	4.44

Table 5.3.6 Increase in life expectancy and cost for patients of different ages for the decision tree (DT) and Markov (M) models between the baseline and treatment scenario

Age (years)	40	50	60	70	80
Increase in LE (DT)	1.09	0.81	0.59	0.42	0.28
Increase in LE (M)	2.50	1.96	1.45	0.98	0.58
Increase in cost (DT)	150	150	150	150	150
Increase in cost (M)	492	477	448	403	346

Table 5.3.7 Cost effectiveness for the treatment scenario compared to the baseline for the decision tree (DT) and Markov (M) models

Age (years)	40	50	60	70	80
Decision tree	138	186	252	356	544
Markov	197	243	309	412	593

The baseline life expectancy for patients having an event is the same for the decision tree and the Markov model (Table 5.3.5). The increase in cost and life expectancy between the baseline and the treatment scenario is greater for the Markov model than the decision tree across all ages (Table 5.3.6). This happens because the decision tree only assessed one intervention compared to multiple interventions in the Markov model.

In this example, the cost of the intervention is independent of how old the patient is or how long it will be before they die. For this case, the cost effectiveness (ICER) of the intervention is lower for the decision tree model than the Markov for all ages (Table 5.3.7). The proportional difference in the ICER between the Markov model and the decision tree is greater in the cohorts with the youngest starting age. For example the ICER of the 40 year old cohort is 43% larger for the Markov model than the decision tree whereas the ICER of the 80 year old cohort is only 9% larger for the Markov model than the decision tree.

Table 5.3.8 Number of interventions for the treatment scenario run with cohorts of different ages

Age (years)	40	50	60	70	80
Decision tree	1.00	1.00	1.00	1.00	1.00
Markov	3.28	3.18	2.99	2.69	2.31

Table 5.3.9 Increase in life expectancy per intervention for the treatment scenario for the first intervention compared to subsequent interventions

Age (years)	40	50	60	70	80
1st intervention	1.09	0.81	0.59	0.42	0.28
Subsequent interventions	0.62	0.53	0.43	0.33	0.24

The reason for the lower cost effectiveness for the decision tree was then examined. Table 5.3.8 shows the number of interventions for the treatment scenario run for each of the models. Table 5.3.9 shows the relative benefit of the interventions for the first intervention compared to subsequent interventions. It shows that the increase in life expectancy for the first intervention is greater than for subsequent interventions. Clearly the benefit of the intervention is related to the patient's life span remaining. By definition, the initial intervention will always be before subsequent interventions and the patient will be younger at the time of this intervention. Thus the initial intervention will always have a larger increase in life expectancy than subsequent interventions. In this example, all interventions are assumed to cost the same and so as a subsequent intervention produces a smaller increase in life expectancy than the initial intervention, the ICER will always be lower for the decision tree. (This assumes that the cost effectiveness is positive.)

5.3.3 Discounting

The results presented in the preceding sections were undiscounted. The results are now discounted. In the case of the decision tree the intervention happens at the start of the run and so the costs of the intervention are undiscounted whilst the benefits of the intervention will be discounted. For the Markov model, the costs and benefits occur throughout the life of the cohort and so both the costs and benefits are discounted. Results from the discounting for the decision tree and Markov models are shown in Table 5.3.10-5.3.11 where costs and benefits are discounted at 3%.

Table 5.3.10 Discounted cost effectiveness (ICER) results from the Decision tree model for baseline and treatment scenario runs with benefits discounted at 3%

Age (years)	**40**	**50**	**60**	**70**	**80**
Increase in life expectancy	0.67	0.56	0.45	0.35	0.24
Increase in cost	150	150	150	150	150
ICER	223	267	330	433	622

Table 5.3.11 Discounted cost effectiveness (ICER) results from the Markov model for baseline and treatment scenario runs with costs and benefits discounted at 3%

Age (years)	40	50	60	70	80
Increase in life expectancy	1.42	1.25	1.02	0.75	0.49
Increase in cost	348.9	370.4	373.8	357.2	322.4
ICER	245	297	368	475	661

With the use of an equal discount rate of 3% for cost and benefits, the ICER is worse (or higher) for the two models in each of the age groups compared to the undiscounted case. As before the ICER is lower for the decision tree than for the Markov model but in this case the ICER results between the models are less variable than before especially for the younger age cohorts. The difference between the ICER results from the Markov model and decision tree varied by 10% for 40 year old cohort and 6% for 80.year old cohort. As mentioned above in section 5.2, the modeller will have to decide if this level of 'error' is acceptable but we consider in this dissertation that it is acceptable and that this error is unlikely to significantly alter the conclusion from the results.

5.3.4 Sensitivity analysis

In this section sensitivity analyses are performed and the conclusions from sections 5.3 – 5.3.3 are examined by looking at examples with higher and lower event rates. Thus in the higher event rate example, there will be more interventions in the cohort than in the example above. Similarly in the lower event rate example, there will be fewer interventions in the cohort. The data used for these examples are shown in Table 5.3.12 and 5.3.13.

In any year the probability of experiencing a disease event and dying from that event will be the product of the annual probability of the event itself and the probability of dying from it. In both of the sensitivity analyses this probability will be as shown in Table 5.3.1 and 5.3.2. In the sensitivity analysis with more interventions, the annual probability of an event is doubled (Table 5.3.12). Conversely, in the sensitivity analysis with fewer interventions, the annual probability of an event is halved (Table 5.3.13).

Table 5.3.12 Baseline and treatment scenario data used for more interventions

Age (years)	40	50	60	70	80
Annual probability of event	0.1	0.2	0.3	0.4	0.5
Probability of dying from event (baseline)	0.15	0.15	0.15	0.15	0.15
Probability of dying from event (treatment)	0.125	0.125	0.125	0.125	0.125

Table 5.3.13 Baseline and treatment scenario data used for fewer interventions

Age (years)	40	50	60	70	80
Annual probability of event	0.025	0.05	0.075	0.100	0.125
Probability of dying from event (baseline)	0.6	0.6	0.6	0.6	0.6
Probability of dying from event (treatment)	0.5	0.5	0.5	0.5	0.5

In these examples the differences between the results from the two models are increased for the run with more interventions. This is shown in Table 5.3.14 for the 60 year old cohort.

Table 5.3.14 Percentage change in cost and life years saved for the sensitivity analyses and the original run for the Markov model compared to the decision tree for the 60 year old cohort

%	More interventions	Original	Fewer interventions
Life years saved	334	144	50
Cost	463	200	66

Figure 5.3.2 compares the percentage increase in cost effectiveness for different event rates for the Markov model compared to the decision tree. For the higher event rate, the difference is greatest between the Markov model and the decision tree model. As seen in previous sections there is a greater difference between the models for the younger age groups, but it was shown in section 5.3.3 that if the results are discounted, the differences between the models will be similar for all age groups.

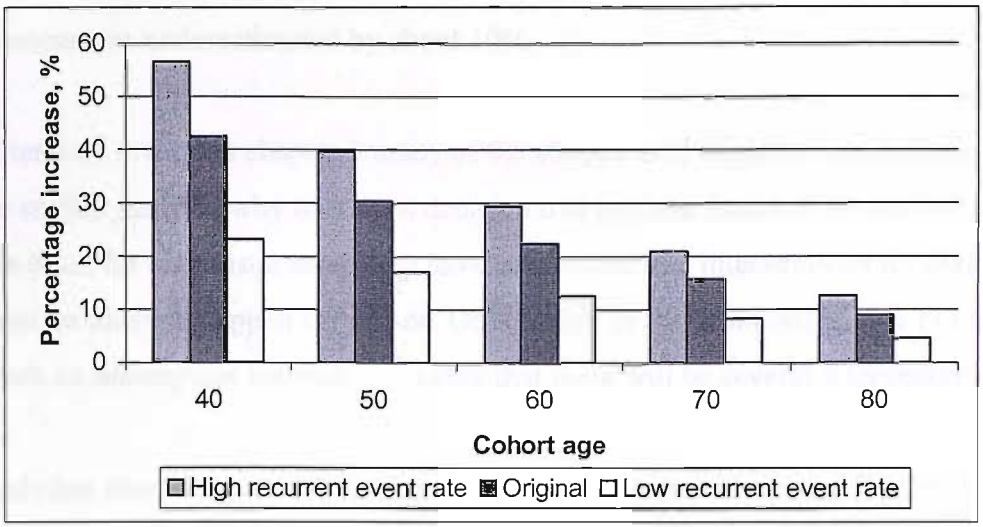

Figure 5.3.2 Comparison of undiscounted cost effectiveness for different event rates; proportional increase of Markov model compared to decision tree

5.3.5 Discussion

In the preceding sections the use of models for short term interventions has been considered. It has been shown that:

H1) If the system modelled involves time related transitions between health states, DES will most accurately model these transitions.

H2) If short term interventions are modelled, and this intervention happens only once in a patient's lifetime decision trees would be an appropriate modelling technique.

H3) If short term interventions are modelled and this intervention happens more than once in a patient's lifetime, decision trees will underestimate the total costs and health benefits incurred.

It has also been shown that the decision tree models will underestimate the cost effectiveness and this underestimate will be exacerbated by more frequently occurring events. Furthermore if the probability of the event is related to age then there will be a bias such that the relative ICER underestimate is greatest in the younger age bands. However with equal discount rates, the relative difference in ICER for the decision tree

compared to the Markov model is similar for all age bands. For the example used, cost effectiveness was underestimated by about 10%.

In the literature review in chapter 3 many of the studies used decision tree models. None of these studies justified why they used decision tree models. Some of the studies, for example those for diagnostic tests, may have considered that interventions for diagnosis would not be likely to happen very often. Others such as for thrombolysis are not able to make such an assumption because it is likely that there will be several interventions.

This study has shown that the decision tree may underestimate the cost effectiveness compared to the Markov and simulation models. However, an underestimate as shown in our example is unlikely to materially affect the conclusions for the recommendation of the intervention or otherwise. This conclusion will be reviewed for a more realistic model of ambulance and thrombolysis response time in chapter 7.

5.4 Long term intervention models

In this section models for long term intervention are considered. A long term intervention is defined to be one which has a continued added benefit over a long time period, for example, a course of medication which may reduce the risk of serious health consequences for a particular disease over a long term horizon.

The simple models are in a similar format to the secondary prevention drug model which is developed in chapter 8. The models are similar to those used for short term intervention models and the models are represented by the same Figures 5.2.1-3. Individuals are at risk from a disease event and when they experience this event they have a risk of dying from it. If they survive, they will have a chance of a further event. The intervention reduces the chances of suffering an event. Individuals can also die from non related causes.

The simple model uses an age dependent distribution for the annual probability of an event, where $p(\text{event}) = e^{-4.586+0.03x}$, where x is the age of the individual. This

distribution is chosen as it is similar to that seen for long term MI survival, see section 6.5. It assumes that older patients are at a greater risk of an event than younger patients and this risk increases exponentially. The probability of death from this event is taken to be 0.3 for all ages. The probability of non disease death is taken from the Office of National Statistics (see section 6.4.3).

The treatment scenario uses a reduction in the probability of suffering an event of 25% with a cost of £300 per year per person for each intervention. The simulation models were run for 1000 individuals for 100 iterations.

As seen in Figure 5.2.1, it is not possible to use a decision tree model for long term interventions. In order to model this using a decision tree the life expectancy needs to be known for the group on the treatment compared to the group not on the treatment.

In Figure 5.2.1, the probability of dying from a disease event is the same for the treatment scenario and the baseline. Thus the difference between the baseline and treatment scenario is merely the estimate of life expectancies. Life expectancy[age] will be a function of the non disease death rate and the disease death rate. In the treatment scenario, there will be a different disease death rate but the non disease death rate will stay the same and so it will not be possible to estimate the overall life expectancy without using a Markov model or a simulation model. Thus it has been shown:

H4) Decision trees are an inappropriate choice of modelling technique for long term or chronic interventions.

The undiscounted and discounted results from each of the Markov and simulation model runs are shown in Table 5.4.1-5.4.4. As with the short term models, the simulation and Markov models give similar results. The life expectancies and ICERs are slightly higher for the simulation model than for the Markov model for each of the age groups. The mean absolute errors between the models for undiscounted treatment life expectancy, cost and ICER are 1%, 2.7% and 3.5% respectively. The mean absolute errors between the models for discounted life expectancy, cost and ICER are 0.6%, 4% and 2% respectively.

Table 5.4.1 Patient life years, cost and cost effectiveness (ICER) results from the Markov model for baseline and treatment scenario runs

Age (years)	40	50	60	70	80
Life expectancy Baseline	29.4	22.8	16.8	11.4	7.0
Life expectancy Treatment	31.7	24.7	18.1	12.2	7.4
Increase in LE	2.4	1.8	1.3	0.8	0.4
Cost	9515	7399	5428	3663	2226
ICER	4032	4080	4261	4637	5287

Table 5.4.2 Patient life years, cost and cost effectiveness (ICER) results from the simulation model for baseline and treatment scenario runs

Age (years)	40	50	60	70	80
Life expectancy Baseline	29.6	23.1	17.1	11.6	7.1
Life expectancy Treatment	31.9	24.8	18.3	12.4	7.5
Increase in LE	2.3	1.8	1.2	0.7	0.4
Cost	9418	7296	5332	3544	2105
ICER	4077	4169	4370	4855	5689

Table 5.4.3 Patient life years, cost and cost effectiveness (ICER) results from the Markov model for baseline and treatment scenario runs; results discounted at 3% for costs and benefits

Age (years)	40	50	60	70	80
Life expectancy Baseline	18.2	15.5	12.4	9.2	6.0
Life expectancy Treatment	19.3	16.4	13.2	9.7	6.4
Increase in LE	1.0	0.9	0.8	0.5	0.3
Cost	5775	4921	3952	2907	1909
ICER	5621	5320	5239	5415	5914

Table 5.4.4 Patient life years, cost and cost effectiveness (ICER) results from the simulation model for baseline and treatment scenario runs; results discounted at 3% for costs and benefits

Age (years)	40	50	60	70	80
Life expectancy Baseline	18.3	15.6	12.6	9.3	6.2
Life expectancy Treatment	19.3	16.5	13.3	9.6	6.4
Increase in LE	1.0	0.9	0.7	0.5	0.3
Cost	5649	4795	3832	2778	1782
ICER	5593	5362	5320	5592	6167

5.5 Cohort versus population approach

In the previous sections in this chapter, decision tree, Markov and simulation models have been compared using the cohort approach. In other words the models started with a homogeneous cohort and followed them until they all had died. In the population approach, this cohort is combined with an incident population, which join each year. The population is followed for a predefined time. The population approach is explained in more detail in section 2.2.6.

The same model is used as previously described in section 5.4. In this section only the simulation model is used. Initially the differences between the approaches were shown using the 60 year old cohort with the simulation model. Each of the models was run for 1000 individuals for 100 iterations. The population model was run for 100 years with an incident population of 60 each year.

Table 5.5.1 and 5.5.2 show the results for the cohort and population runs where the results are undiscounted and discounted at 3% for costs and benefits. The results from the two approaches are more meaningful in slightly different formats. The cohort run shows the life years saved and cost per individual who had the treatment. On the other hand the population run shows the life years saved and cost for the population. The population run results can be averaged across all individuals in the population to give the results per individual.

Table 5.5.1 and Table 5.5.2 show the increase in cost and life expectancy for individuals for the two approaches. The increase in costs and life expectancy for the population runs is less than for the cohort approach. This is because in the population runs there are still many individuals alive at the end of the run who have not received their full benefit from the intervention. Nevertheless the cost effectiveness (ICER) of the two approaches is similar. The ICER from the cohort approach is less than the population approach by 9% and 4.5% in the undiscounted and discounted cases respectively. Table 5.5.3 shows the life years saved and increase in cost for the population simulation.

Table 5.5.1 Results from the cohort simulation runs shown for each individual; discounted results are discounted at 3% for costs and benefits

	Increase in life expectancy	**Increase in cost**	**ICER**
Undiscounted	1.22	5332	4379
Discounted	0.72	3833	5320

Table 5.5.2 Results from the population simulation runs shown for each individual; discounted results are discounted at 3% for costs and benefits

	Increase in life expectancy	**Increase in cost**	**ICER**
Undiscounted	1.05	5054	4818
Discounted	0.3	1684	5569

Table 5.5.3 Results from the population simulation shown for each year; discounted results are discounted at 3% for costs and benefits

	Increase in life expectancy	**Increase in cost**	**ICER**
Undiscounted	73.5	354290	4818
Discounted	21.2	118028	5569

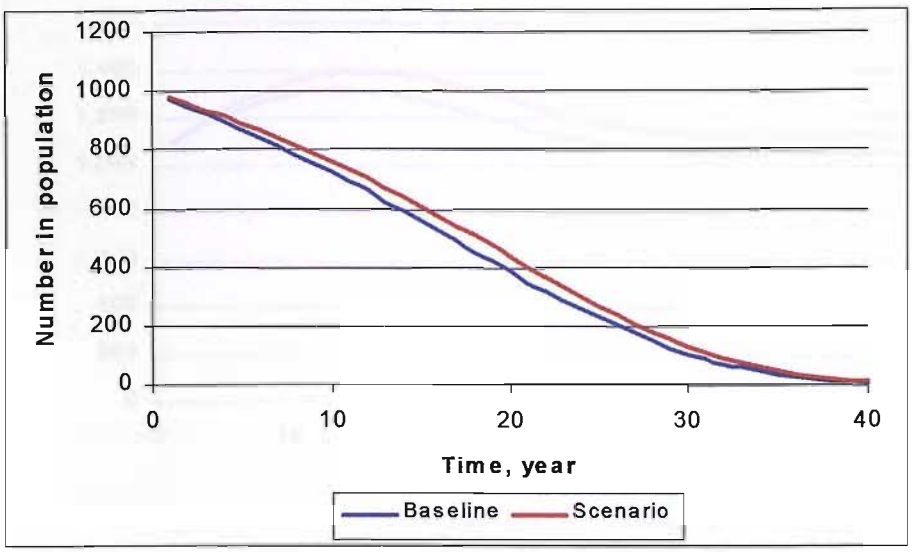

Figure 5.5.1 Population size over time for the cohort population

Figure 5.5.1 and Figure 5.5.2 show the size of the population over time for the cohort and population populations. The Figures are not directly comparable as in the cohort simulation the population all dies within 40 years whereas in the population simulation the population remains fairly static. However Figure 5.5.2 would be more useful to the health care planner as it shows the likely change in population over time, and shows that there is a long term benefit to the population. In contrast, the cohort population will be the same size after 40 years for the baseline and the treatment scenario ie zero. Over this time period the treatment scenario will always have a larger population alive than the baseline.

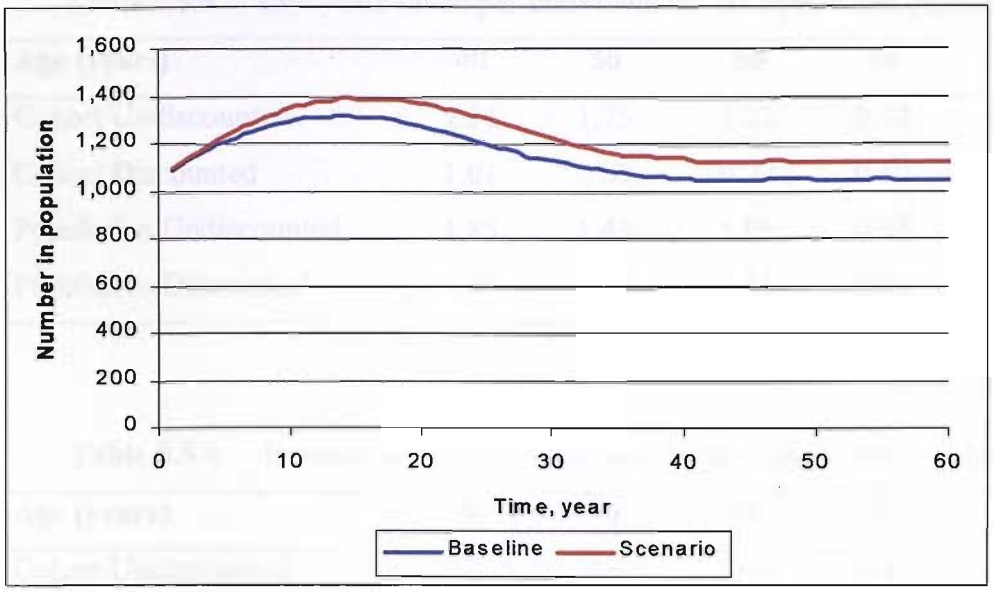

Figure 5.5.2 Population size over time for the population simulation

5.5.1 Comparing the cohort and population runs for all ages

The analysis in section 5.5 was now extended for all ages. Table 5.5.4 shows the number of patients who joined the population run each year. These numbers were chosen so that the population size remained fairly static for each age.

Table 5.5.4 Number of patients who joined the population run each year for different ages

Age	**40**	**50**	**60**	**70**	**80**
Patients	30	45	60	80	120

Table 5.5.5 and 5.5.6 show the life years saved per individual and the increase in cost for the cohort and population runs respectively for the discounted and undiscounted cases. For all runs, the life years saved per individual and the increase in cost is lower in the population runs than the cohort simulation. The relative difference between the outcomes for the two approaches is slightly higher for the cost than the life years saved.

Table 5.5.5 Life years saved per individual for the cohort and population runs

Age (years)	40	50	60	70	80
Cohort Undiscounted	2.31	1.75	1.22	0.73	0.38
Cohort Discounted	1.01	0.89	0.72	0.50	0.29
Population Undiscounted	1.85	1.43	1.05	0.68	0.36
Population Discounted	0.49	0.40	0.32	0.21	0.11

Table 5.5.6 Increase in cost per individual for the cohort and population runs

Age (years)	40	50	60	70	80
Cohort Undiscounted	9418	7296	5332	3544	2105
Cohort Discounted	5649	4795	3833	2778	1782
Population Undiscounted	8301	6629	5060	3567	2294
Population Discounted	2828	2201	1744	1196	764

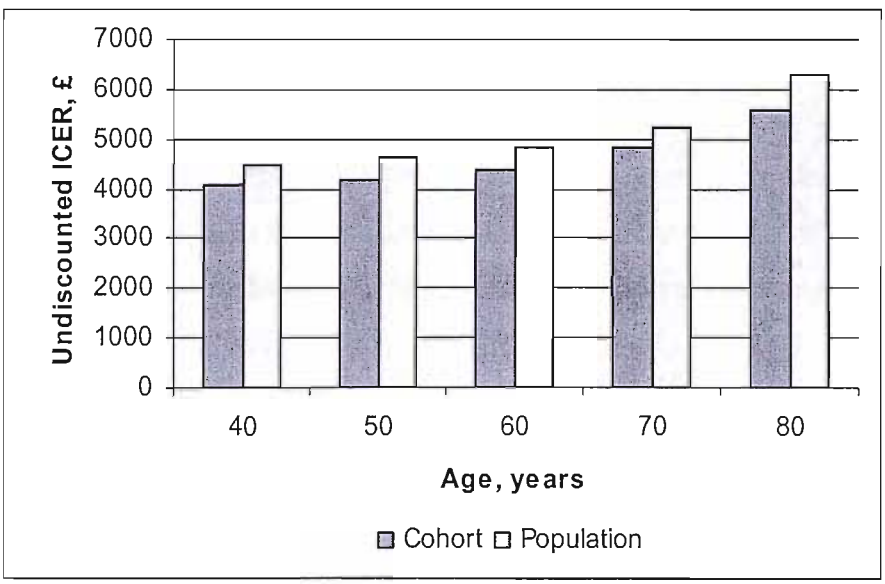

Figure 5.5.3 Undiscounted ICER for all ages

Figure 5.5.3 and 5.5.4 show the results for the cost effectiveness (ICER) for the treatment scenario for the undiscounted and discounted cases respectively for all ages. The figures show that the percentage difference between the cost effectiveness (ICER) for the population and cohort is similar for all ages. In all cases, the ICER for the

population runs is greater than for the cohort runs. For the undiscounted results, the ICER for the population runs is greater than the cohort runs by between 8 and 12%. For the discounted results, the ICER for the population runs is greater than the cohort runs by between 3 and 8%. In addition the ICER is similar across all ages. For example, the ICER for the discounted population runs varies between £5550 and £6700.

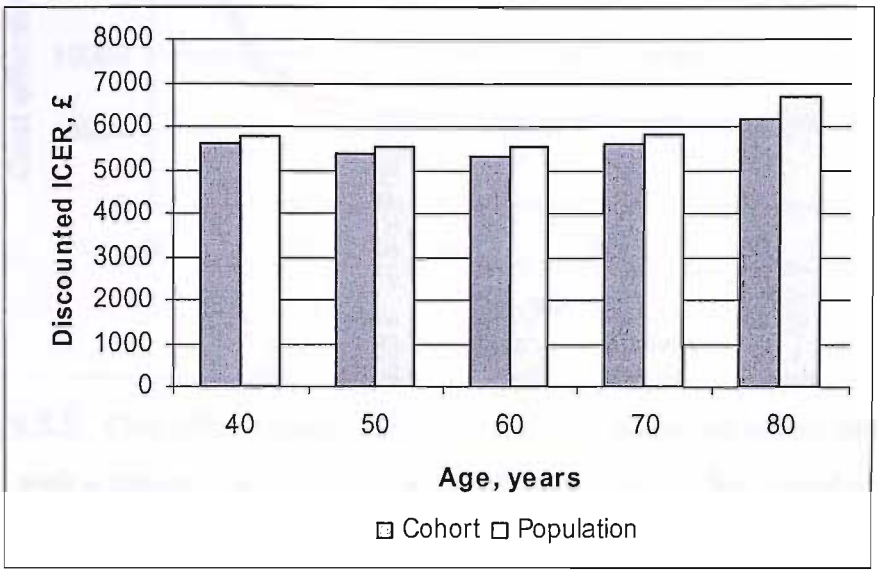

Figure 5.5.4 Discounted ICER for all ages, costs and benefits discounted at 3%

The reason for higher ICER for the population runs is clear and is illustrated by Figure 5.5.5. Briefly the benefits from the intervention lag behind the cost of the intervention. This Figure shows how the ICER changes over time for a simulation run with a cohort of 60 years old. Initially the ICER is much higher but after about 40 years the ICER has levelled out. For the cohort simulation, the benefit of the intervention will be shared between the whole of the cohort. In the population simulation there will always be many patients still alive who have not received all the benefits from the intervention. Clearly the population runs will always contain a proportion of people who have been in the simulation less than 40 years. Therefore the ICER for these people will be higher than the cohort simulation and so therefore the ICER for the population simulation will always be higher than the cohort simulation. For the population simulation, the ICER continues to decrease for many years. Thus, the ICER in this case is £6000 after 40 years, £5525 after 100 years and eventually stops decreasing after about 250 years at £5450.

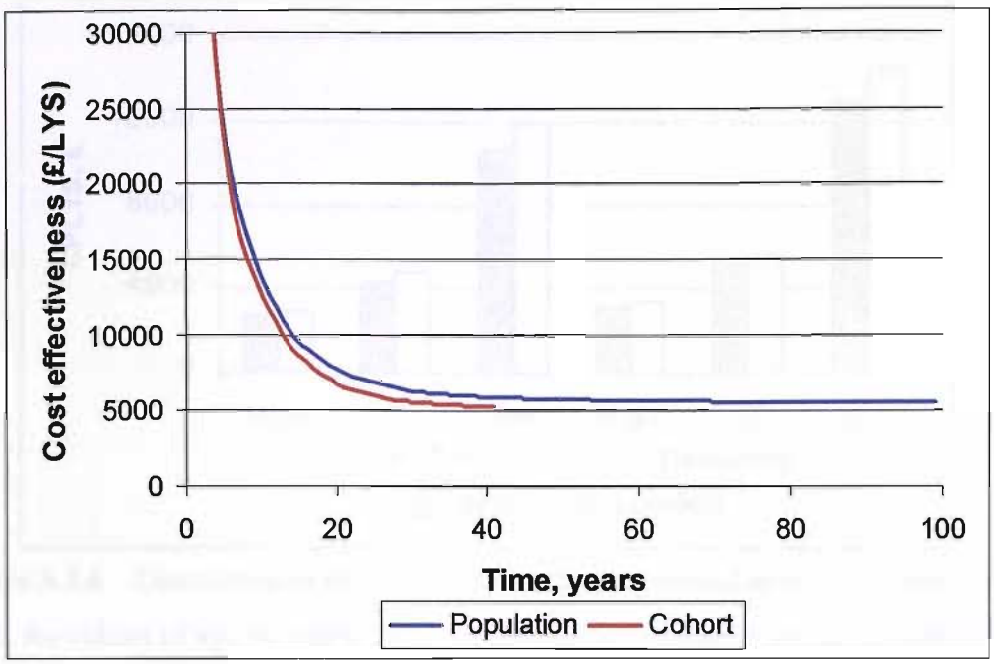

Figure 5.5.5 Cost effectiveness (ICER) for the population and cohort simulation runs with a cohort of age 60 years with costs and benefits discounted at 3%

5.5.2 Sensitivity analyses

Sensitivity analyses were performed by using treatment scenarios where the intervention had a higher and lower benefit than the scenarios described above. In the higher and lower benefit scenario, the intervention reduced the probability of suffering an event by 40% and 10% respectively. The sensitivity analyses were run for all ages for the cohort and population approaches and the results are shown in Figure 5.5.6 for the 60 year old age group.

The results from the sensitivity analyses were similar to the results seen for the original runs. The cost effectiveness (ICER) results for the population approach is higher than for the cohort approach. The ICER results for the population approach are roughly 10% higher than the cohort for all runs.

Further sensitivity analyses were conducted with different event rates and death rates. The difference between the ICER for the population and cohort models was similar to that seen in the analyses above.

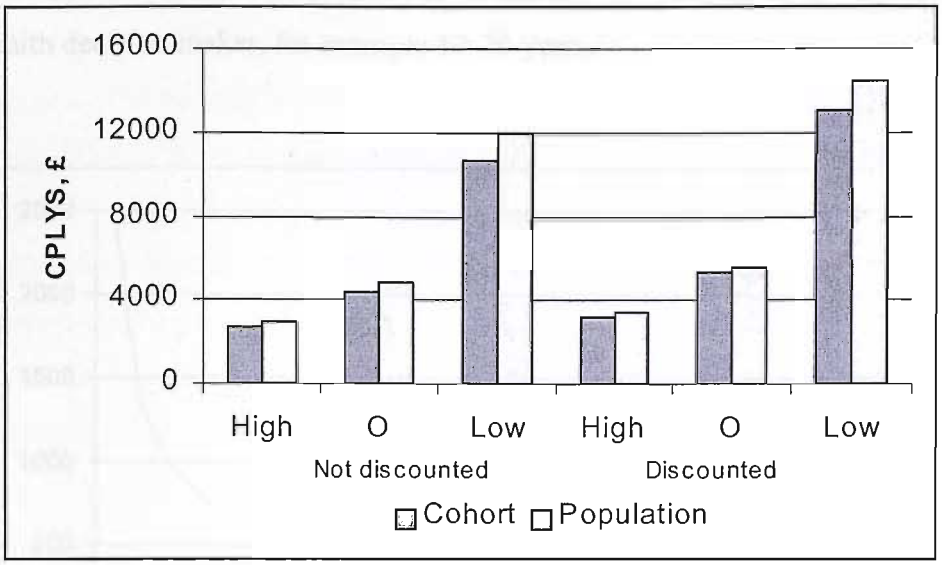

Figure 5.5.6 Discounted (with costs and benefits discounted at 3%) and undiscounted ICER for cohort of age 60 years, for an intervention with higher and lower efficacy than the original (O)

5.5.3 Time horizon

In the results shown in the previous sections, the cost effectiveness for the cohort approach for model runs has been calculated over a patient's lifetime, and for the population approach for model runs of 100 years. However as shown in the literature review in chapter 3, many other time horizons are chosen. The time horizon is critical to the results and conclusions. If too short a time horizon is adopted, the cost effectiveness may appear much worse than expected. However, if a long time horizon is chosen, there may be difficulties in making assumptions about interventions beyond the length of known evidence. In addition new technologies may be introduced in subsequent years which would affect the assumptions made in the model.

Figures 5.5.5 and 5.5.7 show the effect of varying the time horizon for the cost effectiveness of the long and short term interventions, assuming that the effectiveness of the intervention remains the same throughout a patient's lifetime. In both cases, the ICER is much more favourable over longer time horizon. For example in Figure 5.5.7, time horizons of 5, 10 and 20 years would overestimate the ICER by 230%, 50% and 9% respectively, compared to the lifetime ICER. One solution would be to present a

range of time horizons, or present ICER for the time horizon likely to be of interest to the health decision maker, for example 10-20 years.

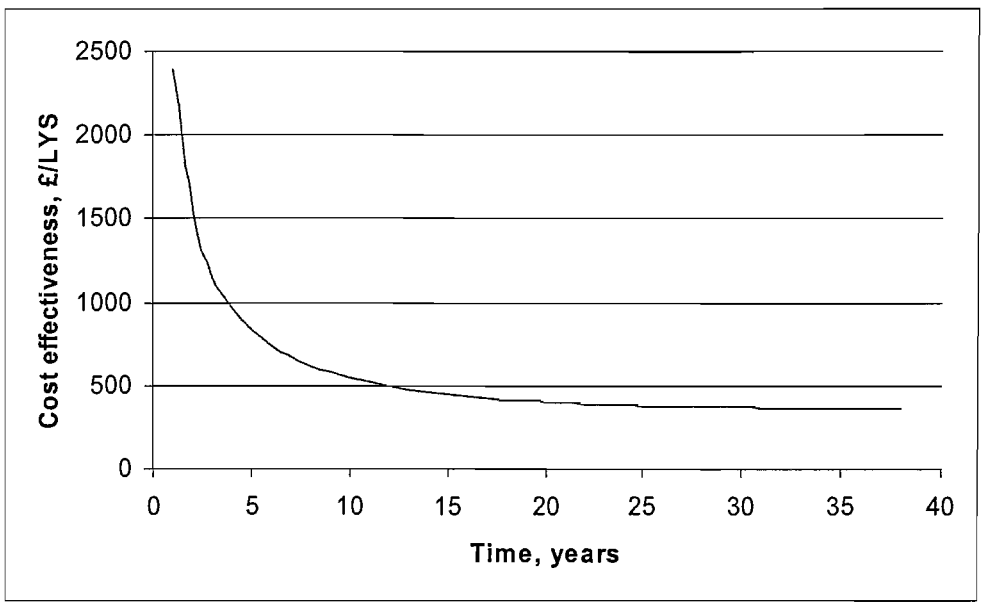

Figure 5.5.7 Discounted cost effectiveness ratio for the short term intervention; costs and benefits discounted at 3%

5.5.4 Discussion

Using the population approach the health care planner can ascertain not only whether a new treatment is cost effective, but what the costs and health outcomes are likely to be in the population of interest, and for this reason its use is recommended above that of the cohort analysis. Thus it has been shown that a population analysis provides a more comprehensive summary of the value of the intervention for the health care planner than a cohort analysis. In addition, the cost and health benefit outcomes of an intervention are as important an output as cost effectiveness.

5.6 Resource-constrained interventions

In this section resource-constrained interventions are investigated. Resource-constrained interventions are those for which there may be some decision rules concerning the

allocation of the resources and these are typified by the referral and subsequent waiting of patients for elective hospital procedures. It is investigated whether:
H5) For dynamic systems which involve constraints or where patients compete for resources, DES is the most appropriate technique.

Experiments are conducted using the population simulation model described in section 5.5. Instead of using a scenario where patients take a drug that reduces their risk of future disease events, in this model patients can have an intervention which stops them having any further disease events. Thus they only die from non disease death. It is assumed that all patients who have a disease event are referred for the intervention. They wait on a queue until such time as there are the resources available for them to have the intervention. All other parameters are as described in section 5.5. The intervention costs £30,000. There is a prevalent population of 1000 patients and an incident population of 60 patients of starting age of 60 years. The simulation is run for 100 iterations for 40 years.

Table 5.6.1 shows the results from the simulation runs. As can be seen from the table when there are 4 and 5 interventions per month the average waiting time is very short at only 56 and 20 days respectively. When there are only 3 interventions per month there is a much longer waiting time of over 2½ years. In this case there are 12% fewer interventions performed and the cost effectiveness ratio is almost 20% lower for the scenario with the longest waiting time.

Table 5.6.1 Average annual costs (£000s), patient life years and cost effectiveness ratios for the simulation runs with queues; discounted ratios at 3% for costs and benefits

		Interventions / month		
	Baseline	**3**	**4**	**5**
Cost		1079	1216	1212
Patient Life years	1196	1278	1313	1312
Undiscounted ICER		13236	10401	10502
Discounted ICER		16000	13176	13360
Waiting time (months)		30.9	1.8	0.6

So it is concluded that in this scenario modelling the waiting time was significant to the results of the interventions. However the intervention can also be modelled without using a queue but merely building a waiting lag in the model. A comparative model was built without queues where patients wait for a set time period equivalent to the average queuing time shown in Table 5.6.1. This waiting lag could have been estimated using an analytical queuing model or from an observation of the real life system. The results are shown in Table 5.6.2. There is little difference between the results and those in Table 5.6.1. Certainly the inclusion of queues has not materially affected the results. Thus a resource-constrained intervention has been modelled without the use of queuing and so systems with a queue system can be modelled effectively without the need for DES.

Table 5.6.2 Average annual costs (£000s), patient life years and cost effectiveness ratios for the simulation runs with no queues; discounted ratios at 3% for costs and benefits

		Interventions / month		
	Baseline	**3**	**4**	**5**
Cost		1156	1209	1211
Patient Life years	1196	1284	1311	1311
Undiscounted ICER		13194	10575	10506
Discounted ICER		16421	13456	13375
Waiting time (months)		30.9	1.8	0.6

5.7 Conclusions

In this chapter the choice of modelling technique was explored through the construction of simple models. In particular the hypotheses set out in the previous chapter were investigated. Simple decision tree, Markov and simulation models were constructed for short term and long term interventions. The results were compared and the hypotheses tested empirically. The models used hypothetical data to make the comparison between the models easier to interpret.

As a result of testing the hypotheses H1-H5, it has been concluded that for short term interventions, where the intervention happens more than once in a patient's lifetime, decision trees will underestimate the total costs and health benefits incurred compared to the other modelling techniques. When modelled using the same data and assumptions, the Markov and simulation models give similar results which converge as the cycle time of the Markov model decreases. It has been shown that the cohort and population-based approaches will yield different results and the population-based approach will give a worse cost effective ratio compared to the cohort-based approach. The appropriate choice of time horizon for the model is critical to the obtaining the suitable results and conclusions. Finally a resource-constrained intervention can be modelled without the use of queuing and so systems with a queue system can be modelled effectively without the need for DES.

Chapter 6

The Development of Models for Coronary Heart Disease

Abstract

This chapter presents the development of models for Coronary Heart Disease which will be used in the subsequent chapters. The key parameters are outlined, for example CHD incidence and prevalence rates, in and out of hospital death rates and non cardiac death rates. The long and short term risks of myocardial infarction are derived from available data. A CHD model using these parameters is developed that is validated for death rates and heart attack against published national data and shows a good match.

Chapter 6 The Development of Models for Coronary Heart Disease

6.1 Introduction

This chapter describes the development of models for coronary heart disease. These models are described in more detail in chapters 7 to 9. Although the models describe different interventions with different structures, the underlying disease process is similar. The underlying clinical process is described and the main parameters are explained and derived. Finally the model is validated against national datasets.

6.2 Clinical aspects of coronary heart disease

The clinical aspects of coronary heart disease are described in more detail in section 3.1.1. Briefly, patients with coronary heart disease usually have coronary arteries which have narrowed due to the build up of fatty materials (atherosclerosis). These narrowings or stenoses influence the patient's survival and may lead to them developing angina pectoris, a heart attack or cardiac arrest.

Angina is a chest pain which is exacerbated during exercise or stress. Patients with angina are usually given medication to relieve their symptoms such as nitrates, beta blockers or calcium antagonists. If the symptoms become bad they may be referred for further investigations such as an electrocardiogram (ECG), or angiogram. If the patient's arteries are sufficiently bad they may be offered surgical treatment such as coronary artery bypass graft (CABG) or percutaneous transluminal coronary angioplasty (PTCA) to improve the blood supply to the heart.

In unstable angina, chest pain may occur at rest and may increase in severity, frequency, or duration at low levels of activity or for no identifiable reason. If one or more of the coronary arteries become blocked a heart attack or cardiac arrest may occur. Those who experience heart attack are a high risk of cardiac arrest and immediate death. They are

usually admitted to hospital as emergencies and treated as soon as possible with clot busting medication (thrombolysis) and aspirin. They may be referred for further immediate investigation and medical treatment.

Patients with coronary heart disease are increasingly offered secondary prevention medication to reduce the risk of further coronary events. These drugs include aspirin, beta blockers, ACE inhibitors and statins.

6.3 Modelling the treatment of heart disease

The models built in this chapter are based upon research completed by the author as part of the UK Coronary Heart Disease Policy Model working team (Appendix I). In particular much of the data have been collected by other members of the group and is described in more detail in the Stable angina, Unstable angina and Myocardial Infarction Working papers (Chase et al. 2003). Furthermore the modelling work here was done by the author in consultation with other members of the group.

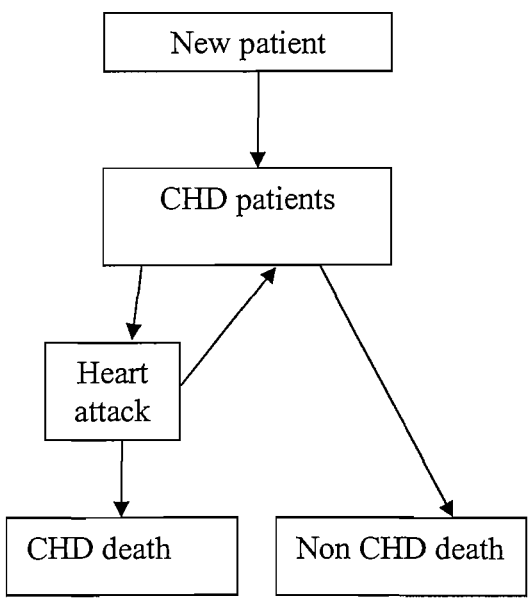

Figure 6.3.1 A simple population model of the treatment of coronary heart disease

The basis of the population models of coronary heart disease treatment described in chapters eight and nine are shown in Figure 6.3.1. They consist of a prevalent pool of patients with varying severity of coronary heart disease, for example some of these may suffer from anginal symptoms and others may have had a heart attack in the past. Over the course of the model runs, the prevalent population will be added to by new CHD patients who have no previous history of CHD. These patients may suffer a heart attack at any time and the length of time until they have a heart attack will be related to their risk factors, for example age, history of heart attack, severity of diseased arteries. Some of the heart attacks will be fatal. The CHD patients may also die from causes not related to CHD.

The cohort models in chapter 7 are also illustrated using the same Figure but in this case there will be no new patients entering the models.

6.4 Parameters for coronary heart disease models

The parameters for the coronary heart disease models are explained in more detail in the next sections. The parameters were age dependent, for example the prognosis for older patients is worse than for younger patients, and in some case is gender specific, for example the incidence and prevalence is higher for males than females. In addition, patients who had a history of heart attack or myocardial infarction (MI) were at greater risk of further coronary events and the prevalence of CHD is shown according to three classifications: Angina only, angina and history of MI, history of MI. The parameters derived assume independence of events.

6.4.1 Incidence of new patients

The population models generate new patients with stable angina, unstable angina and MI who have not had previous coronary events. The incidence was taken from the Bromley Heart Study (Sutcliffe et al. 2003). These data were broken down by age and sex. Unfortunately, no Bromley data were available for men and women for the age band 75-84 and so data had to be found from other sources and related to the Bromley

data. The Framingham data (Lerner and Kannel 1986) set was used to estimate the stable angina and MI incidence and the Finished Consultant Episodes (1998) were used to estimate unstable angina in the older age group (Table 6.4.1).

In each of the population models, the annual incidence in each age group for each gender is the product of the incidence and the total population of that age (see Appendix II). For example there are about 3.9% of the total population who are males of age 65-74. For a total population of one million, there would be an annual incidence of about 255 for angina only.

Table 6.4.1 Incidence of new coronary heart disease patients (% of total population in age band) (Data from Sutcliffe et al. 2003 and *Lerner et al. 1986; Table from Cooper et al. 2003)

	Angina		Unstable angina		Myocardial infarction	
Age band	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**
35 - 44	0.06	0.01	0.02	0	0.06	0.01
45 - 54	0.238	0.098	0.043	0.029	0.225	0.03
55 - 64	0.548	0.357	0.08	0.03	0.359	0.165
65 - 74	0.655	0.33	0.19	0.039	0.71	0.236
75 - 84	0.3	0.6	0.21	0.048	1.01	0.59
85+*	0.34	0.47	0.21	0.048	0.18	0.53

6.4.2 Prevalence of CHD patients

The population models begin with a prevalent CHD population. The prevalence was taken from the General Practitioners Research Database (GPRD 1998). The National dataset was stratified by age and sex. However the models needed the data to be broken down further by history of previous MI. The GPRD data have been obtained for the West Midland area with prevalence stratified by age, sex and disease state.

Overall, the CHD prevalence for the West Midlands was 4% higher than for England

and Wales. The West Midland data were adjusted so that the total CHD prevalence is the same as the England and Wales estimate for each of the age and sex bands (Table 6.3.2).

In each of the population models, the prevalence in each age group for each gender is the product of the prevalence and the total population of that age (see Appendix II). For example there are about 3.9% of the total population who are males of age 65-74. For a total population of one million, there would be a prevalence of about 4095 for angina only.

Table 6.4.2 Prevalence of CHD patients (% of age band) (Data from GPRD 1998; Table from Cooper et al. 2003)

% in age band	Angina, no MI		Angina, previous MI		MI, no angina	
Age Band	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**
35 - 44	0.3	0.15	0.1	0.02	0.1	0.02
45 – 54	1.6	1.1	0.6	0.2	0.8	0.1
55 – 64	5.1	3.8	2.5	0.5	1.9	0.5
65 – 74	10.5	8.2	5.1	1.7	2.8	1.3
75 – 84	12.0	11.6	6.6	3.1	4.5	2.0
85+	9.7	10.9	3.6	2.4	3.6	2.4

6.4.3 Non cardiac death rate

The mortality statistics were taken from ONS Death and population statistics (see appendix III), for 1998 for England and Wales. These statistics are broken down for different categories including coronary heart disease deaths. CHD deaths are those with International Classification of Diseases (ICD) codes 410-414. It was assumed that the non cardiac death rate for patients with no coronary heart disease was the same as that for those with coronary heart disease. The non cardiac death rates for male and females have been averaged to give a combined annual probability. There were no population data available on the number of people above the age of 90 and so these data have been estimated by assuming a continual increase in non cardiac probability.

Table 6.4.3 Annual probability of non cardiac death (NCD) for male and females of different age (Office of National Statistics, 1998)

Age	P(NCD)	Age	P(NCD)
45	0.0018	75	0.0319
46	0.0019	76	0.0361
47	0.0020	77	0.0391
48	0.0022	78	0.0416
49	0.0025	79	0.0489
50	0.0027	80	0.0527
51	0.0028	81	0.0582
52	0.0034	82	0.0645
53	0.0036	83	0.0718
54	0.0040	84	0.0806
55	0.0045	85	0.0879
56	0.0047	86	0.0995
57	0.0053	87	0.1077
58	0.0060	88	0.1204
59	0.0064	89	0.131
60	0.0070	90	0.14
61	0.0077	91	0.15
62	0.0086	92	0.16
63	0.0094	93	0.17
64	0.0105	94	0.18
65	0.0114	95	0.19
66	0.0127	96	0.2
67	0.0143	97	0.21
68	0.0155	98	0.22
69	0.0178	99	0.23
70	0.0200		
71	0.0221		
72	0.0245		
73	0.0270		
74	0.0298		

For each age, the annual probability of non cardiac death was calculated by dividing the number of non cardiac deaths at a particular age by the total number of people of that age in the population.

For the Markov models, the transition probability for non cardiac death is simply that specified by the age and sex of the patient as shown in Table 6.4.3. For the simulation models, a cumulative probability distribution was generated starting from the current age of the person until age 100. The model samples from this cumulative probability distribution to find a time to non cardiac death, using the inverse transform method. The cumulative probability that a person of age n, will have died by age x where x>n is the combined probability that the person will have died by age x-1 or he/she will die in the current year. The cumulative probability that a person of age n, will have died by age x where x>n is

$$1 - (1-p(n+1)).(1-p(n+2)).....(1-p(x-1)).(1-p(x)).$$

6.4.4 Death from heart attack

Patients who have a myocardial infarction are at a high risk of CHD death and this may happen either out of hospital or in hospital. This risk is influenced by the timeliness of ambulance and thrombolysis response. The models in Chapter 7 evaluate improvements in ambulance and thrombolysis response times in reducing the out of hospital and in hospital deaths respectively.

The data for out of hospital and in hospital deaths were taken from UKHAS (Norris 1998). There were no values available for ages above 75 years. These ranges were estimated using the Nottingham study (Brown et al. 1997).

Table 6.4.4 Out of hospital and in hospital death rates, % (Norris 1998 and * Brown et al. 1997)

Age band	Out of hospital	In hospital
35 - 44	20	2
45 – 54	25.5	4.1
55 – 64	29.2	15
65 – 74	37	25.3
75+*	50	46

6.4.5 Myocardial infarction

In the models in chapters seven to nine, myocardial infarctions are sampled from fitted probability distributions. Patients who suffer a myocardial infarction may die in or out of hospital as described in section 6.4.4 from that myocardial infarction and it was assumed that all patients that die from coronary heart disease first suffer a myocardial infarction.

Table 6.4.5 Derived annual probability of MI (x is age of patient) (Cooper et al. 2003)

Patients	Annual probability of MI
Angina only	$0.0107\exp^{0.0155x}$
History of MI: first year after MI	$0.0325\exp^{0.0337x}$
History of MI: after first year after MI	$0.0159\exp^{0.03x}$

The EMMACE dataset (Lawrance et al. 2001) and the British Regional Heart Study (BRHS) (Lampe et al. 2000) are used to estimate the rates of myocardial infarctions. According to these datasets, the probability of death is significantly higher in the first year than in subsequent years and the probability of coronary events is significantly higher for patients with a history of MI than for those with angina only. Accordingly, probability distributions were derived for three categories: probability of MI for patients with angina only, probability of MI for patients with history of MI in the first year after MI, probability of MI for patients with history of MI after first year after MI. These

probabilities are shown in Table 6.4.5. The derivation of these parameters is shown in Appendix IX.

6.4.6 Discussion

The data derived in the preceding sections and in Appendix IX relates to the model for coronary heart disease presented in chapters seven to nine. In particular there is an extensive explanation of the derivation of the probability distributions for myocardial infarctions. These derivations were necessary, because the best available data, the EMMACE data, did not show the proportions of patients who had fatal or non fatal MI within the trial - only those who died from all causes in the five years of follow up.

The probability distributions presented are in the form of annual risk of MI in the next year, according to the present age of the patient. The Markov models will use this probability in this form in the models, to determine if the patient suffered an MI in that year. For the simulation models, it is more complex. Although a lookup table could have built and sampled from to find the time to event, it is more mathematically appealing to construct a probability distribution with the same annual risk values and sample from this. The derivation of this distribution is shown in the appendix V.

6.4.7 Unstable angina rate

Unstable angina is a serious complication for CHD patients and is costly in terms of the use of resources, however the data concerning unstable angina occurrence were poor and so several assumptions have been made. Unstable angina may occur from any state. It was necessary to predict times to event for unstable angina for different patient ages, disease state and vessel disease. The distribution of time to unstable angina was assumed to follow a Gompertz distribution in as similar manner to MI. The age gradient was used as shown for stable angina.

There was no evidence for influence of gender, previous MI or vessel severity on progression to unstable angina. There were data for the rate of patients progressing to unstable angina from the RITA 2 trial (1997). The trial was predominately made up from patients with single or two vessel disease. From these results it was estimated that

a 58 year old CHD patient with no previous history of MI with one or two vessel disease had an annual risk of unstable angina of 3.49%. Using the age gradient in the section above, it was estimated that the progression to unstable angina was $0.0141e^{0.0155t}$, where t is age in years, giving an event rate at age 55 of 3.33% and an age gradient between 55 and 70 years of 1.26

6.5 Validation of the derived data

In this section a validation of a model using the derived probability distributions for MI is presented compared to the original EMMACE data. The probability distributions derived in Appendix IX contain several assumptions and it was possible to test the validity of these assumptions.

A Markov cohort model was constructed using the simple model shown in Figure 6.3.1. Cohorts of 1000 individuals for five age bands who had survived a MI (as in the EMMACE study) were followed for five years with a cycle length of one year. The data for the transitions between the states have been described above.

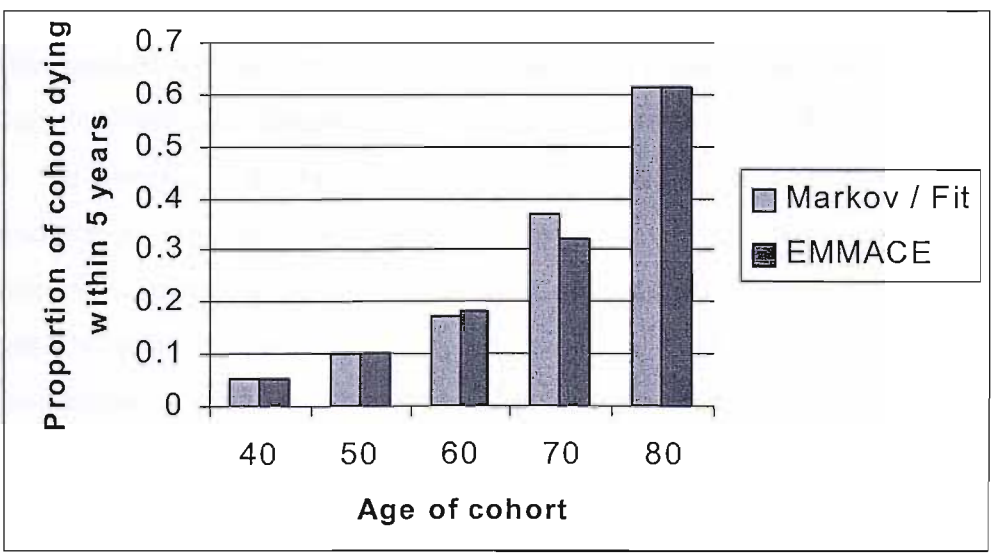

Figure 6.5.1 Comparison between EMMACE data and Markov run results for all cause mortality over five years

The results are shown in Figure 6.5.1. This shows the proportion of the cohort who suffered all cause mortality during the five year follow up for the EMMACE dataset and the Markov model. The Markov shows a good fit for all ages with the exception of the 70 year old year group. The model results differ from the EMMACE data on average by about 4%. A possible reason for the difference for this age group is that there were fewer deaths in the EMMACE dataset for the 70 year old age group than one might have expected.

6.6 Validation of the CHD model

One advantage of the population approach over the cohort approach is that the former is easier to validate. The population model imitates what is happening or what will happen in the wider population. The results can be compared to National Statistics or other large observational datasets, particularly for end points such as death. On the other hand, the cohort model presents a more unnatural environment and is more problematic to validate, unless there is a trial which has been carried out which is similar to the model setting.

In this section, a validation of the population model is presented. The model uses the parameters derived in the preceding sections and has been described in sections 6.2 and 6.3. The model used for the validation was a simulation model and has been run for a population of 125,000 for 100 iterations. The model uses the baseline parameters for ambulance and thrombolysis response times, secondary prevention and revascularisation as described in chapters seven, eight and nine respectively. The baseline case uses parameters and a baseline scenario from before the National Service Framework was introduced. The CHD Modelling team estimated that the results from the model at the start of the simulation run would simulate real life population from the year 1998 onwards.

Validation data are available in several forms: 1) routinely collected data such as death certificates and in-patient episodes, 2) published studies such as incidence and

prevalence estimates and 3) research databases. In attempting to validate the model, data were used from different sources from those used in the model. The model has been validated for coronary heart disease events. The CHD events are validated by year and by age breakdown.

6.6.1 CHD deaths

CHD deaths in the model were validated against mortality data from the Office for National Statistics, based on death certificates. Compared to these data, the model underestimated total deaths by an average of 4.5% in 1998 (see Figure 6.6.1) and is within 5% of the total deaths for the years 1998 – 2001 (see Figure 6.6.2).

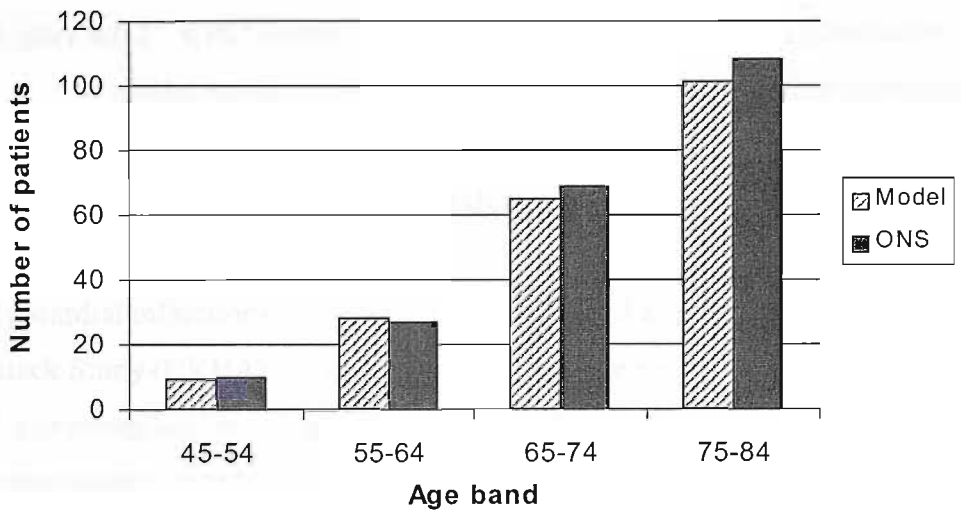

Figure 6.6.1 CHD deaths, ICD codes 410-414, for 1998 for a population of 125,000; model estimates compared to the Office of National Statistics data.

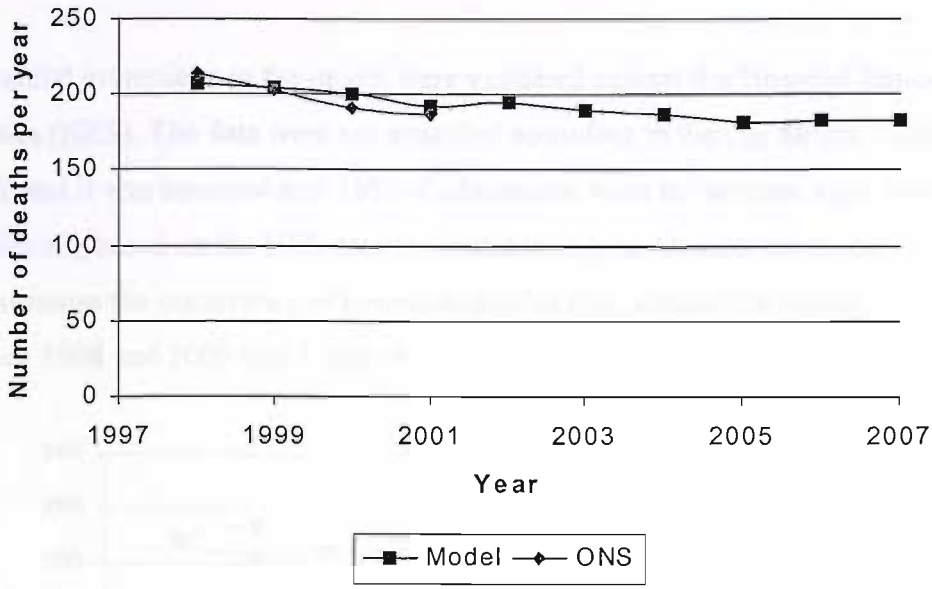

Figure 6.6.2 CHD deaths, ICD codes 410-414, per year for a population of 125,000; model estimates compared to the Office of National Statistics data.

6.6.2 Out of hospital myocardial infarction

Myocardial infarctions in the model were validated against the United Kingdom Heart Attack Study (UKHAS). The study did not include people over the age of 75 so the 75-85 age group has been extrapolated from the Framingham study. Overall the model overestimates the total occurrence of myocardial infarction by 3.6% (see Figure 6.6.3).

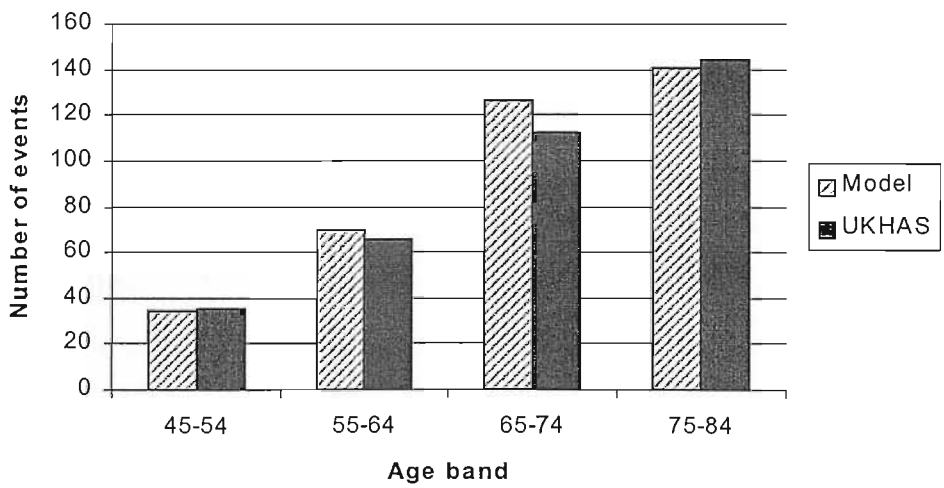

Figure 6.6.3 Myocardial infarctions, for 1998 for a population of 125,000; model estimates compared to the United Kingdom Heart Attack Study data.

6.6.3 Myocardial infarction hospital admissions

Myocardial infarctions in the model were validated against the Hospital Episode Statistics (HES). The data were not stratified according to the age ranges used in the model, and it was assumed that 10% of admissions were for persons aged less than 45 and over 85, based on the HES data for unstable angina. Overall the model overestimates the occurrence of myocardial infarction admissions between 6 and 12% between 1998 and 2000 (see Figure 6.6.4).

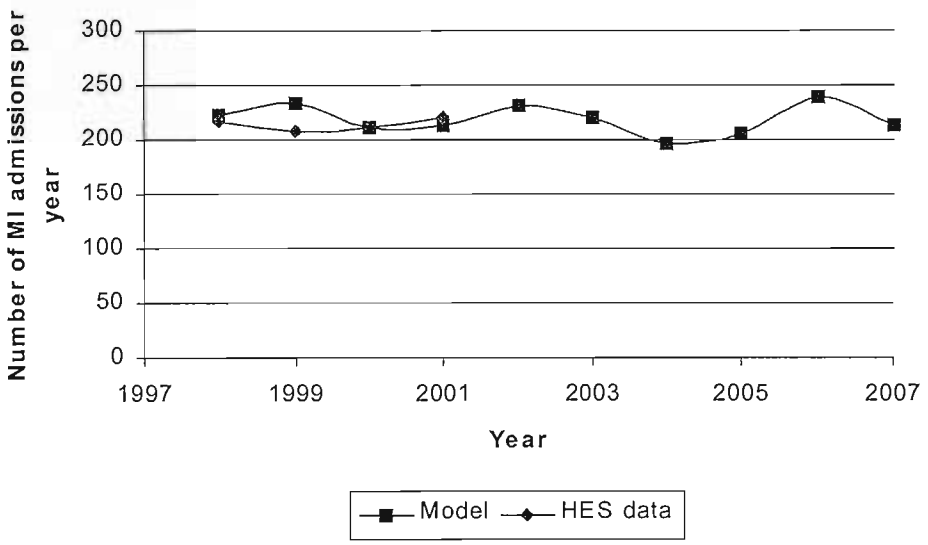

Figure 6.6.4 Myocardial infarction admissions, for a population of 125,000; model estimates compared to the Hospital Episode Statistics data.

6.7 Conclusion

This chapter has presented the development of models for Coronary Heart Disease which will be used in the subsequent chapters. The underlying clinical process for coronary heart disease has been described. The key parameters were outlined, for example CHD incidence and prevalence rates, in and out of hospital death rates and non cardiac death rates. The long and short term risks of myocardial infarction were derived from available data. A CHD model using these parameters has been developed that was validated for death rates and heart attack against published national data and shows a good match.

The collection of relevant and accurate data for modelling purposes is problematic. Nevertheless, validation against different datasets showed an excellent fit for cardiac death and MI.

Chapter 7

Acute Treatment Interventions: Models for Ambulance and Thrombolysis Response Time

Abstract

In this chapter decision tree, Markov and simulation cohort models are built to evaluate the costs and benefits from faster ambulance and thrombolysis response times for coronary heart disease patients experiencing MIs. The choice of modelling technique is investigated for acute (short-term) treatment interventions using the case study approach. Some of the conclusions from chapter 5 for the simple experimental models are tested for a more complex and realistic model to see if they still hold true.

The models results show that improving ambulance response times is likely to be a cost effective intervention but improving thrombolysis response times is much less cost effective. The decision tree, Markov and simulation models estimate an incremental cost effectiveness ratio of between £3750 and £4160 per life years saved for the ambulance intervention. The decision tree model estimates an incremental cost effectiveness ratio of £21,800 per life years saved.

Using these models it is concluded that decision tree models are an appropriate technique for modelling the cost effectiveness of short term interventions. However, as shown in chapter 5, when the intervention occurred more than once in a patient's lifetime the decision tree underestimated the total costs and benefits. For more accurate life time costs and benefits for the intervention a Markov or simulation model should be used. Using the models developed in this chapter, interventions for faster ambulance response are shown to have a favourable cost effectiveness ratio, whereas those for faster thrombolysis response time have a much less favourable cost effectiveness ratio.

Chapter 7 Acute Treatment Interventions: Models for Ambulance and Thrombolysis Response Time

7.1 Introduction

In Chapter 3 it is concluded that decision trees were often used to estimate the cost effectiveness of short term interventions, although none of the studies had justified their use of this modelling technique. In Chapter 5, simple models for short term interventions were examined. It was shown that the decision tree was an appropriate technique to use if the modelled short term intervention happens only once in a patient's lifetime. It was also shown that decision trees underestimated the cost and health benefits incurred if the intervention happened more than once. It was concluded that decision trees may be an appropriate technique for cost effectiveness if the results can be shown to be similar to those of the Markov and simulation model and their use does not materially bias the conclusion of the study. In this chapter some of these hypotheses and conclusions are examined with a real life example from Coronary Heart Disease for interventions for faster ambulance and thrombolysis response times.

Unless indicated otherwise, the results for the models are shown in terms of cost (£), effectiveness (years of life saved) and cost effectiveness (incremental cost effectiveness ratio, ICER, £/life years saved). The incremental cost effectiveness ratio is shown as the difference in cost between the intervention scenario and baseline divided by the difference in effectiveness between the intervention scenario and baseline.

7.2 Ambulance and Thrombolysis response times

This models built in this chapter are based upon research completed by the author as part of the UK Coronary Heart Disease Policy Model working team (Appendix I). Some of the results from the UK CHD Policy Model have been submitted to a journal (Chase et al. 2005) but those results have not been presented in this chapter. In particular much of the data have been collected by other members of the group and is described in more

detail in the Model Parameters Working paper (Cooper et al. 2003). Furthermore the modelling work here was done in consultation with other members of the group.

Individuals who suffer an out of hospital heart attack or cardiac arrest are at considerable risk of mortality. Studies have shown that survival after a cardiac arrest is improved if an ambulance arrives at the scene quickly (Cobbe et al. 1991). Furthermore, the survival after a heart attack (myocardial infarction) is improved if the patient is treated quickly with an anti-blood clotting drug known as thrombolysis upon hospital arrival (FTT 1994 and Boersma et al. 1996).

The UK government has set guidelines for the treatment of Coronary Heart Disease in the National Service Framework (DOH 2000). These guidelines included a target of 75% of calls to be reached within 8 minutes by ambulances and for 75% of eligible individuals to receive thrombolysis within 30 minutes of hospital arrival.

In this chapter models are built which evaluate the health gains and costs associated with moving to these targets. These gains are compared to a baseline ambulance and thrombolysis response for the year 2000.

7.2.1 Description of the models

The ambulance and thrombolysis cohort model follows individuals who have had an out of hospital MI. Some of these may die out of hospital or in hospital. The remainder of the cohort will have a probability of dying from a non-cardiac death or suffering a further MI. The model will follow the cohort until they have all died.

Life years are calculated by summing the number of CHD patients in the cohort for each year over the whole model run. Life years saved were the difference between the total number of patient life years associated with each intervention and the base run.

The parameters used in the model are event rates for MI and non cardiac death, out of hospital and in hospital death rates for patients suffering MI and costs. In the following sections, the out of hospital and in hospital death rates are derived for faster ambulance response (sections 7.2.2-7.2.4) and faster thrombolysis response (sections 7.2.5-7.2.7).

The cost parameters are described in section 7.2.8. Finally the models are described in more detail in section 7.3, including the event probabilities.

7.2.2 Parameters for the ambulance scenarios

The Scottish Heartstart study (Cobbe et al. 1991) provided data on the survival rate after cardiac arrest until hospital discharge for different ambulance response times (Table 7.2.1).

Table 7.2.1 Survival data for cardiac arrest patients who survive to hospital discharge from HeartStart, 1991-8 (Table from Cooper et al. 2003)

Time (Mins)	Number of calls	Cum. No. calls	Cum. % of total	% discharged
0 – 1	37	37	0%	32
1 –2	99	136	2%	18
2 – 3	343	479	5%	13
3 – 4	626	1105	12%	14
4 – 5	911	2016	22%	11
5 – 6	1022	3038	34%	10
6 – 7	983	4021	45%	9
7 – 8	957	4978	55%	7
8 – 9	868	5846	65%	5
9 – 10	685	6531	72%	7
10 – 11	606	7137	79%	4
11 –12	438	7575	84%	4
12 –13	390	7965	88%	4
13 – 14	278	8243	91%	6
14 – 15	178	8421	93%	2

At the time of the study, the survival rate was better than the national average for England. These data were used to estimate a new ambulance response distribution, by moving the 75% percentile of ambulance response to 8 minutes as described below. For each of these scenarios a new survival rate to hospital for cardiac arrest patients is

calculated. It is assumed that survival in hospital was worse for cardiac arrest survivors than for other MI patients.

The data are for 9028 cardiac arrest patients, of whom 7.9% survive to hospital discharge. The mean ambulance arrival time is 8.3 minutes after call for help and the median ambulance arrival time is 7.5 minutes. The inter-quartile ranges are 5.2 and 10.4 minutes; the 90% percentile is 13.6 minutes.

7.2.3 Estimation of a new ambulance scenario

The new ambulance scenario was estimated by moving the 75% quartile of ambulance response times from 10.4 to 8 minutes. There are many ways that this could be done. For example for an optimistic 'best' scenario, many of those call response times which are reduced to less than an 8 minute response time could have a response time of 0-2 minutes. On the other hand, for a pessimistic 'worse' scenario, many of those call response times reduced to less than 8 minutes response time could have a response time of 7 – 8 minutes. A more realistic scenario was attempted as follows. Table 7.2.2 shows how the frequency of calls changes from the baseline to the scenario for the different time bands.

Table 7.2.2 Changes to the baseline ambulance response times for the improved ambulance scenario

Time for ambulance response (mins)	
Baseline	**Scenario**
< 8	Same as baseline
8 – 10.4	Response times < 8 minutes
> 10.4	All baseline response times reduced by 2.4 minutes

For the middle category in Table 7.2.2 the new response times are estimated to have the same distribution as that in the baseline < 8 minutes time band. Figure 7.2.1 below shows the estimated distribution of ambulance response times. Table 7.2.3 below shows a summary of the ambulance response times.

Table 7.2.3 The frequency of the estimated ambulance response times in each time band, % (Table from Cooper et al. 2003)

Mins	Baseline	Scenario
0 - 4	12	22
4 - 8	43	53
8 - 12	29	17
>12	16	8

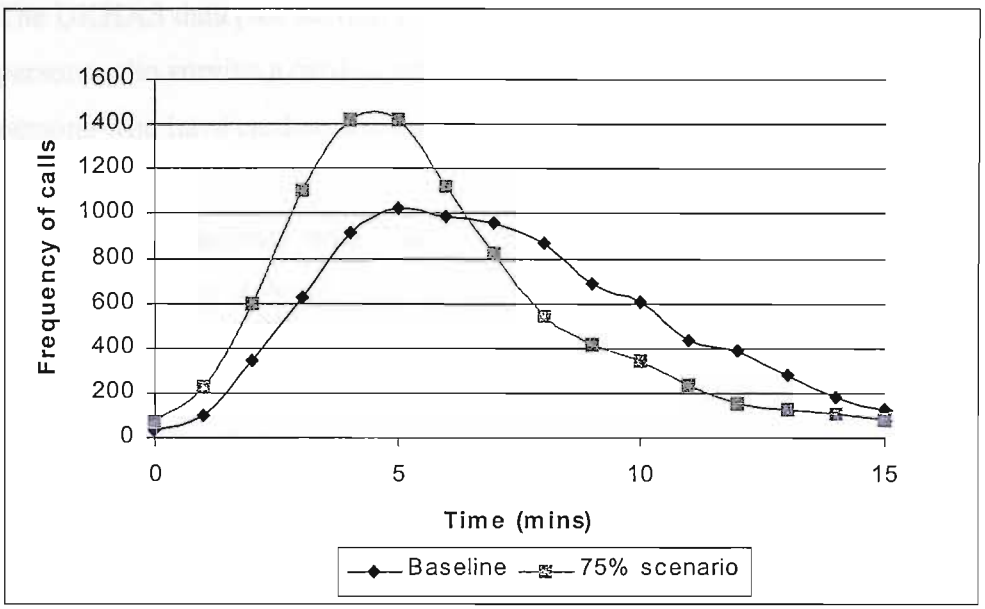

Figure 7.2.1 Frequency distribution of the ambulance response times for each scenario (Figure from Cooper et al. 2003)

7.2.4 New MI mortality rates from improved ambulance response times

The data from the HeartStart study for cardiac arrest and UKHAS (Norris 1998) for MI are combined in order to estimate the new mortality rates for patients suffering an out of hospital MI using simple mathematics. These patients will include those who had suffered a cardiac arrest and those who had only suffered a MI.

Of all cardiac arrests C, a proportion are witnessed c_w and the rest are not witnessed c_u.

$$c_w + c_u = 1$$

Of those witnessed, the survival rates s_j to discharge depend on the timing band j. If the proportion of the witnessed cardiac arrests in each time band is c_{wj} then the baseline overall survival rate of all cardiac arrests, S, assuming all unwitnessed cardiac arrests die is

$$S = c_w . \sum_{j=1}^{\infty} c_{wj} . s_j + 0 . c_u$$

The survival rates are calculated in this way for the baseline, S_0 and the intervention (S_1).

The UKHAS data (see section 6.4.4) gives the in hospital death rate (d_i) of those persons who survive a cardiac arrest. From this the out of hospital death rate (d_o) for persons who have cardiac arrest is calculated.

The number of patients with cardiac arrest who die out of hospital = $C.d_o$,
Those who die in hospital = $C(1 - d_o).d_i$
And those who survive to hospital discharge = $C.(1 - d_o) - C(1 - d_o).d_i = C.S.$

$$1 - d_o - (1 - d_o).d_i = S$$

$$(1 - d_o).(1 - d_i) = S$$

$$\therefore (1 - d_o) = \frac{S}{(1 - d_i)}$$

$$\therefore d_o = 1 - \frac{S}{(1 - d_i)}$$

Thus d_o, the out of hospital death rate for patients with cardiac arrest, has been calculated. According to UKHAS, all deaths out of hospital are due to cardiac arrest. It is assumed that there is the same in hospital death rate for cardiac arrest survivors as for those who had a MI, and the baseline out of hospital death rate, d_{o0}, and the out of hospital death rate, d_{o1}, for a scenario are calculated. A relative risk for the effect of the intervention on cardiac arrest mortality is calculated to be $\frac{d_{o1}}{d_{o0}}$. Thus the old out of

hospital MI mortality rate is multiplied by this relative risk for each age band to find the new MI mortality rate.

However, in UKHAS, those patients who had a MI who survived an out of hospital cardiac arrest were four times as likely to die in hospital than those who had not had an out of hospital cardiac arrest. If more of these out of hospital cardiac arrest patients survive to hospital then the overall death rate in hospital will increase for all MI patients.

Let the number of patients who suffer a cardiac arrest outside hospital and survive be C_h, those who die in hospital C_d, those who merely have a MI but do not suffer a cardiac arrest outside hospital be M_h, and of these those who die in hospital be M_d.

The total number of deaths in hospital is $C_d + M_d$

The death rate in hospital is $\frac{(C_d + M_d)}{(C_h + M_h)}$, the in hospital death rate for cardiac arrest patients is $\frac{C_d}{C_h}$ and for non cardiac arrest patients is $\frac{M_d}{M_h}$.

Now if more cardiac arrest patients survive c_h^1, to hospital then the new overall death rate is $\frac{(C_d^1 + M_d)}{(C_h^1 + M_h)}$

If fact c_d^1 is an unknown but can be estimated by $\frac{C_h^1 C_d}{C_h}$

Those patients who survived an out of hospital cardiac arrest were four times as likely to die in hospital than those who had not had an out of hospital cardiac arrest,

$$C_d^1 = 4C_h^1 . \frac{M_d}{M_h}$$

So the formula for the out of hospital death rate is $\frac{(C_d^1 + M_d)}{(C_h^1 + M_h)}$

$$= \frac{(4C_h^{\,1}M_d / M_h + M_d)}{(C_h^{\,1} + M_h)}$$

$$= \frac{M_d(4C_h^{\,1} + M_h)}{M_h(C_h^{\,1} + M_h)}$$

It is assumed that patients who subsequently survive a cardiac arrest because of faster ambulance response times have the same long term prognosis as post MI patients. The derived out-of-hospital death rate for patients who suffer an out of hospital MI is shown in Table 7.2.4 for the baseline and faster ambulance response time scenario.

Table 7.2.4 Derived out of hospital MI mortality rate, %

Age band	Baseline	Ambulance
35-44	20	19.4
45-54	25.5	24.7
55-64	29.2	28.3
65-74	37	35.9
75-84	50	48.5

7.2.5 Parameters for the thrombolysis scenarios

Faster thrombolysis administration also results in better survival for patients suffering acute MI. Estimates of thrombolysis efficacy were taken from the Fibrinolytic Therapy Trialists' Collaborative Group (FTT group) meta-analysis (FTT 1994). The data for efficacy was related to the time from onset of symptoms. Data on contra-indications to thrombolysis and current use of thrombolysis was taken from UKHAS (Norris 1998) and a West Midlands audit for baseline data (Birkhead et al. 1997). The FTT study used data from large trials (>1000 patients). An alternative study by Boersma et al (1996) incorporated other studies that the FTT group considered too small to include. The

relative risk reduction associated with faster thrombolysis administration is shown in Table 7.2.5.

Table 7.2.5 Weighted relative risk associated with thrombolytic therapy onset to thrombolysis (Table from Cooper et al. 2003)

Time from symptoms to thrombolysis (hours)	Relative risk FTT	Time from symptoms to thrombolysis (hours)	Relative risk Boersma et al
0-1	0.73	0-1	0.52
2-3	0.77	>1-2	0.6
4-6	0.84	>2-3	0.73
7-12	0.87	>3-6	0.73
13-24	0.95	>6-12	0.84
		>12-24	0.9

It is difficult to say whether the FTT or the Boersma paper provides the better estimate for the benefits of thrombolysis (Chase et al. 2005). The FTT paper is more methodologically sound. It only includes trials of 1000 patients or more. It is well known that smaller studies are more likely to suffer from bias. However, the Boersma paper could be said to address the question better. The smaller trials included in this paper included many more patients who received thrombolysis much earlier and the findings, showing much greater benefit in the initial hour, are backed up by other experimental studies. For the purpose of this study the FTT has been taken for the benefits and sensitivity analyses have been conducted with the Boersma data.

The National Service Framework target is to reduce the time from hospital arrival to thrombolysis administration. As mentioned above, the target was for 75% of eligible patients to receive thrombolysis within 30 minutes and this target would be further improved to 75% within 20 minutes.

The West Midlands data consisted of 16000 patients who had out of hospital MI. The times between onset of symptoms, hospital arrival and thrombolysis administration,

together with their survival was recorded. Table 7.2.6 shows the frequency distribution of people who received thrombolysis in hospital for different times from hospital arrival to thrombolysis administration. These patient times were adjusted for faster hospital arrival to thrombolysis administration to obtain a new distribution for the time from symptom onset to thrombolysis administration. Using these data, new in-hospital mortality rates were calculated.

Table 7.2.6 Original 'door to needle' response distribution from the West Midlands dataset (Birkhead et al. 1997; Table from Cooper et al. 2003)

Time (mins)	Frequency	%	Cum. %
0-10	227	3.7	3.7
10-20	642	10.5	14.2
20-30	951	15.6	29.8
30-40	819	13.4	43.2
40-50	702	11.5	54.7
50-60	539	8.8	63.5
60-70	390	6.4	69.9
70-80	327	5.4	75.3
80-90	273	4.5	79.7
90-100	211	3.5	83.2
100-110	206	3.4	86.6
110-120	114	1.9	88.4
120-180	388	6.4	94.8
180 – 240	147	2.4	97.2
240 – 480	121	2.0	99.2
480 – 720	18	0.3	99.5
720 – 960	7	0.1	99.6
960 – 1200	4	0.1	99.6
1200 - 1440	3	0.0	99.7
1440 - 9645	19	0.3	100.0

There is a slight mismatch between the government target which attempts to reduce the time from hospital arrival to thrombolysis administration (so called 'door to needle time') and the benefits of thrombolysis which are related to the time since pain started. In practice, many people may wait several hours before calling for an ambulance and even speedy thrombolysis may have little effect because of this delay. So for our model it is necessary to incorporate this delay whilst also evaluating the benefits of moving to the new targets.

UKHAS (Norris, 1998) estimated that about 50.2% of patients who arrived at hospital after a MI actually had thrombolysis. The majority of the other patients would have been refused treatment for various medical reasons.

7.2.6 Estimation of a new Thrombolysis scenario

Using the in hospital times, the new in-hospital thrombolysis scenario is estimated by moving the 75% quartile to 30 minutes. As for the ambulance scenario, this could be done in several ways that would give a range of scenarios from highly optimistic to pessimistic. A realistic method was chosen.

The baseline data has a mean hospital arrival to thrombolysis time of 73 minutes, median of 45 minutes and 75% quartile of 80 minutes. Each of the individual patients is given a new time from hospital arrival to thrombolysis by multiplying their current time by the target time / the baseline 75% quartile time, ie 30/80 for the 30 minute scenario (Table 7.2.7 and Figure 7.2.2).

Table 7.2.7 'Door to needle time' response distributions for thrombolysis

Response time (mins)	Baseline, % of patients	Improved scenario, % of patients
0 – 29	29.8	75.3
30 – 59	33.7	18.1
59 – 119	24.9	4.9
120 – 239	8.8	1.1
> 240	2.5	0.6

The time from onset of symptoms to thrombolysis is now recalculated by using the newly calculated time from hospital arrival to thrombolysis added to the original time from onset of symptoms to hospital arrival (Table 7.2.8).

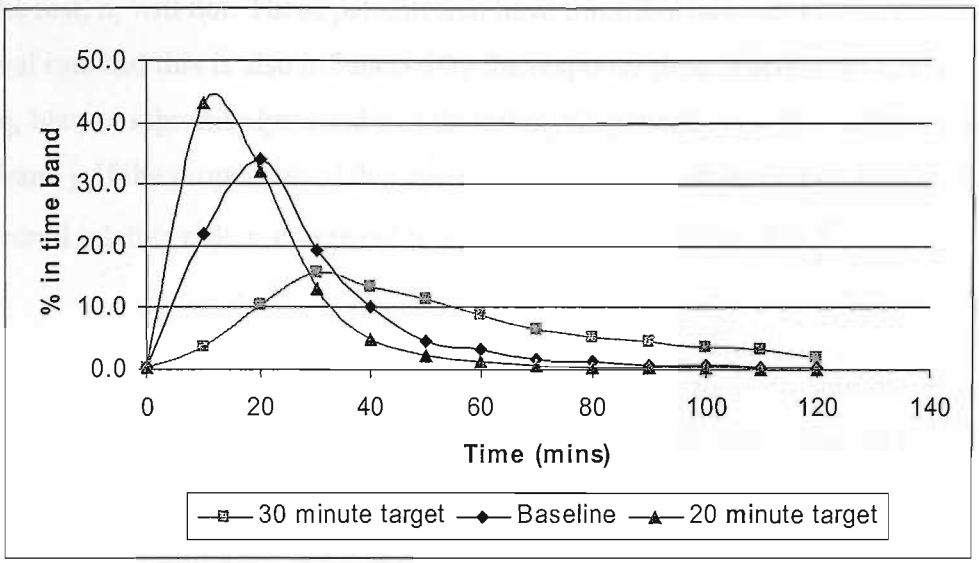

Figure 7.2.2 Estimated 'door to needle' thrombolysis response distributions (Figure from Cooper et al. 2003)

Table 7.2.8 Time from onset of symptoms to thrombolysis (using time bands as for FTT study) (Table from Cooper et al. 2003)

Time (hrs)	Baseline	30 minute target	20 minute target
0-1	9.8	20.5	24.3
2-3	46.1	46.1	44.4
4-6	27.2	19.5	17.7
7-12	12.2	10.1	9.9
13-24	4.6	3.9	3.7

7.2.7 New MI mortality rates from improved response times for thrombolysis

Using the new frequency distribution for the thrombolysis response times, new mortality rates are derived using simple mathematics.

For patients arriving at hospital after a MI, a proportion, θ, will receive thrombolysis and the rest, n, will not. Those patients that have thrombolysis will have an increased survival rate and this is also influenced by the response time. There is an overall relative risk, r_j, between thrombolysis and non thrombolysis patients, which is different for each time band j. If the proportion of the patients thrombolysed in each time band is θ_j, then the overall relative risk, r, compared to patients not thrombolysed is $\sum_{All\,\theta} \theta_j r_j$.

If the patients who are not thrombolysed have a mortality rate of m_n and those who are thrombolysed have a mortality rate of m_θ then the overall mortality rate, m is

$$m = \theta m_n r + n m_n = m_n(\theta r + n)$$

$$\therefore m_n = \frac{m}{(\theta r + n)}; \; m_\theta = r m_n$$

For a different scenario, the new overall mortality rate for thrombolysed and non thrombolysed patients m^1 is calculated. First the relative risk for using thrombolysis (r^1) is calculated as shown above, then the new mortality rate for thrombolysis,

$$\frac{r^1}{r} m_\theta$$

and so as before the total mortality can be expressed in terms of the proportions of non thrombolysed and thrombolysed patients,

$$m^1 = \theta^1 m_\theta \frac{r_s}{r} + n^1 m_n$$

Table 7.2.9 shows the baseline and 30 minute 'door to needle' in hospital mortality rates for MI patients.

Table 7.2.9 In hospital mortality rates for MI patients for FTT study, %

Age band (years)	Baseline	30 minutes for 'door to needle'
35 – 44	2.0	2.0
45 – 54	4.1	4.0
55 – 64	15	14.8
65 – 74	25.3	25.1
75 – 84	46	45.7

7.2.8 Cost parameters

Published studies by the Review of Ambulance Performance Standards (RAPS) (NHS Executive, 2000) and Fischer et al. (2000) have estimated the cost of improving ambulance response rates for England (excluding London) and the Surrey Ambulance Service respectively.

The Review of Ambulance Performance Standards estimated the cost for attaining a 75% ambulance response time within 8 minutes as £15m, (£18m if grossed up to include London). This was estimated in 1994/5 when the national average proportion of calls met in 8 minutes was around 45%. The RAPS data excluded London, which is likely to have higher costs and has the lowest proportion of calls reached in 8 minutes of any service. The RAPS report, which was supported by two reports by ORHealth, was before national targets were imposed (DOH, 1995). The Department of Health has subsequently used the RAPS estimates for the cost of meeting the new standards. If these costs are updated to 2000 prices this corresponds to £390,100 per million population. The year 2000 was used as this is the same year used for the baseline scenario for the ambulance and thrombolysis response times.

Fischer et al. (2000) estimated the expected decrease in response time and increase in cost by adding one ambulance to the number currently used by Surrey Ambulance Service. They estimated that there would be an increase in ambulance costs of £28,000 per second gained in response time for a population of 1.25 million for the Surrey Ambulance Service. If these costs are updated to 2000 prices this corresponds to £2,335,400 per million population for the 75% target.

The Department of Health estimated the increased spending required to improve ambulance response times and to provide relevant equipment for CHD in England to be £48.4 million from the end of 1999 to the end of 2002. This consists of:

- £21m for additional staffing and vehicles
- £3.4 million for satellite navigation,
- £24 million for ECGs and defibrillators.

Thus it seems that £48.4 million is the cost of improving the proportion of priority calls reached within 8 minutes from the figure of 47% in 1999 to the target of 75% by 2002. The sustained cost to meet the target in subsequent years will be £18m per year or very close to the grossed up RAPS estimate.

The two published studies provide boundary estimates and indications of the problems involved with estimating costs. Fischer's work is limited to one service, which if extrapolated nationally implies a cost increase of £112m. The RAPS report, which has the benefit of explicitly addressing the cost for England (but excluding London) puts the cost of meeting the 75% target at £15m. The CHD modelling team adopted the RAPS figures extrapolated to include London and updated to the year 2000 (Chase et al. 2005) and these figures are also used in this chapter.

7.2.9 Costing issues in thrombolysis

The costs to improve the thrombolysis response times have not yet been published. However several papers have reported that the targets can be achieved with extra nurse training and recruitment, for example (Qasim et al. 2002; Wilmshurst et al. 2000).

The CHD modelling team estimated a range of costs to meet the target equivalent to an increase of between one and five nurses of grade G for each A&E department which treats MI (Chase et al. 2005) and these costs are also used in this chapter. The MINAPS report (Birkhead 2003) lists 215 A&E departments in England. This works out at between 4.3 and 21.5 extra nurses per million population needed. The yearly cost of a G grade nurse with 40% added for overheads is £35,000. Thus the cost per million population for extra nurses is between £150,500 and £752,500. For the purposes of this study a midpoint cost of £451,500 is taken.

7.3 Modelling cohorts

Each of the models use homogeneous cohorts of the same age. In sections 7.2.8 and 7.2.9, the cost for the ambulance and thrombolysis scenarios was described per million population, however it is necessary to estimate the cost per individual. The cost for the ambulance scenario was split between all those that have an out of hospital MI, which was taken from UKHAS (Norris 1998), see table 7.3.1. The cost per individual who has a MI was estimated to be about £150. The cost for thrombolysis was split amongst the cohort and is estimated to be about £175 per person who have a MI (or £275 per person with MI who arrives at hospital).

Table 7.3.1 Frequency of out of hospital MI and survivors to hospital from UKHAS scaled to a million population

Age band (years)	Cohort start age	Number of MI	Number of MI who survive to hospital
35-44	40	69	55
45-54	50	283	211
55-64	60	522	370
65-74	70	897	565
75-84	80	864	432
Total		2635	1633

7.3.1 The decision tree model

Decision tree methodology has been described in detail in section 2.3.1. The ambulance and thrombolysis decision tree is shown in Figure 7.3.1. The original analysis consists of two scenarios: original (or baseline) and ambulance scenario where 75% of ambulance arrivals at scene are within 8 minutes.

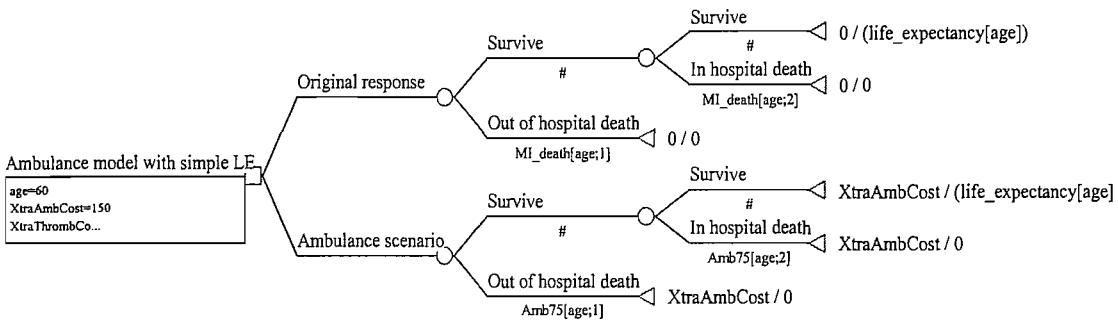

Figure 7.3.1 Decision tree for the ambulance model

The probabilities relating to out of hospital death and in hospital death in the various scenarios and the methodology used to derive them are described in section 7.2 and the parameters are shown in Tables 7.2.4 and 7.2.9. Those patients who survive to hospital discharge are assigned a life expectancy appropriate for their disease and age, whilst those who do not survive have a life expectancy of zero. The life expectancies have been calculated using a simple Markov model in Treeage as described below. For the scenarios, each person in the cohort will incur the cost of the strategy just once. None of the future MIs will be costed and equally none of the future benefits of improved treatment incorporated. The cost of the strategies is shown at the end of each of the branches. This equates to the total extra money spent on this strategy divided by the number of people who had an out of hospital MI and is estimated to be £150 for each out of hospital MI for the ambulance scenario.

7.3.2 Life expectancy model

The simple life expectancy model is shown in Figure 7.3.2. Markov models are described in section 2.3.2. The simple model consists of three states *Survive, Non cardiac death* or *CHD death* where the death states are absorbing states. The simple life

expectancy model calculates the life expectancy from the point of hospital discharge after a non fatal MI. The model incorporates a higher death rate for CHD death in the first year, which is seen in the EMMACE data, see Appendix IX. The data for non CHD death are described in section 6.4.3. Life expectancy was calculated for male and female combined (Table 7.3.2).

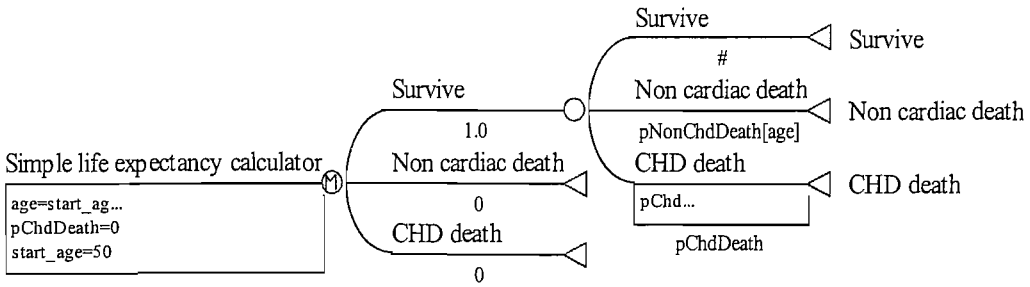

Figure 7.3.2 Simple Markov model used to calculate life expectancy for MI survivors

Table 7.3.2 Life expectancy (age at death) for MI survivors estimated by a simple Markov model and used in the decision tree

Age	Male and female
40	66.6
50	69.4
60	72.7
70	77.6
80	83.8

7.3.3 The Markov model

The ambulance and thrombolysis Markov model is shown in Figure 7.3.3. The model consists of four states, *Post MI 1st year*, *Post MI subsequent years*, *Cardiac death*, and *Non cardiac death*. *Cardiac death* and *non cardiac death* are absorbing states. Individuals who survive a MI have an increased risk of a further MI in the first year than in further years. In each cycle individuals can move between the states or remain in the same state. If an individual has a MI in a cycle then they will move to the *Cardiac death* state if the MI is fatal or the *Post MI 1st year* if the MI is non fatal. Those

individuals who are in the *Post MI 1st year* state will move to the *Post MI subsequent years* state if they do not have a MI in the next cycle.

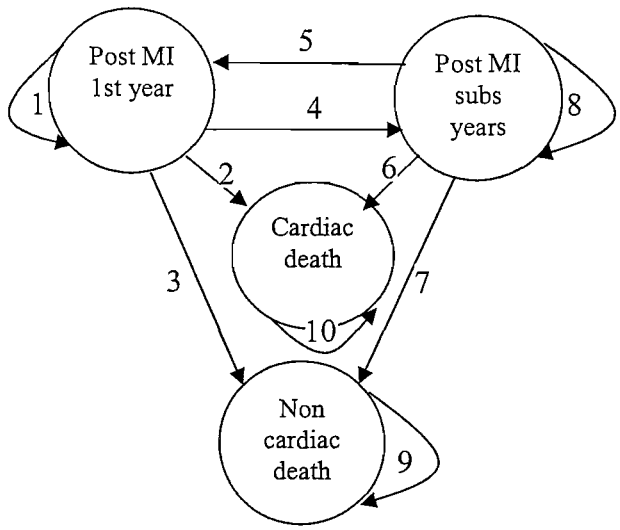

Figure 7.3.3 States of the Markov model for the ambulance and thrombolysis model

The transitions in the model (numbered on diagram) are as follows:

1) Patient has non fatal MI during 1st year post MI
2) Patient has fatal MI during 1st year post MI
3) Patient has Non cardiac death during 1st year post MI
4) Patient has no events during 1st year post MI and joins post MI subs years state
5) Patient has non fatal MI during subs years post MI
6) Patient has fatal MI during subs years post MI
7) Patient has Non cardiac death during subs years post MI
8) Patient has no events during subs years post MI
9) Non cardiac death (Absorbing state)
10) Cardiac death (Absorbing state)

The simple model for calculating life expectancy in section 7.3.2, describes the transition to the cardiac death state by the probability of dying from a sudden cardiac death from the EMMACE dataset. In contrast, the Markov model described here describes transition to the cardiac death state by means of the probability of an MI and then the conditional probability of dying from it. This annual probability of the fatal or

non fatal MI rate has been derived from the EMMACE data (Lawrance et al. 2001) as described in Appendix IX. Thus the probabilities of cardiac death used in the simple life expectancy model in section 7.3.2 can be considered to be more accurate in representing the EMMACE data than the model in section 7.3.3.

Table 7.3.3 Transition probabilities for the Markov model for the ambulance and thrombolysis model (Death rate DR in or out of hospital from UKHAS Table 6.4.4, ONS = Office of National Statistics Table 6.4.3)

Transition	Data source / derived equation	Value for age 40
1)	$0.0325\exp^{0.0337x}*0.641*(1 - \text{DR in out hosp})$	0.062
2)	$0.0325\exp^{0.0337x}*0.641*(\text{DR in out hosp})$	0.017
3)	ONS	0.0013
4)	1 – T1 – T2 – T3	0.92
5)	$0.0159\exp^{0.03x}*0.641*(1 - \text{DR in out hosp})$	0.0264
6)	$0.0159\exp^{0.03x}*0.641*(\text{DR in out hosp})$	0.0074
7)	ONS	0.0013
8)	1 – T5 – T6 – T7	0.965
9)		1
10)		1

The probability of MI or death in 1st year is $0.0325\exp^{0.0337x}$ and in subsequent years is $0.0159\exp^{0.03x}$ where x is the age of the individual. The non cardiac death rate is taken from the Office of National Statistics (1998) (section 6.4.3) and the MI death rate for an individual is taken from the UKHAS (section 6.4.4). The EMMACE dataset had a combination of secondary prevention drugs, which was equivalent to a risk reduction of 0.641 seen in the EMMACE dataset. The transition probabilities are shown in Table 7.3.3 for an individual of age 40.

The model is shown in Figure 7.3.4 as a Treeage model. It includes some of the branches from the decision tree for in and out of hospital death. For the ambulance and thrombolysis scenarios, the changes to out of hospital or in hospital death rate will affect the transition probabilities.

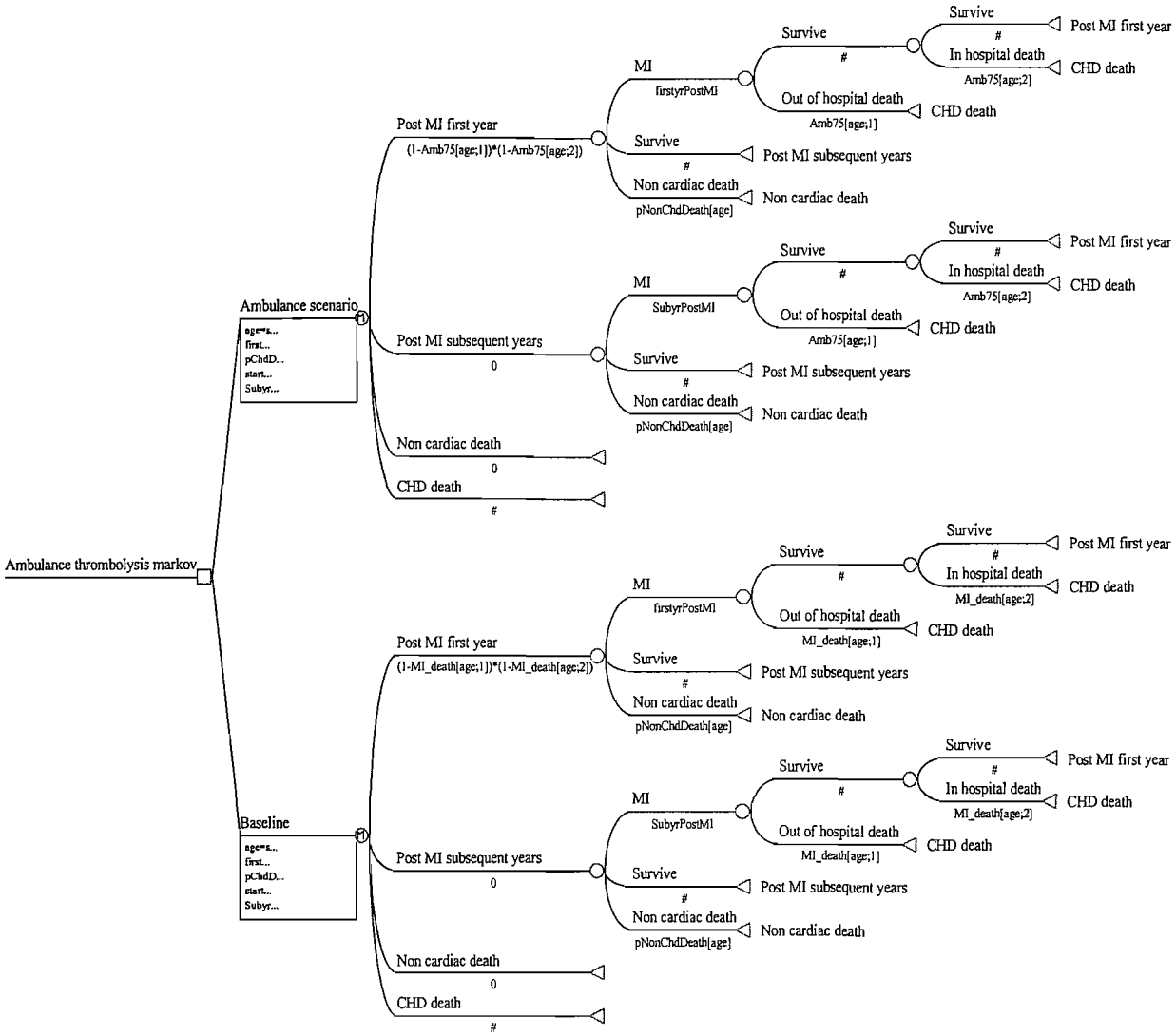

Figure 7.3.4 Treeage diagram of the ambulance and thrombolysis Markov model

In order to compare the Markov model with the decision tree of the ambulance and thrombolysis scenarios the Markov model was set up so that it starts immediately after the initial MI. To do this the initial proportions in the Post MI 1st year state is set to be the proportion of MI survivors (ie 72% at age 50) and set the proportion of initial CHD death to be those who had fatal MI (ie 28% at age 50) from the initial MI. The same data have been used and the same assumptions made as for the decision tree model.

7.3.4 The simulation model

Simulation and Simul8 models have been described in section 2.3.3. The Simul8 screen shot of the model is shown in Figure 7.3.5. It consists of four activities and starting and ending queues.

The cohort is set up in a queue area where each of the individuals have their original characteristics set, ie age, time to MI, time to non cardiac death. The cohort proceeds immediately to the *Next health event.* In order to avoid individuals queuing for this event, the function in Simul8 is replicated many times. Simul8's so called 'Visual logic' is used to set up a mini calendar and the individual's first occurring event is chosen and the individual is routed to the appropriate health event. The individual will wait in this activity until the time of the next event. This is executed by setting the service time of the event to be that of the time to the next event.

If the next event is a MI, the individual proceeds to the *Heart attack* event. At this event, some will have a fatal MI and proceed to *CHD death*. The remainder will have a time set for their next MI and will proceed back to the *Next health event.*

If the next event is a non CHD death, the individual proceeds to the *Non cardiac death* work centre at the appropriate time.

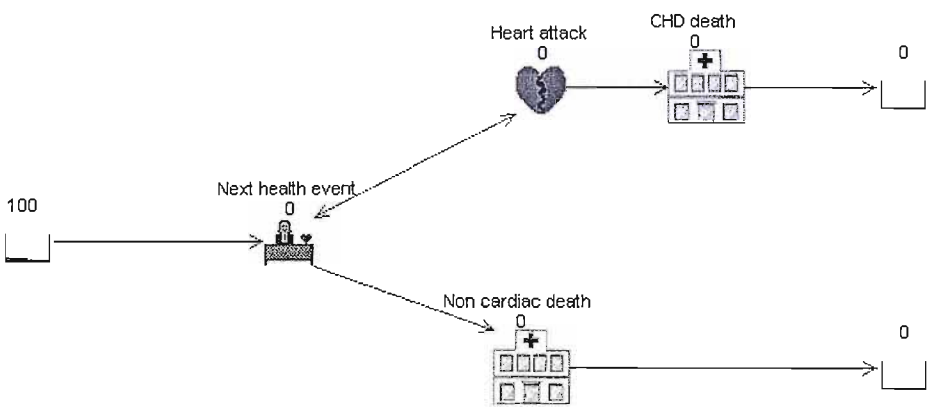

Figure 7.3.5 Simul8 diagram of the ambulance and thrombolysis simulation model

The model uses the ONS data for non cardiac death, EMMACE data for fatal or non fatal MI rate and the UKHAS data for the MI death rate as described in section 6.4.4. The model is run with a cohort of 1000 patients.

As for the Markov model, the cohort starts immediately after their initial MI. To do this the initial time of the next MI event is set to be 0 so that all patients proceed immediately to the *Heart attack* event. The same data and assumptions have been made as for the decision tree model and the Markov model.

7.4 Results from the three models

The models were run for cohorts of different ages who have an initial MI. The simulation model was run for a cohort of 1000 individuals for 50 iterations. The confidence intervals for the runs deviated from the mean by < 1% for each of the age bands.

Table 7.4.1 shows the life expectancy of MI patients of different ages for the different scenarios. Table 7.4.2 shows the increase in life expectancy of the patients for the improved ambulance scenario. The increase in life expectancy varies according to the age of the cohort.

Table 7.4.1 Life expectancy (years of life remaining) of MI patients for the decision tree (DT), Markov (M) and simulation (S) models

Age (years)	**40**	**50**	**60**	**70**	**80**
Baseline (DT)	20.85	13.86	7.64	3.58	1.03
Ambulance (DT)	20.99	13.99	7.70	3.61	1.03
Baseline (M)	20.92	13.80	7.79	3.70	1.15
Ambulance (M)	21.16	13.98	7.87	3.74	1.16
Baseline (S)	21.12	13.91	7.90	3.78	1.16
Ambulance (S)	21.31	14.07	7.98	3.82	1.16

Table 7.4.2 Increase in life expectancy (years)

Age (years)	40	50	60	70	80
Decision tree	0.142	0.125	0.056	0.029	0.006
Markov	0.240	0.184	0.083	0.038	0.008
Simulation	0.198	0.160	0.082	0.043	0.006

Table 7.4.3 shows the increase in cost for the different age cohorts for the models. Using the costs shown above the cost effectiveness is calculated. The gains in life expectancy are largest for the younger age groups and consequently the cost effectiveness is best in these groups (Table 7.4.4). Table 7.4.5 shows the cost effectiveness with costs and benefits discounted at 3%.

Table 7.4.3 Increase in cost (£)

Age (years)	40	50	60	70	80
Decision tree	150	150	150	150	150
Markov	356	315	267	224	185
Simulation	351	311	264	222	183

Table 7.4.4 Cost effectiveness (£/LYS) with no discounting

Age (years)	40	50	60	70	80
Decision tree	£1056	£1200	£2655	£5226	£26,316
Markov	£1480	£1715	£3230	£5860	£23,751
Simulation	£1773	£1939	£3210	£5120	£30,431

Table 7.4.5 Cost effectiveness (£/LYS) with costs and benefits discounted at 3%

Age (years)	40	50	60	70	80
Decision tree	£1990	£1838	£3380	£5899	£27,533
Markov	£1908	£2109	£3874	£6749	£26,447
Simulation	£2035	£2217	£3688	£5862	£30,665

In this case, it may be unethical or unpractical to adopt the ambulance intervention for some age groups and not others so the cost effectiveness of the whole population may be of more relevance. To calculate this, each of the age bands' cost effectiveness ratios are weighted according to the prevalence of MI in that age band (Table 7.4.6).

Table 7.4.6 Annual frequency of MI in a population of one million (Norris 1998)

Age band	**35-44**	**45-54**	**55-64**	**65-74**	**75-84**	**Total**
Frequency of MI	69	283	522	897	864	2635

For a million population, the increase in cost for each age group will be the increase in cost in Table 7.4.3 multiplied by the prevalence of MI in Table 7.4.6. The total cost will be the sum of all the age group costs. This is shown in Table 7.4.7. In a similar way the increase in life expectancy for a million population for each of the age groups is calculated.

Table 7.4.7 Increase in cost (£) for a million population

	35-44	**45-54**	**55-64**	**65-74**	**75-84**	**Total**
Decision tree	10 350	42 450	78 300	134 550	129 600	395 250
Markov	24 543	89 117	139 374	201 287	159 408	613 729
Simulation	24 225	87 897	137 830	199 164	158 016	607 131

Table 7.4.8 Increase in life expectancy (years) and cost effectiveness (£/LYS) for a million population

	35-44	**45-54**	**55-64**	**65-74**	**75-84**	**Total**	**ICER**
Decision tree	10	35	29	26	5	105	£3752
Markov	17	52	43	34	7	153	£4011
Simulation	14	45	43	39	5	146	£4157

The cost effectiveness for the population is found by dividing the total increase in cost for the population by the total increase in life expectancy, and ranges from £3752 for the

decision tree model to £4157 per life year saved for the simulation model. If the costs and benefits are discounted at 3% the cost per life year saved for the population is £5005 for the decision tree, £5074 for the Markov and £4954 for the simulation model.

The results from these runs follow a similar pattern to the simple models in section 5.3. In this case more complex data have been used. For patients in this model there is a higher risk of a repeat event in the first year than in subsequent years. In the decision tree model described here, the parameters used for the life expectancy was calculated without using event rates for MI (section 7.3.2). In contrast, for the Markov model and simulation model further assumptions were necessary in order to estimate the event rate for MI as described in Appendix IX. These assumptions may have introduced some further inaccuracies such that, in this case, the life expectancy estimated for the decision tree may be more accurate than those estimated for the Markov and simulation models.

The results for the simulation model are similar to those from the decision tree and Markov models. Table 7.4.1 shows the average life expectancy for cohorts of different ages for each of the models. The Markov and simulation models have increased benefits from future interventions but also increased cost compared to the decision tree (Table 7.4.2 and Table 7.4.3). However, the undiscounted and discounted cost effectiveness is similar for each of models (Table 7.4.4 and Table 7.4.5).

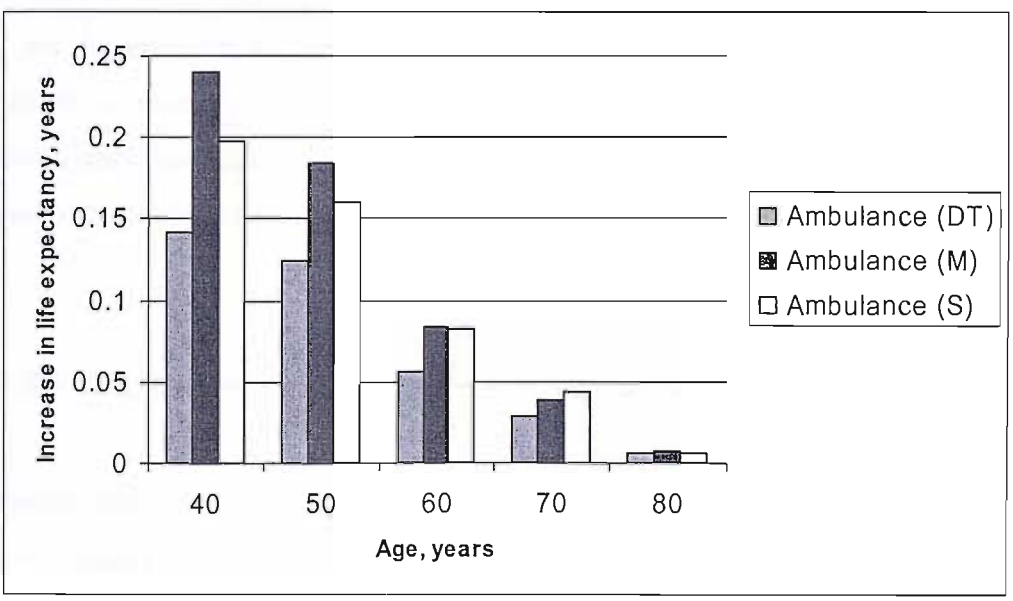

Figure 7.4.1 Increase in life expectancy between the baseline and ambulance scenarios

The undiscounted cost effectiveness is highest in the simulation model, followed by the Markov model and the decision tree model. The reasons for this have been discussed in detail in section 5.2 and 5.3. The mean absolute error between the ICER results from the decision tree and the simulation models is 10%. However when the model results are discounted at 3% the cost effectiveness is very similar between each of the models with a difference of only £120 (or <3%) between the most and least cost effective.

7.4.1 Discussion

The three models give similar results for the cost effectiveness of the ambulance scenario. The decision tree model is not able to evaluate any benefit or costs from any recurrent MI and would underestimate the future costs and benefits of the intervention (hypothesis H2). However, in this case, the decision tree estimates slightly better (or higher) undiscounted cost effectiveness compared to the other models but the discounted cost effectiveness is consistent between all three models.

In the literature review in chapter 3, the decision tree with a Markov model, to estimate life expectancy at the end of the tree's branches, is most commonly used to evaluate short term interventions. The decision tree model was the simplest and quickest model to build and did not need extra analysis to estimate the MI rate. As concluded in chapter 5, the decision tree will underestimate the total costs and benefits but is still able to provide a reasonable estimate of the cost effectiveness. Based on the results seen for the initial analyses and the ambulance scenario a decision tree model was chosen for the rest of the ambulance and thrombolysis scenarios.

7.5 Further results and sensitivity analyses

Further results and sensitivity analyses were performed using the decision tree model. The results and sensitivity analyses are as follows:

7.5.1 Ambulance response times:

The following analyses were compared with the baseline and ambulance ('Ambulance 75') scenarios as described above in section 7.4.

1. 'Best' ambulance scenario. The distribution for ambulance response time gives the same target response time as for the ambulance 75 scenario, ie 75% of calls reached within 8 minutes. The distribution was altered from that shown in Figure 7.2.1 to one with more responses in the quicker time bands, ie the distribution is skewed to the left.

2. 'Worst' ambulance scenario. The distribution for ambulance response time gives the same target response times but the response times were moved the minimal amount possible to achieve that target, ie in the 7-8 minute time bands.

3. Ambulance 90 scenario. 90% of 'life threatening' calls to receive an ambulance response within 8 minutes. The distribution for ambulance response is calculated in a similar way to that for the ambulance 75 scenario.

4. Ambulance and thrombolysis scenario. The Ambulance 75 scenario is combined with the Thrombolysis 30 FTT scenario.

7.5.2 Thrombolysis response times:

The following analyses were compared with the baseline as described above in section 7.4.

1. Thrombolysis 30 FTT scenario. 75% of eligible patients to receive thrombolysis within 30 minutes of hospital arrival using the FTT study (FTT 1994) for the relative mortality risk of thrombolysis.

2. Thrombolysis 20 FTT scenario. 75% of eligible patients to receive thrombolysis within 20 minutes of hospital arrival using the FTT study for the relative mortality risk of thrombolysis.

3. Thrombolysis 30 BMA scenario. 75% of eligible patients to receive thrombolysis within 30 minutes of hospital arrival using the Boersma study (Boersma et al. 1996) for the relative mortality risk of thrombolysis.

7.5.3 Data for the scenarios

The scenarios were run with the data in Tables 7.5.1-7.5.3. The extra cost for the scenarios were £150 for the Ambulance 75 scenarios, £480 for the Ambulance 90 scenario and £175 for the Thrombolysis scenarios, see section 7.2.8.

Table 7.5.1 Out of hospital (OH) and in hospital (IH) mortality rates (%) for the baseline and ambulance 75% scenarios

Cohort	Baseline		Ambulance 75	
age	OH	IH	OH	IH
40	20	2	19.4	2.1
50	25.5	4.1	24.7	4.21
60	29.2	15	28.3	15.41
70	37	25.3	35.9	25.99
80	50	46	48.5	47.26

Table 7.5.2 Out of hospital (OH) and in hospital (IH) mortality rates (%) for the ambulance scenarios

Cohort age	Best Amb 75		Worst Amb 75		Ambulance 90		Ambulance and thrombolysis	
	OH	IH	OH	IH	OH	IH	OH	IH
40	19	2.1	19.8	2	19.0	2.1	19.4	2.0
50	24.2	4.275	25.2	4.065	24.2	4.31	24.7	4.18
60	27.7	15.75	28.85	15.07	27.7	15.78	28.3	15.30
70	35.2	26.575	36.5	25.45	35.2	26.61	35.9	25.81
80	47.4	48.45	49.3	46.34	47.5	48.39	48.5	46.93

Table 7.5.3 Out of hospital (OH) and in hospital (IH) mortality rates (%) for the thrombolysis scenarios

Cohort age	Thrombolysis 30 FTT		Thrombolysis 20 FTT		Thrombolysis 30 BMA	
	OH	IH	OH	IH	OH	IH
40	20	2.0	20	2.0	20	1.9
50	25.5	4.0	25.5	4.0	25.5	4.0
60	29.2	14.8	29.2	14.8	29.2	14.7
70	37	25.1	37	25.0	37	24.9
80	50	45.7	50	45.6	50	45.4

7.5.4 Results from the Ambulance scenarios

The results from the ambulance scenarios are shown in Table 7.5.4 – 7.5.6. Table 7.5.4 shows the benefit in life years for the 60 year old cohort compared to the baseline scenario. Tables 7.5.5 and 7.5.6 show the cost effectiveness for each of the age bands, both undiscounted and discounted at 3%.

Table 7.5.4 Undiscounted increase in life expectancy for the 60 year old cohort compared to the baseline scenario

Ambulance 75	Ambulance 75 'Best'	Ambulance 75 'Worst'	Ambulance and thrombolysis	Ambulance 90
0.056	0.093	0.031	0.066	0.086

Table 7.5.5 Undiscounted cost effectiveness (£/LYS) for the ambulance scenarios

Age (years)	40	50	60	70	80
Ambulance 75	1056	1200	2660	5226	26316
Ambulance 75 'Best'	625	691	1613	3538	37500
Ambulance 75 'Worst'	2830	2459	4839	7009	18750
Ambulance 90	2008	2341	5581	11881	120000
Ambulance and thrombolysis	2241	2500	4924	8690	27083

Table 7.5.6 Cost effectiveness (£/LYS) for the ambulance scenarios with benefits discounted at 3%

Age (years)	40	50	60	70	80
Ambulance 75	1990	1838	3386	5899	27533
Ambulance 75 'Best'	1179	1060	2055	3993	39234
Ambulance 75 'Worst'	5325	3763	6159	7910	19618
Ambulance 90	3789	3591	7110	13411	125549
Ambulance and thrombolysis	4223	3829	6271	9808	28339

The results for the Ambulance 75 scenarios are seen to be very sensitive to how the distribution of calls is chosen. For example for the 60 year old age cohort, the increase in life expectancy varies between 0.03 and 0.09 years for the best and worse scenarios years and the undiscounted cost effectiveness varied between £1610 and £4840 per life years saved.

Figure 7.5.1 shows the overall cost effectiveness for the whole population for the ambulance scenarios. The ambulance 90 scenario and ambulance and thrombolysis scenarios are less cost effective than all the ambulance 75 scenarios.

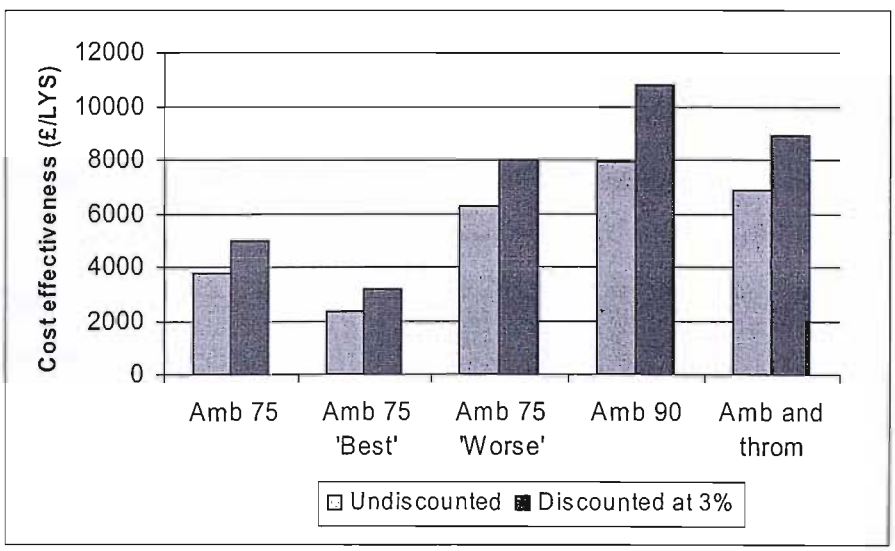

Figure 7.5.1 Cost effectiveness for the ambulance scenarios estimated for the whole population

7.5.5 Results from the thrombolysis scenarios

The results from the thrombolysis scenarios are shown in Tables 7.5.7 - 7.5.9. A 'worse' intervention for the thrombolysis 30 FTT scenario was performed in a similar way to the two Ambulance 75 interventions. The results were similar to the Thrombolysis 20 FTT scenario but are not shown here.

Table 7.5.7 Undiscounted increase in life years for the 60 year old cohort for the thrombolysis scenarios

Thrombolysis 30 FTT	Thrombolysis 20 FTT	Thrombolysis 30 BMA
0.014	0.016	0.023

Table 7.5.8 Undiscounted cost effectiveness (£/LYS) for the thrombolysis scenarios

Age (years)	40	50	60	70	80
Thrombolysis 30 FTT	21875	14583	12500	17500	29167
Thrombolysis 20 FTT	19444	13462	10938	14583	25000
Thrombolysis 30 BMA	15909	10938	7609	9722	14583

Table 7.5.9 Cost effectiveness (£/LYS) for the thrombolysis scenarios with benefits discounted at 3%

Age (years)	40	50	60	70	80
Thrombolysis 30 FTT	41128	22299	15906	19745	30516
Thrombolysis 30 BMA	29913	16726	9683	10971	15259
Thrombolysis 20 FTT	36559	20584	13918	16455	26157

The results were sensitive to the study used for the mortality relative risk estimates. For example, for the 60 year old cohort, benefits from the thrombolysis intervention varies between 0.014 (FTT) and 0.023 (Boersma) years while the undiscounted cost effectiveness varies between £12500 (FTT) and £7600 per life years saved (Boersma).

There was little additional benefit seen by the Thrombolysis 20 FTT scenario. For these analyses it was assumed that the cost for the 20 minute scenario was similar to the 30 minute scenario which may not be the case.

Figure 7.5.2 shows the estimated cost effectiveness for a population. As discussed in section 7.2.8 the cost used for these scenarios was the mid point from a range of cost estimates. Using these costs, the thrombolysis scenarios were less cost effective than the ambulance scenarios. If the full range of cost estimates for thrombolysis are used the results are much more varied. The Thrombolysis 30 FTT varied between £5000 and £25000 using the range of cost estimates for thrombolysis.

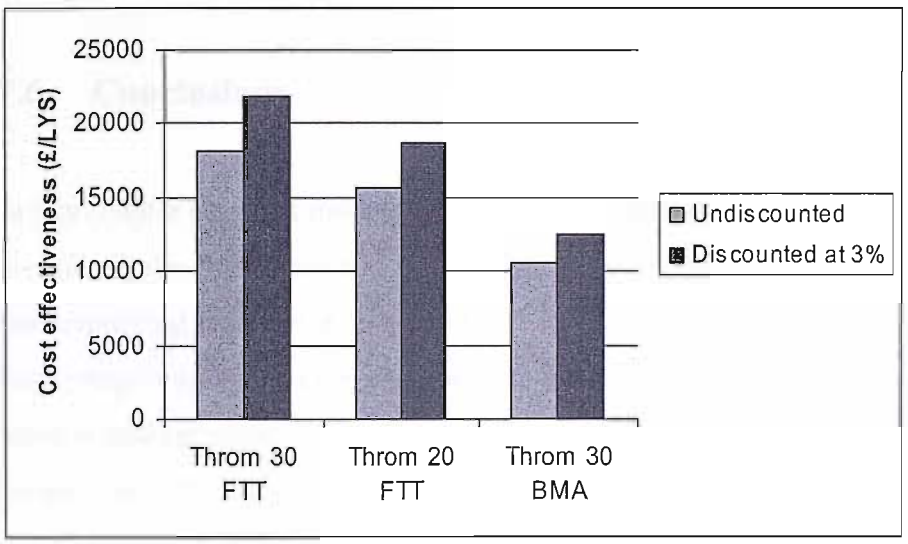

Figure 7.5.2 Cost effectiveness (£/LYS) for the thrombolysis scenarios estimated for the whole population

7.5.6 Discussion on the ambulance and thrombolysis scenarios

The results from the ambulance and thrombolysis scenarios indicate that improving ambulance response times is likely to be a cost effective intervention. The intervention for thrombolysis response time is much less cost effective. Furthermore little benefit is seen from moving from the 30 minute to the 20 minute thrombolysis target. This is likely to be because there are often long delays between the onset of pain and when the patient calls for an ambulance.

The models for ambulance and thrombolysis presented in this chapter estimate the cost effectiveness of reaching the NSF targets. However there are several potential limitations to the models. Firstly, the models assume an average effect across England and Wales. Clearly there will be wide variation in the ability of individual ambulance services to achieve the NSF targets. The figures presented here assume that hospital units will achieve the targets based on the extra NHS spending allocated. There has been much speculation in the popular press on the reliability of ambulance response targets which are measured by the individual ambulance services. Further the thrombolysis costing was based upon expert opinion as changes to the implementation of thrombolysis were still at an experimental stage.

7.6 Conclusions

In this chapter complex models for short term interventions have been developed to describe faster ambulance and thrombolysis response times. The models results show that improving ambulance response times is likely to be a cost effective intervention but improving thrombolysis response times is much less cost effective. The decision tree, Markov and simulation models estimate an incremental cost effectiveness ratio of between £3750 and £4160 per life years saved for the ambulance intervention. The decision tree model estimates an incremental cost effectiveness ratio of £21,800 per life years saved for the thrombolysis intervention.

Using these models it has been shown that decision trees models are an appropriate technique for modelling the cost effectiveness of short term interventions. In our example the cost of the intervention is constant over time, and there is a more optimistic undiscounted estimate of the cost effectiveness of the intervention by the decision tree model compared with the simulation and Markov models. However the discounted cost effectiveness for the decision tree was similar to those estimates from the Markov and simulation model.

Where the study is interested in the long term benefit (eg patient lifetime) of the intervention, the decision tree is particularly effective where the intervention is only

likely to occur once (Hypothesis 1). It has been shown that if the intervention occurs more than once in the long term, the decision tree will only give the cost and benefits from the first of these interventions. This led to an underestimate of the actual lifetime costs and benefits for this intervention. For more accurate estimates of the true lifetime costs and benefits a Markov or simulation model should be used (Hypothesis 2).

The decision tree model is also useful for evaluations which use an intermediate outcome measure or where the data are not in the required format for the Markov and simulation models. For example in our model, the data gave longer term death rates after MI; however there was no information on future MI event rates. Thus it was easier (and probably more accurate) to estimate the life expectancy of these patients rather than to derive the MI event rates needed for the Markov and simulation models.

Chapter 8

Chronic Treatment Interventions: Models for Secondary Prevention Drugs

Abstract

In this chapter Markov and simulation cohort and population models are built to evaluate the costs and benefits from secondary prevention drugs for coronary heart disease patients. The choice of modelling technique for chronic (long-term) treatment interventions is investigated using the case study approach. Some of the conclusions from chapter 5 for the simple experimental models are tested in a more complex and realistic model to see if they still hold true.

It was estimated that the additional annual cost of expanding the use of secondary prevention drugs according to the National Service Framework for Coronary Heart Disease would be about £250 million for the UK. The secondary prevention drugs would save an estimated 6000 lives per year and 60 000 patient life years. Increasing aspirin and beta blocker usage would be excellent value for money with ICER of £690 and £740 respectively. Increasing ACE inhibitor and statin use would also be good value for money with ICER of £3080 and £5400 respectively.

Using these models it is concluded that in the first instance the Markov model was the most suitable model to be used. However, the realism of the models is increased by introducing more assumptions and parameters and the simulation model became the most suitable model to use. Furthermore it was more complex to build the population-based than the cohort model. It is concluded that there was a threshold complexity level below which the Markov was the most appropriate and above which the simulation should be chosen.

Chapter 8 Chronic Treatment Interventions: Models for Secondary Prevention Drugs

8.1 Introduction

In this chapter, long term interventions are studied, in particular the use of secondary prevention drugs in coronary heart disease. DES and Markov models are developed for secondary prevention drugs.

In Chapter 3 it was concluded that Markov models were most often used to estimate the cost effectiveness of long term interventions although none of the studies justified the use of this modelling technique. Furthermore, virtually all of the studies used the cohort rather than population approach. In Chapter 5, simple Markov and simulation models for long term interventions were examined. The results were compared and were similar for the two models. The results were compared for the population and cohort approach and it was concluded that the population based approach provided a more comprehensive summary of the value of the intervention for the health care planner than a cohort analysis. In this chapter some of these hypotheses and conclusions are examined with a real life example from Coronary Heart Disease for secondary prevention drugs. Markov and simulation based models are built using the population and cohort approaches.

Unless indicated otherwise, the results for the models are shown in terms of cost (£), effectiveness (years of life saved) and cost effectiveness (incremental cost effectiveness ratio (ICER, £/life years saved)). The incremental cost effectiveness ratio is shown as the difference in cost between the treatment scenario and baseline divided by the difference in effectiveness between the treatment scenario and baseline.

8.2 Secondary prevention for Coronary Heart Disease

This models built in this chapter are based upon research completed by the author as part of the UK Coronary Heart Disease Policy Model working team (Appendix I). In particular much of the data have been collected by other members of the group and is described in more detail in the Secondary Prevention Working paper (Roderick et al. 2003). Furthermore the modelling work here was done in consultation with other members of the group.

Secondary prevention treatment has been shown to lead to significant reductions in CHD mortality and events. Secondary prevention refers to the use of drugs and other treatments which reduce the risk of recurrent coronary heart disease events in patients with existing coronary heart disease. It includes drug therapy (eg aspirin, beta blockers, ACE inhibitors and statins) and lifestyle change (eg cardiac rehabilitation). In the studies in this chapter only the benefits of drug therapy are considered.

3-Hydroxy-3Methylglutaryl-Coenzyme A (HMG-CoA) Reductase Inhibitors or 'statins' reduce the production of cholesterol in the liver, and so reduce the risk of both initial or primary CHD events and recurrent or secondary CHD events. The most common statins are atorvastatin, fluvastatin, pravastatin, simvastatin, lovastatin and cerivastatin. Beta blockers act to slow the heart rate and lower blood pressure by blocking the effects of adrenaline. Angiotensin converting enzyme (ACE) inhibitors blocks an enzyme normally present in the body and so causes the blood vessels to relax. Antiplatelet drugs, such as aspirin and clopidogrel, help to stop the blood clotting by reducing its viscosity.

The Government in the United Kingdom planned to increase considerably the resources spent on patients with coronary heart disease (CHD) (Department of Health, 2000). The National Service Framework proposed higher secondary prevention interventions, including 80-90% of patients using aspirin, statin and beta blocker after a myocardial infarction (MI). We evaluated the health gains and costs associated with increasing the provision of secondary prevention drugs in line with the National Service Framework targets using discrete event simulation and Markov models.

8.2.1 Other studies for secondary prevention drugs

The other studies that have evaluated secondary prevention drugs are described in more detail in section 3.5 and 3.6.

8.2.1.1 Statins

The cost effectiveness of statins has been assessed by many studies (Tsevat et al. 2001; Prosser et al. 2000; Russell et al. 2001; Goldman et al. 1991; Huse et al. 1998; Johanesson et al. 1997; Pharoah and Hollingworth 1996; Elliott and Weir 1999; van Hout and Simoons 2001; Muls et al. 1998; Cobos et al. 1999; Maclaine et al. 2001; Ganz et al. 2002; Grover et al. 1998, 1999; Pickin et al. 1999; Ebrahim et al. 1999; Ashraf et al. 1996; Palmer et al. 2003; Scuffham and Chaplin 2004), see Table 3.5.1. Most of the studies measured the outcome of life years saved, rather than quality adjusted life years saved. The quality of life of patients on statins was assumed to be not statistically different to those not on statins.

Several of the studies have compared the cost effectiveness of individual statins (Russell et al. 2001; Huse et al. 1998; Elliott and Weir 1999; Cobos et al. 1999; Maclaine et al. 2001; Palmer et al. 2003) with each other (section 3.5.1). Other studies use one statin or other, often according to the statin used in a particular trial, to assess the effectiveness of statins. As mentioned above, statins reduce cholesterol levels and this in turn reduces the risk of CHD events. Some of the studies have calculated the reduction in cholesterol levels and applied survival equations (Russell et al. 2001; Huse et al. 1998; Maclaine et al. 2001; Elliott and Weir 1999; Goldman et al. 1991; Grover et al. 1998, 1999; Johanesson et al. 1997) for example the Framingham equations, while others have used a risk reduction applied to the CHD event rate (Ashraf et al. 1996; Ebrahim et al. 1999; Ganz et al. 2000; Muls et al. 1998; Pharaoh and Hollingworth 1996; Pickin et al. 1999; Tsevat et al. 2001; Van Hout and Simoons 2001). Several studies have simulated and then extended clinical trials, for example the CARE trial (Tsevat et al. 2001; Van Hout and Simoons. 2001), PLAC I & II (Ashraf et al. 1996; Muls et al. 1998), 4S (Johannesson et al. 1997; Van Hout and Simoons 2001), LIPID (Van Hout and Simoons 2001), LIPS (Scuffham and Chaplin 2004). All of the studies conclude that statins represent good value and the higher the risk of the patient of CHD

events, the more cost effective statins are. Furthermore, the general consensus was that statins should be considered for individuals with coronary heart disease and individuals without CHD but who are at high risk of developing CHD.

8.2.1.2 Other secondary prevention drugs

The cost effectiveness of medical therapies have been assessed by several studies (Phillips et al. 2000; Doyle et al. 2002; Gaspoz et al. 2002; Lindgren et al. 2004; Tsevat et al. 1997; Thaulow et al. 2002), see Table 3.6.1. Philips et al. (2000) and Gaspoz et al. (2002) both used the Coronary Heart Disease Policy model to evaluate beta blocker use after MI, and aspirin and clopidogrel respectively. Lindgren et al. (2004) used a Markov model and Main et al. (2004) used a decision tree to evaluate clopidogrel for patients with acute coronary syndromes. Tsevat et al. (1997) used a Markov model to evaluate captopril therapy after MI. Doyle et al. (2002) used a Markov model to evaluate the use of amlodipine. Thaulow et al. (2002) used a decision tree to evaluate amlodipine in patients undergoing angioplasty procedures. Each of the secondary prevention drugs were found to be cost effective.

8.2.2 Parameters for the secondary prevention models

Secondary prevention drugs have been shown to lead to significant reductions in CHD mortality and events. For the purpose of the model, parameters for the efficacy of the drugs are required in terms of their reduction in coronary heart disease events and the current use of the drugs by CHD patients. The efficacy data have been derived from randomised control trials and systematic overviews with meta-analyses. The current use of the drugs has come from observational surveys and audits. The following clinical evidence has been researched by the UK CHD Modelling Team (Roderick et al. 2003.)

8.2.2.1 Clinical evidence for Aspirin

The Antiplatelet trialists Collaboration (1994) completed an overview of aspirin usage in approximately 40 000 patients with a history of MI and other cardiovascular disease. They concluded that the risk of fatal and non fatal events would be reduced by

approximately 25%. The reduction in CHD mortality risk was less than that for non fatal MI.

'*The overview included all published or unpublished trials by 1990 and provided conclusive evidence for the effectiveness of aspirin in secondary prevention of CHD. Most trials included were of a relatively short duration and the authors were not able to comment on the optimal duration of treatment. The weighted average duration of trials, post MI, was 27 months. The consensus is that treatment with aspirin should be life-long for people with CHD who have no contra-indications and who can tolerate treatment. The APTT information was extended with publication of ATT analysis in 2002. This included 287 trials to 1997 involving 135,000 patients. The effect of aspirin was similar regardless of sex, age group or co-morbidity with hypertension or diabetes.*' (Roderick et al. 2003).

The APTT study reported a non compliance rate of 20% at one year. Campbell et al reported 8.5% of patients had contra-indications to aspirins due to ulcer or allergies.

8.2.2.2 Clinical evidence for Beta blockers

The use of beta blockers reduces the relative risk of mortality after an MI by 23% with a similar relative risk reduction for non-fatal re-infarction (Freemantle et al. 1999). There is no current evidence that there is a prognostic benefit for beta blockers in treating stable angina. The use of beta blockers is limited by the proportion of CHD patients with contra-indications to their use. This was approximately 29% in one study but other authors have suggested contra-indications as low as 10%. Withdrawal rates of 24% are quoted in trials (Campbell et al. 1998).

8.2.2.3 Clinical evidence for ACE inhibitors

ACE inhibitors were initially used after an MI only in people with overt heart failure after benefits were shown in the AIRE trial (1993). The SAVE (1992) and TRACE (Kober et al. 1995) trials have shown benefits for patients without heart failure after MI. A meta-analysis of these trials and others showed a reduction in deaths of 26% and non fatal MI of 20% (Flather et al. 2000). The HOPE trial (Yusuf et al. 2000) showed

similar benefits in those at risk of CHD which includes patients with no history of MI. Non compliance was 40% by 18 months in the AIRE trial and 29% in the HOPE trial. Contra-indications ranged between about 2% and 11% in the trials.

8.2.2.4 Clinical evidence for Statins

There have been several trials which have demonstrated the benefits of statins, for example 4S (1994), CARE (Sacks et al. 1996), LIPID (1998), and WOSCOPS (1997). The MRC/BHF (2002) study showed statins to be effective in reducing coronary events in all ages, both sexes, at any level of baseline cholesterol and were independent of other secondary prevention treatments. The trial estimated that statins reduced the risk of non fatal MI and CHD death by 27% over five years. Five per cent of the trial had contra-indications and 18% were non compliant at five years.

8.2.2.5 Summary of clinical evidence

Table 8.2.1 shows the relative risk reductions of CHD deaths derived from these trials. Aspirin was found to have a higher relative risk reduction for non fatal MI than for CHD mortality. In the models in this chapter, the conservative assumption is made that the relative risk reduction was the same for MI as for deaths because the model treats MI and deaths together.

Table 8.2.1 Relative risk of death compared to those not taking the drugs. (Sources: 1) APTT (2000) 2) Freemantle et al (1999) 3) Flather et al (2000) 4) MRC/BHF (2002) (Table from Roderick et al. 2003)

	Aspirin	**Beta Blocker**	**ACE Inhibitor**	**Statin**
Angina, no MI	0.75[1]	1	0.8[3]	0.73[4]
After MI	0.75[1]	0.77[2]	0.8[3]	0.73[4]

Each of these types of drug has side effects for some people, and so there is a proportion of people for whom they are contra-indicated. It is assumed that the impact of each

drug was independent of the others and that the probability of a person suffering side effects from one drug was independent of the probability of them suffering side effects from the others.

8.2.3 Use of secondary prevention drugs

The models in this chapter use estimates for the current drug use. These data are stratified according to patient age, health state (angina, MI) and the patient arrival status (prevalent or new). Table 8.2.2 shows the current percentage of patients who are already taking the secondary prevention drugs, (derived from recent audits) or are prescribed to them when they present as new patients. Where possible the most recent and more representative studies have been chosen. These estimates were from Health Survey for England (Eren et al. 1999), North West Anglia Audit (2001), PRAIS (Collinson 2000), and SHIP (Jolly et al. 1999), MINAP (2001) and UKHAS (Norris 1998).

Table 8.2.2 Patients currently taking drugs used for secondary prevention (Sources 1) HSE, 2) NWAHA, 3) SHIP, 4) MINAP, 5) PRAIS, 6) UKHAS; Table from Roderick et al. 2003)

%	Aspirin	Beta Blocker	ACE Inhibitor	Statin
Prevalent CHD patients				
Angina – no MI	40[1]	28[1]	13[1]	16[1]
Angina – post MI	70[2]	27[1]	31[1]	23[1]
No angina – post MI	70[2]	17[1]	24[1]	18[1]
New CHD patients				
Stable angina	76[3]	41[5]	13[1]	16[1]
Myocardial infarction	88[4]	41[5]	30[6]	30[6]
Contra-indications	10	10	5	5

8.2.4 Costs

A more detailed discussion of the data for coronary heart disease costs can be found in the UK Coronary Heart Disease Policy Model Working paper on Costs (Raftery et al. 2003). A full list of the derived costs for coronary heart disease is shown in Appendix VI. The estimated cost per patient is £368 per year which includes GP and cardiology appointments and non secondary prevention drugs costs (such as nitrates and calcium channel blockers). The estimated cost per MI admission is £2,200 which includes the cost of the hospital stay, CCU, thrombolysis and the ambulance. This cost includes the cost of unstable angina which is assumed to happen at the same rate as MI. The estimated cost for revascularisation is £5.4 million per million population and is assumed to be unchanged by any of the secondary prevention scenarios.

The model includes the effects and costs of drugs at class rather than individual drug level. The cost of drugs is based on Defined Daily Dosages (DDDs) obtained from the Prescription Pricing Authority (PPA) (Raftery et al. 2003). Table 8.2.3 shows the estimated annual cost for each patient for each of the secondary prevention drugs.

Table 8.2.3 Secondary prevention drug costs

	Aspirin	**Beta Blocker**	**ACE Inhibitor**	**Statin**
Cost per patient per year, £	20	52	95	237

8.3 Description of the models

The Markov and DES models in this chapter are developed, as far as possible, to be identical to each other. Accordingly, they use the same parameters for transitions between states and costs.

8.3.1 The simulation model

Figure 8.3.1 shows the CHD discrete event simulation model for statins. The model starts with a prevalent population of CHD patients who have angina but no history of previous MI, angina and previous MI, and MI but no angina. Individuals with no previous CHD enter the model with new cases of angina, MI and unstable angina each year. For each individual, times are sampled from distributions for their time to MI and this may be either fatal or non fatal. Each of the health states have different distributions for their time to MI. They may also die from a non CHD cause.

The model and the general CHD parameters are described in more detail in section 6.3. The prevalence and incidence data are taken from the General Practice Research Database (Lawrance et al. 2001) and the Bromley study (Sutcliffe et al. 2003) and are shown in section 6.4 (Table 6.4.1 and 6.4.2). The non cardiac death rates are from ONS and are shown in Table 6.4.3. The annual probabilities of a MI for the different states have been derived from EMMACE in appendix IX and are shown in Table 8.3.1. The in and out of hospital death rates are from UKHAS and are shown in Table 6.4.4.

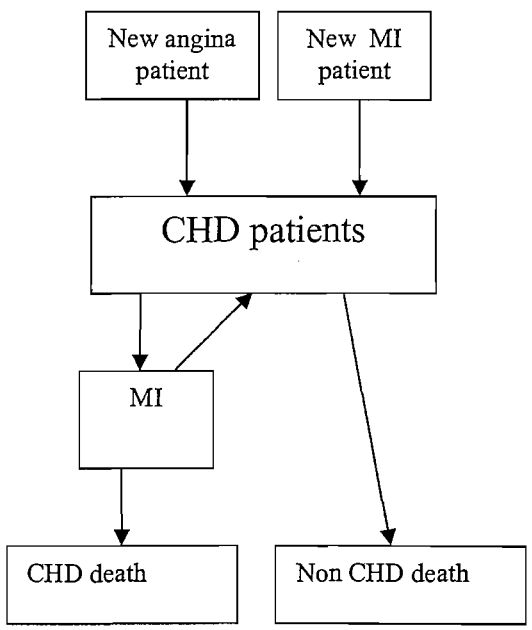

Figure 8.3.1 The discrete event simulation model of the treatment of coronary heart disease for secondary prevention drugs

Table 8.3.1 Derived annual probability of MI (x is age of patient)

Patients	Annual probability of MI
Angina only	$0.0107\exp^{0.0155x}$
History of MI: first year after MI	$0.0325\exp^{0.0337x}$
History of MI: after first year after MI	$0.0159\exp^{0.03x}$

In the model, individual patients are allocated randomly to each of the secondary prevention drugs. Prevalent patients and new patients are initially allocated drugs according to the Table 8.2.2. Patients who have a MI will be re-allocated drugs according the new MI arrivals in this Table.

A patient's risk of MI will be changed according to the product of all the relative risks of the secondary prevention drugs to which they have been allocated. For each secondary prevention drug, the relative risk for the population, RR_{iP} is

$$1/(1 - prev_i(1 - RR_i))$$

where $prev_i$ is the proportion of people on that drug and RR_i is the relative risk for a person on that drug. As mentioned above, each of the drugs work in a slightly different way to reduce coronary events and there has been some evidence from studies that their effects are independent. Thus it is assumed independence between the benefits of the drugs, and so the overall effects of the drugs on the population is the product of the relative risk for the individual drugs on the population.

The discrete event simulation is a simpler version of that developed by Davies et al (2003a). It does not include other treatments, such as revascularisation, ambulance and thrombolysis or cardiac rehabilitation. In addition it does not model unstable angina occurrence. However the costs from these events are modelled in relation to the number of patients in the model. For example, the ambulance and thrombolysis and unstable angina costs are added in relation to the number of MIs, and the revascularisation costs are added in relation to the total population modelled. The costs are described in more detail in the Appendix VI.

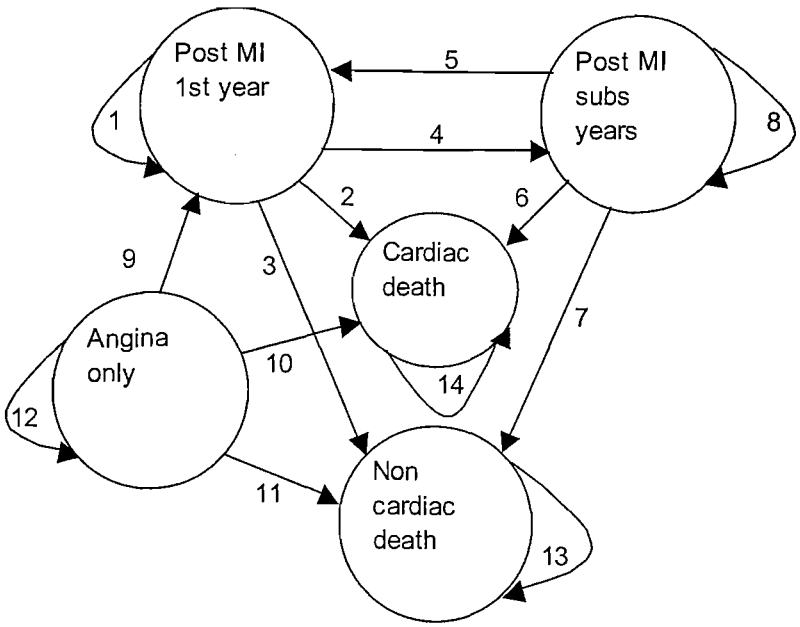

Figure 8.3.2 The Markov model of the treatment of coronary heart disease for secondary prevention drugs

8.3.2 The Markov model

The Markov model is shown in the Figure 8.3.2 with the 14 possible transitions between the states. The model shown in the diagram is the cohort model. The population based model follows a prevalent starting cohort and then new cohorts are added each year. The cycle length is one year. The prevalent starting states are Angina only and Post MI subs years, and incident patients begin in Angina only and Post MI 1st year. The method for the population analysis for the Markov model is shown in more detail in section 2.2.6. It uses the information from the Markov cohort model. This consists of a cohort model for six ten-year age bands for each of the three possible starting states. The transition rates between the states have been described above for the simulation model.

The transitions in the model (numbered on diagram) are as follows:

1) Post MI patient has non fatal MI during 1st year post MI
2) Post MI patient has fatal MI during 1st year post MI
3) Post MI patient has Non cardiac death during 1st year post MI

4) Post MI patient has no events during 1st year post MI and joins post MI subs years state

5) Post MI patient has non fatal MI during subs years post MI

6) Post MI patient has fatal MI during subs years post MI

7) Post MI patient has Non cardiac death during subs years post MI

8) Post MI patient has no events during subs years post MI

9) Angina patient has non fatal MI

10) Angina patient has fatal MI

11) Angina patient has Non cardiac death

12) Angina patient has no events

13) Non cardiac death (Absorbing state)

14) Cardiac death (Absorbing state)

Table 8.3.2 Transition probabilities for the Markov model for the secondary prevention model (with baseline relative risks RR1 = 0.84, RR2 = 0.7; Death rate DR in or out of hospital from UKHAS Table 6.4.4; ONS = Office of National Statistic Table 6.4.3)

Transition	Data source / derived equation	Value for age 40
1)	$0.0325\exp^{0.0337x}$*RR2*(1 - DR in out hosp)	0.068
2)	$0.0325\exp^{0.0337x}$*RR2*(DR in out hosp)	0.019
3)	ONS	0.0011
4)	1 – T1 – T2 – T3	0.91
5)	$0.0159\exp^{0.03x}$*RR2*(1 – DR in out hosp)	0.029
6)	$0.0159\exp^{0.03x}$*RR2*(DR in out hosp)	0.0079
7)	ONS	0.0011
8)	1 – T5 – T6 – T7	0.952
9)	$0.0107\exp^{0.0155x}$*RR1*(1 – DR in out hosp)	0.013
10)	$0.0107\exp^{0.0155x}$*RR1*(DR in out hosp)	0.0036
11)	ONS	0.0011
12)	1 – T9 – T10 – T11	0.98
13)		1
14)		1

The Markov model was written in Excel because it was desirable to use software which is widely available to non health economists. In addition, current versions of TREEAGE are more suitable for cohort analyses and the population analysis has to be calculated from this in Excel. By using Excel, the scenarios are completely interactive, whereas all the scenarios computed in TREEAGE would have to be copied into EXCEL for starting state and age group (ie 18 times for each scenario).

The Markov model took six weeks to write in Excel compared to the two weeks it took to build the simulation model, although the simulation model is similar to that developed by Davies et al (2003a) which reduced the time to build it. Clearly the time to build the models is dependent on the expertise of the modeller and other people may have taken more or less time for either of the models. The time taken is also dependent on the flexibility of the software used. For example if there were a version of TREEAGE that calculated population analyses then the model build time would likely be much shorter.

8.4 Cohort versus population simulation model

In this section the results are compared between the cohort and population based method for the simulation model. Simple cohort and population based models were compared in section 5.5 and it was shown that the cohort and population-based approaches will yield different results and the population-based approach will give a worse (or higher) cost effective ratio compared to the cohort-based approach. In this section this is extended to more realistic models. The simulation model described above was run with a scenario of increased statin usage and compared to the baseline scenario for the cohort and population based method. The model was run for 40 years for the CHD prevalence from a population of 125,000 for all age bands. For the cohort simulation, the model started with the prevalent population and for the population simulation, the model started with the prevalent population and had an incident population entering the simulation each year.

In the baseline run, new patients entering the model are allocated statins according to the rates specified in Table 8.2.2. In the intervention run, 80% of all new individuals are allocated to statins. Prevalent patients who have CHD at the beginning of the simulation runs take the drug as shown in Table 8.2.2.

The results from the runs are shown in Tables 8.4.1 for the cohort based runs and Table 8.4.2 for the population based runs. As before in section 5.5, the cost effectiveness for the population based runs is roughly 11% and 19% worse than the cohort runs for the discounted and undiscounted cases respectively.

Table 8.4.1 Results from the cohort simulation shown for whole population over patient lifetimes for a scenario with increased statin use; discounted results are discounted at 3% for costs and benefits

	Increase in life expectancy (yr.)	**Increase in cost (£ Million)**	**Cost effectiveness (£/LYS)**
Undiscounted	3358	9.9	2950
Discounted	2119	7.2	3420

Table 8.4.2 Results from the population simulation shown for 40 years for population for a scenario with increased statin use; discounted results are discounted at 3% for costs and benefits

	Increase in life expectancy (yr.)	**Increase in cost (£ Million)**	**Cost effectiveness (£/LYS)**
Undiscounted	7908	27.9	3520
Discounted	4191	15.9	3800

8.5 Models for secondary prevention drugs

In this section, the differences between the Markov and simulation models are investigated for the secondary prevention drugs using the population approach. The models use estimates for the current drug use. These data are stratified according to health state (angina with no previous MI, post MI). Table 8.5.1 shows the current percentage of patients who are already taking the secondary prevention drugs, (derived from recent audits). For these models, the drug uptake has been simplified from that shown in Table 8.2.2 and used by Davies et al (2003a). For these models in this section, the proportion of people on the drugs remains constant throughout the runs whereas in the model by Davies et al (2003a) the proportion of people on the drugs increased over time as might be expected in reality. The models were simplified in order to avoid a large increase in the number of states in the Markov model and this is discussed in more detail in later sections.

Table 8.5.1 Patients currently taking drugs used for secondary prevention (Sources 1) HSE (Eren et al. 1999), 2) NWAHA (2001))

%	Aspirin	Beta Blocker	ACE Inhibitor	Statin
Angina – no MI	40[1]	28[1]	13[1]	16[1]
Post MI	70[2]	23[1]	28[1]	21[1]

Table 8.5.2 Increased usage scenario for secondary prevention

%	Aspirin	Beta Blocker	ACE Inhibitor	Statin
Angina – no MI	80	28	80	80
Post MI	80	80	80	80

8.5.1 Results

The models were run for 40 years with a population of 125,000. The simulation model was run with 200 iterations. A baseline run using the drug prevalence in Table 8.5.1 was

compared to a statin scenario using increased statin usage shown in Table 8.5.2. Note that there is no increase in the use of any of the other drugs.

Table 8.5.3 Average results over 40 years from the Markov (M) and simulation (S) models for the statins scenario compared to baseline

	CHD patients	Life Year Saved	Cost (£000s)	Inc Cost (£000s)	All deaths	CHD deaths	ICER (£/LYS)
Baseline M	4,205		3,079		400	229	
Statin M	4,403	198	3,775	696	394	211	3520
Baseline S	4,245		3,147		399	226	
Statin S	4,436	190	3,850	703	393	208	3690

Table 8.5.4 Relative (%) error for the Markov model compared to the simulation model for the results shown in Table 8.5.3

	CHD patients	Life Year Saved	Cost	Inc Cost	ICER
Relative Baseline	0.9		2.2		
Relative Statin	0.7	-3.8	1.9	0.9	4.5

The results are shown in Table 8.5.3 and 8.5.4 and Figures 8.5.1-4 for the statin scenario. Note the axes for each of the graphs have been truncated. The average number of patients is higher in the simulation model than the Markov (Figure 8.5.1). Similarly the average cost is higher in the simulation model than the Markov model. The corresponding number of CHD deaths (Figure 8.5.3) and all cause deaths are higher for the Markov model than for the simulation model. The reason for the higher event rate has been discussed in the simple models chapter (section 5.2.1.2).

The differences between the results from the two models cannot be explained by the variability of the simulation run results. The variance of the simulation runs was calculated and the 95% confidence intervals for CHD patients and costs are +/- 2 and £1.5 respectively. The 95% confidence intervals for life years saved and increase in cost

were +/- 0.5 and £1 respectively. In section 5.2.1.2, it was demonstrated that if the data are interpreted in the same way for the two models, they would yield marginally different results and this is confirmed in this example. Furthermore according to the discussion in section 5.2 on acceptable error between the models, the model results are different to each other (Table 8.5.3) however it is not expected that the differences between the results is large enough to lead to different conclusions from the results from each model.

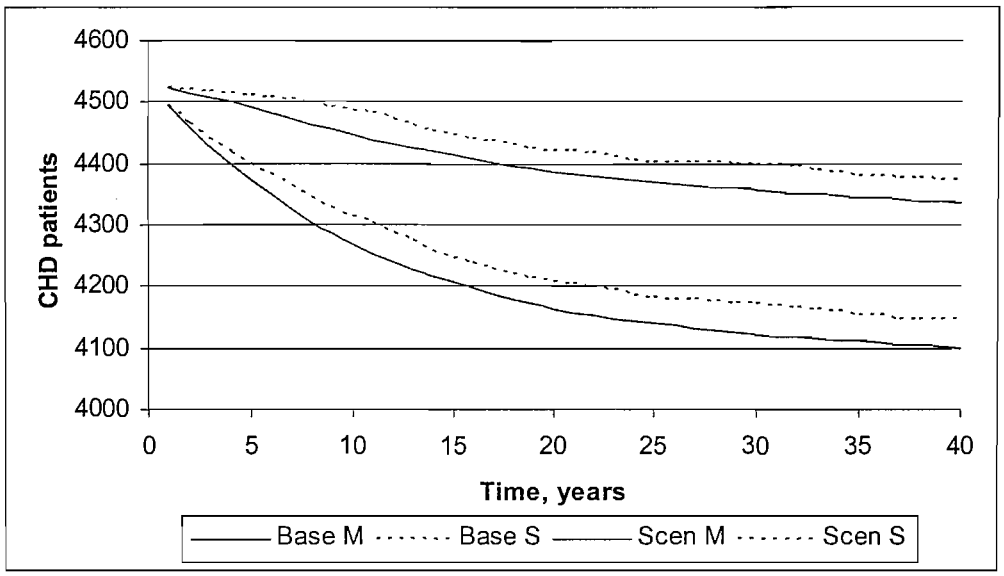

Figure 8.5.1 CHD patients for Markov (M) and simulation (S) models for the baseline and scenario (Note truncated y axis)

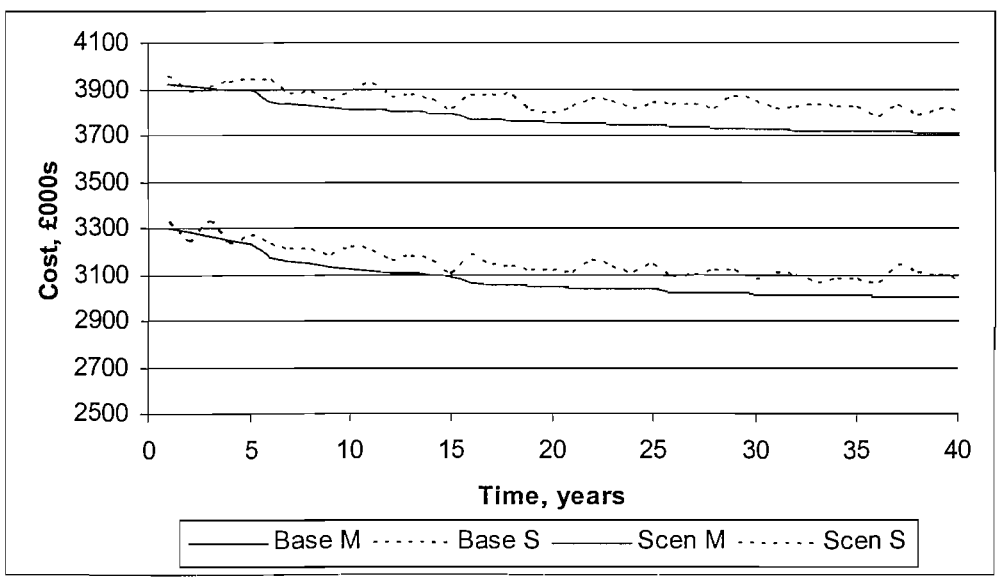

Figure 8.5.2 Costs (£000s) for Markov (M) and simulation (S) models for the baseline and scenario (Note truncated y axis)

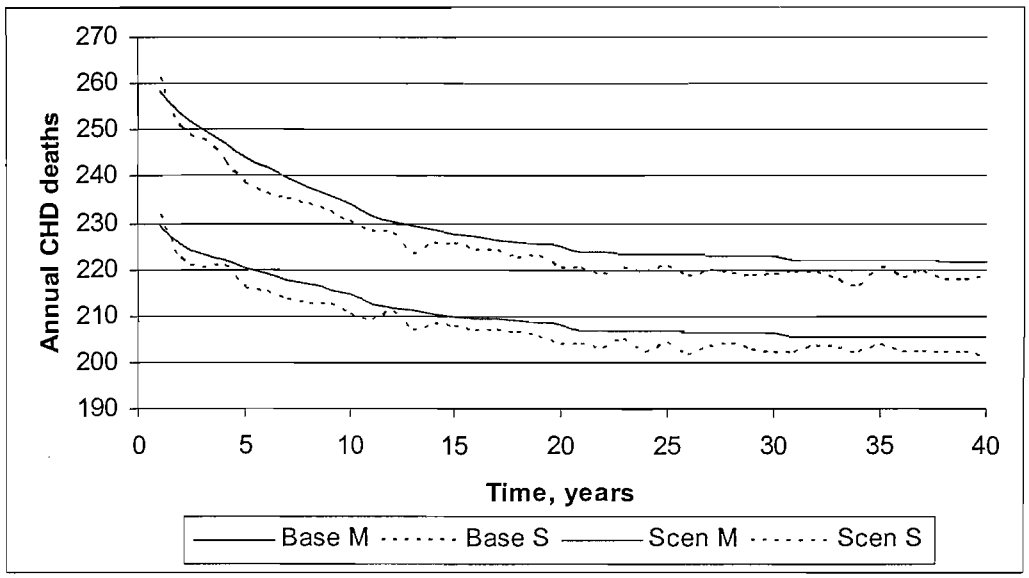

Figure 8.5.3 CHD deaths for Markov (M) and simulation (S) models for the baseline and scenario (Note truncated y axis)

8.5.2 Scenario analysis

Several scenarios were conducted for varying levels of statin use for the angina and MI cohorts and this was compared to the baseline with no one allocated to the drug (Table 8.5.5). The reasons for the differences between the results for the two models were examined, in particular to investigate whether the differences were influenced by the drug use chosen. As before the simulation runs were for 125000 people for 200 iterations for 40 years. No patients were allocated to any of the other drugs.

Table 8.5.5 Parameter values used for statin scenarios

%	Baseline	20%	60%	80%	100%
Angina – no MI	0	20	60	80	100
Post MI	0	20	60	80	100

Table 8.5.6 Average results over 40 years from the Markov model for the statins scenario compared to baseline

	CHD patients	Life years saved	Cost (£000s)	Inc Cost (£000s)	ICER (£/LYS)
0	3,883		2,690		
20%	3,952	69	2,887	197	2850
60%	4,096	213	3,302	613	2870
80%	4,171	288	3,521	832	2890
100%	4,248	365	3,748	1,058	2900

Table 8.5.7 Average results over 40 years from the simulation model for the statins scenario compared to baseline

	CHD patients	Life years saved	Cost (£000s)	Inc Cost (£000s)	ICER (£/LYS)
0	3,913		2,734		
20%	3,987	74	2,948	214	2910
60%	4,131	218	3,375	642	2940
80%	4,202	289	3,588	855	2950
100%	4,271	358	3,795	1,062	2970

Table 8.5.8 Relative (%) error for the Markov model compared to the simulation model for the results shown in Table 8.5.7

%	CHD patients	Life years saved	Cost	Inc Cost	ICER
0	0.8		1.6		
20%	0.9	6.1	2.1	7.9	2.0
60%	0.8	2.2	2.2	4.5	2.4
80%	0.7	0.5	1.9	2.7	2.2
100%	0.5	-2.0	1.2	0.3	2.3

The results from these the Markov and simulation model runs are shown in Table 8.5.6 and 8.5.7 and the relative difference between the results is shown in Table 8.5.8. As before in section 8.6.2, the run results are similar in both the models. In particular the 'error' for cost effectiveness between the models is less than 2.4% for all runs. However, the error for the 20% scenario for the increases in life years saved and cost appear to be larger than for the other scenarios. The reasons for this were investigated.

The simulation model identifies those individuals in the population who have been allocated to the drugs as the simulation follows individuals within the model. In contrast, the Markov model allocates the proportion on the drug in the first cycle and assumes that this proportion remains constant over the run. In fact, people not on the drug will die quicker, on average, than people on the drug and so the actual proportion on the drug will change throughout the simulation run. In order to accurately estimate the correct proportion on the drug, in the Markov model, it would be necessary to introduce extra states for 'on drug' and 'not on drug'.

Table 8.5.9 shows the actual proportions on the drugs averaged over the 40 years for each of the scenarios. For each of the scenarios 20% to 80%, there are about 2% more people on the drug for the simulation than for the Markov model. Thus for the Markov model, there will be an underestimate of the cost and the prevalence of disease.

Table 8.5.9 Average proportion of population on statins for each of the scenarios for the Markov and simulation models for a 40 year run, %

	Markov	**Simulation**	**Difference (S-M)**
0%	0	0	0
20%	20	21.8	1.8
60%	60	62.6	2.6
80%	80	81.8	1.8
100%	100	100	0

Using this information, the error can be calculated for the case if extra states for 'on drug' and 'not on drug' were built (Table 8.5.10). As shown in Table 8.5.10, with these

states the differences between the models is within 2.4% error for all categories and scenarios. When adjusting for these errors in the Markov model, the relative error between the Markov and simulation is similar across all scenarios.

Table 8.5.10 Relative (%) error for the Markov model compared to the simulation model for the 'new' results

	CHD patients	Life Year Saved	Cost	Inc Cost	ICER
0%	0.8		1.6		
20%	0.7	-2.1	1.5	0.1	2.1
60%	0.6	-1.9	1.4	0.6	2.4
80%	0.6	-1.7	1.4	0.6	2.2
100%	0.5	-2.0	1.2	0.3	2.3

8.5.3 More scenarios

Further analyses were conducted for increased statin use for either the angina or MI cohorts and this was compared to the baseline with no one allocated to the drug (Table 8.5.11) to investigate whether this introduced differences in the results from the two models. As before the simulation runs were for 125000 people for 200 iterations for 40 years.

Table 8.5.11 Parameters used for statins scenarios

%	Baseline	Angina only	MI only
Angina – no MI	0	100	0
Post MI	0	0	100

Table 8.5.12 Average results over 40 years for the statins scenario for the Markov (M) and simulation (S) models

	CHD patients	Life Year Saved	Cost (£000s)	Inc Cost (£000s)	ICER (£/LYS)
Baseline M	3,883		2,690		
Angina only M	4,061	178	3,441	751	4210
MI only M	4,080	197	3,015	325	1650
Baseline S	3,913		2,734		
Angina only S	4,086	173	3,487	754	4370
MI only S	4,109	195	3,058	324	1660

Table 8.5.13 Relative (%) error for the Markov model compared to the simulation model for the results shown in Table 8.5.12

	Patients	LYS	Cost	Inc Cost	ICER
Baseline	0.8		1.6		
Angina only	0.6	-3.3	1.3	0.4	3.6
MI only	0.7	-0.7	1.4	-0.1	0.6

The results for the two models are shown in Table 8.5.12-8.5.13. The MI only scenario is more cost effective than the angina only strategy. For the MI only scenario the increased cost of the scenario is much lower than for the angina only scenario as fewer patients are on the drug; however there is a similar increase in patients' life years saved.

8.5.4 Results from the other drugs

In this section the simulation and Markov models are compared for each of the secondary prevention drugs. The simulation and Markov models were run for 40 years for the scenarios for the secondary prevention drugs as shown in Table 8.5.1 and 8.5.2.

Table 8.5.14 Average results over 40 years from the Markov model for the secondary prevention scenarios compared to baseline

	CHD patients	Life Year Saved	Cost (£000s)	Inc Cost (£000s)	ICER (£/LYS)	All deaths	CHD deaths
Baseline	4,205		3,079			4,205	
Statin	4,403	198	3,775	696	3520	4,403	198
Aspirin	4,282	77	3,122	43	560	4,282	77
Beta B	4,288	83	3,138	60	720	4,288	83
ACE	4,343	138	3,367	289	2090	4,343	138
All drugs	4,651	446	4,214	1,135	2550	4,651	446

Table 8.5.15 Average results over 40 years from the simulation model for the secondary prevention scenarios compared to baseline

	CHD patients	Life Year Saved	Cost (£000s)	Inc Cost (£000s)	ICER (£/LYS)	All deaths	CHD deaths
Baseline	4,245		3,147			4,245	
Statin	4,436	190	3,850	703	3690	4,436	190
Aspirin	4,318	73	3,186	39	540	4,318	73
Beta B	4,326	80	3,206	58	730	4,326	80
ACE	4,378	132	3,436	289	2180	4,378	132
All drugs	4,672	426	4,282	1,134	2660	4,672	426

Table 8.5.16 Relative (%) error for the Markov model compared to the simulation model for the results shown in Tables 8.5.14 and 8.5.15

	CHD patients	Life Year Saved	Cost	Inc Cost	ICER	All deaths	CHD deaths
Baseline	0.9		2.2			0.9	
Statin	0.7	-3.8	1.9	0.9	4.5	0.7	-3.8
Aspirin	0.8	-5.8	2.0	-9.4	-3.4	0.8	-5.8
Beta B	0.9	-3.6	2.1	-2.3	1.3	0.9	-3.6
ACE	0.8	-4.3	2.0	0.0	4.2	0.8	-4.3
All drugs	0.4	-4.6	1.6	0.0	4.3	0.4	-4.6

The results shown in the Tables 8.5.14-8.5.15 are similar for both of the models with an acceptable error between them (Table 8.5.16). For all the drugs the cost effectiveness results are about 5% worse for the simulation model than the Markov model. Each of the drugs have similar errors between the two models except aspirin and beta blocker. The differences in the results between the Markov and simulation models for these two drugs is affected by the fact that the proportions allocated to the angina and MI groups are quite different. For aspirin, the baseline proportion on the drug is much lower for the angina group than the post MI group. For beta blocker, the scenario proportion on the drug is much higher for the post MI group than the angina group.

The undiscounted results from the models have been discussed in this section. The discounted results show a similar pattern to the undiscounted results in terms of the differences between the models. The discounted cost effectiveness results for the two models are shown in Figure 8.5.4.

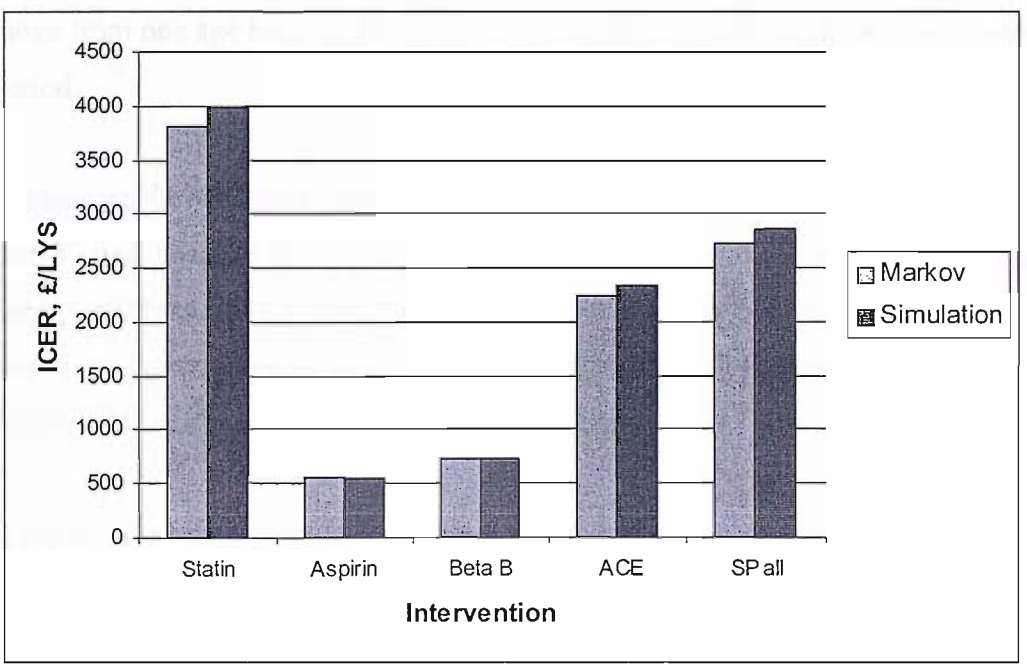

Figure 8.5.4 Cost effectiveness results for secondary preventions interventions for the Markov and simulation models for 40 year runs, with costs and benefits discounted at 3%

8.6 Discussion

8.6.1 Fixed-age cohort models

The Markov model described in this chapter has been built for cohorts of the same starting age which advance by a year in each time period, ie it is an age-dependent cohort model. An alternative method would have been to construct a fixed-age cohort model. This approach would have modelled the whole ten-year age group together with a single transition probability for the whole age band rather than for individual ages. In each year a proportion of the age band would progress to the next age band.

The fixed-age cohort model is simpler than the age-dependent cohort model but is less accurate. For example, the non cardiac death rate is specified at each age and an average of the age band will introduce some inaccuracies, particularly because the non cardiac death rate increases non linearly with respect to age. Furthermore, the proportion who move from one age band to the next may not be the same for each age band in any time period.

In this case the Markov model using the age-dependent cohort approach was constructed, because this seemed the more intuitive method. However it would have been possible to build a fixed-age cohort model and compare the simulation model to this. In this case the simulation would have had to be built in a similar way to the Markov with fixed age cohorts to represent the age bands.

If the models had been built in the same way, similar differences between the two models would be expected using the fixed-age cohort to that seen using the age-dependent cohort. The simulation model is much more flexible to changing between these two approaches. Indeed it would be a simple matter to change in the simulation model whereas in the Markov model built here, it would be necessary to start building the model from scratch.

8.6.2 Flexibility

The differences between the Markov and simulation model results were small and were not large enough to lead to different conclusions from each of the models. For example the difference in the ICER estimates differed by less than 5% for all drugs between the two models. The time to build each of the models was similar and consequently the choice of preferred model was based on the perceived simplicity and transparency of the models and so the Markov model was the preferred model.

In the models constructed, the proportion of the population allocated to the drug was kept constant over the whole run. In reality, the proportion of the population on the drug will increase over time. In order to replicate the same circumstances with the Markov model, it would be necessary to subdivide the population for each of the drugs to identify those 'not on the drug' and 'on drug' and this would mean.increasing the number of states by a factor of 16. In this case it was considerably simpler to use the simulation model and so it was decided to model the final section using only the simulation model.

Thus in this chapter in the first instance for simple models with a small number of health states, the Markov model should be used. At some point, as the complexity of the model and the number of health states increases it becomes considerably easier and more practical to use a simulation model. The threshold for selecting the appropriate model will be explored in the next chapter.

8.7 Evaluating secondary prevention drugs

In this section the population simulation model was run as described above to evaluate all the secondary prevention drugs using the simulation model. The secondary prevention drugs evaluated are aspirin, statins, ace inhibitors and beta blockers. The base values are shown in Table 8.2.2. It was assumed that the uptake of drugs for new patients is higher than the drug use of current patients and in this way the proportion of drug users in the population will increase over time. In the scenarios, there is the same

starting proportion of patients on the drugs as in the base case but the uptake of drugs for all new patients will be 80%. In the case of aspirin, some categories of new patients had an uptake of greater than 80% in the base case and this was assumed to be the same in the scenario. Patients are assumed to take these drugs indefinitely and to continue to benefit from them. A general secondary prevention scenario was considered first where the uptake of all drugs is increased and then each of the secondary prevention drugs were considered in turn.

The CHD patients come from a population of 125 000 and the simulation was run for 40 years (averaged over 200 iterations). The cost effectiveness results are shown over this 40 year period. Many of the other results are shown over 20 years as this time period is likely to be of more interest to health care planners. The results are scaled up for a population of one million.

8.7.1 Results for increasing uptake of all secondary prevention drugs

As a result of secondary prevention drugs, many MI and death events are avoided and so the number of CHD patients increases. There are 6% more patients due to the increased secondary prevention use after 20 years in the scenario compared to baseline (Figure 8.7.1).

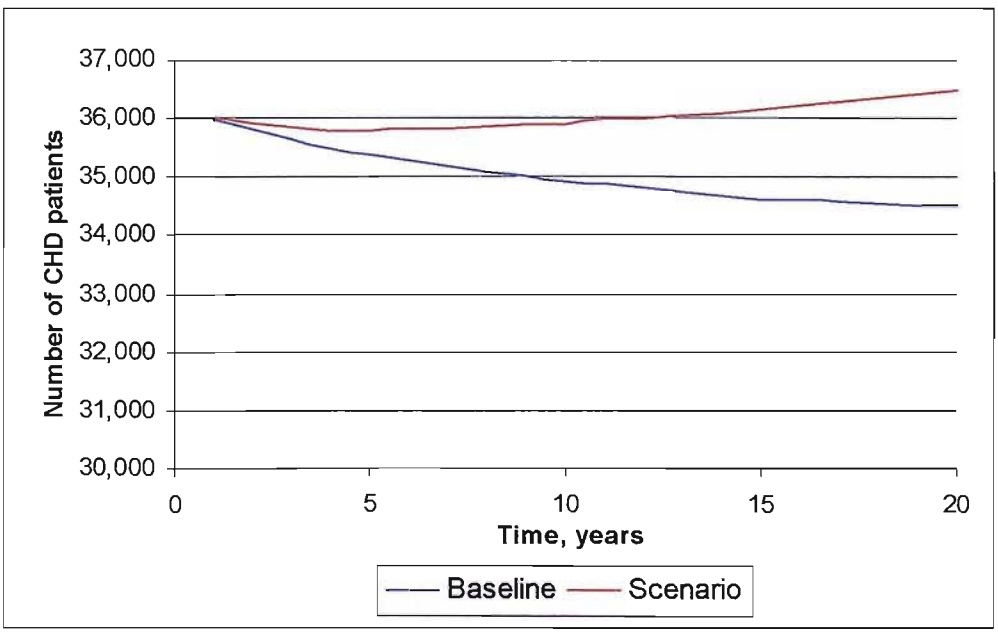

Figure 8.7.1 CHD patients in a population of one million with secondary prevention scenario for a simulation run for 20 years (Note truncated y axis)

In the baseline scenario, the number of annual CHD deaths is predicted to fall by 19% after 20 years compared to present rates. Increasing secondary prevention usage reduces the number of CHD deaths by a further 9% after 20 years (Figure 8.7.2).

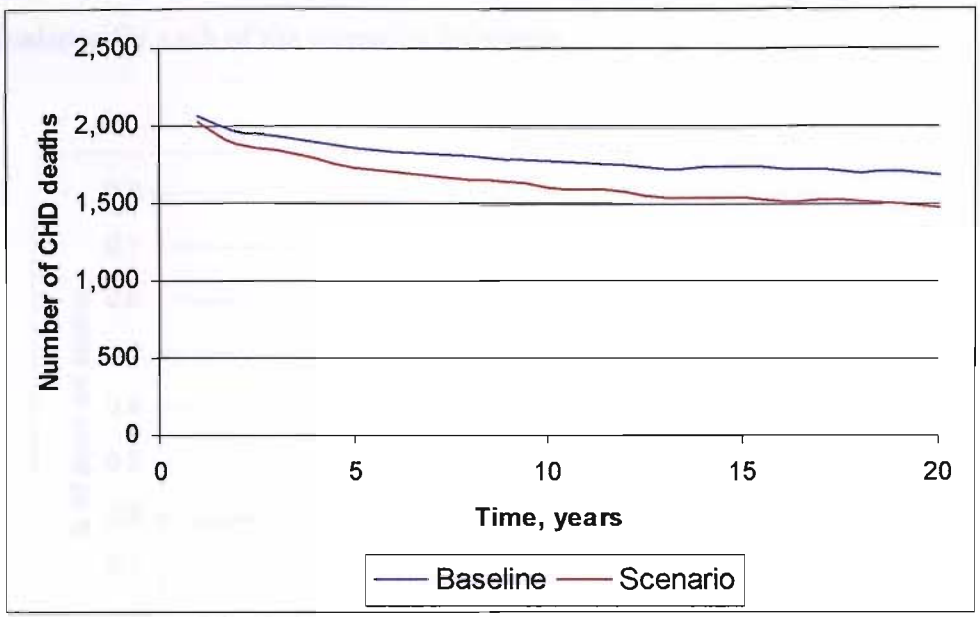

Figure 8.7.2 CHD deaths in a population of one million with secondary prevention scenario for a simulation run for 20 years

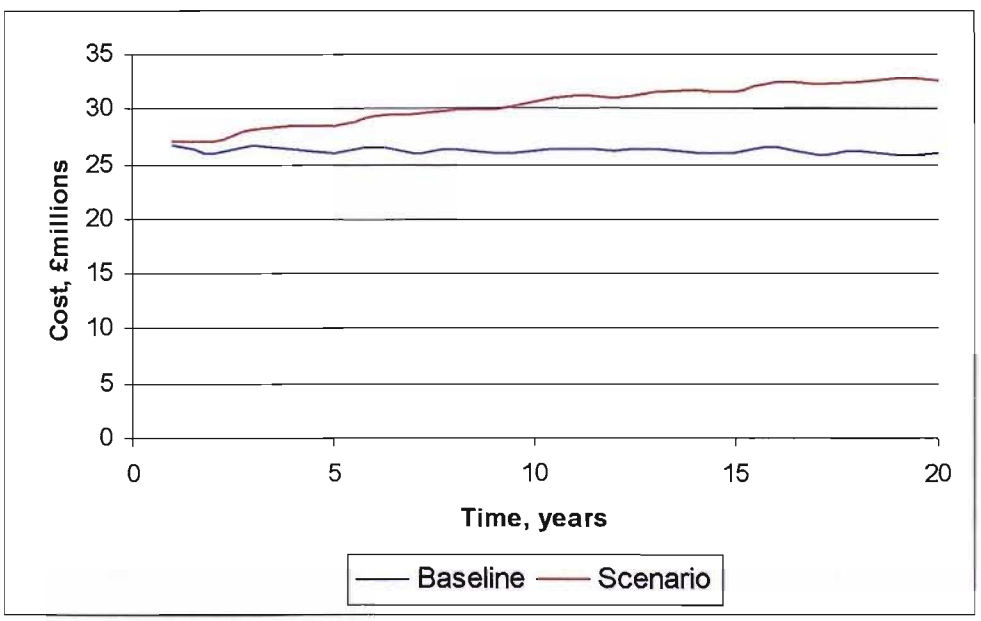

Figure 8.7.3 Undiscounted CHD costs in a population of one million with secondary prevention scenario for a simulation run for 20 years

Figure 8.7.3 shows the undiscounted increase in cost for CHD treatment for the two scenarios for a population of one million. In the base case, the total cost remains roughly constant over the 20 years. The total cost is predicted to continue to increase in the scenario. After 20 years, the annual cost for the scenario is predicted to be 26% greater for the scenario than for the baseline. Figure 8.7.4 shows the increase in drug use prevalence for each of the scenarios for statins.

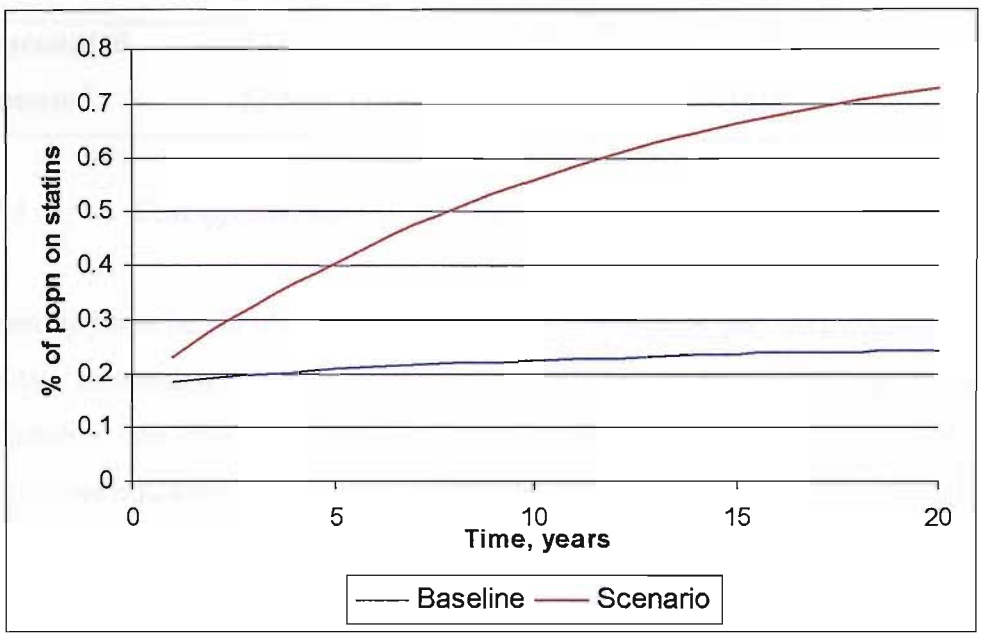

Figure 8.7.4 Drug use prevalence for statins with secondary prevention scenario for a simulation run for 20 years with a population of one million

8.7.2 Cost effectiveness

The total costs of all events, drugs and interventions were calculated for each year for each of the scenario runs. Costs and benefits were discounted at 3%. Table 8.7.1 shows the cost effectiveness for 10, 20 year and 40 year runs. The cost effectiveness is best for the 40 year runs. As noted in chapter 5, the time horizon chosen makes a significant difference to the cost effectiveness ratios calculated for the interventions. For example the discounted cost effectiveness for the 10 year run is 50% higher than for the 40 year run. The scenario produced an annual increase in patient life years of 1009 per year for a million population averaged for the first 20 years. This resulted in an annual increase in cost of £4.1 million for a million population for the first 20 years. The increase in

cost to provide this secondary prevention for England and Wales would cost in the region of an extra £200 million each year.

Table 8.7.1 Undiscounted and discounted (costs and benefits discounted at 3%) cost effectiveness from the simulation runs for 10, 20 and 40 years

Scenario	ICER (£/LYS) 10 year run	ICER (£/LYS) 20 year run	ICER (£/LYS) 40 year run
Undiscounted	5320	4100	3330
Discounted	5390	4210	3510

8.7.2.1 Cost effectiveness of individual drugs

The results from the simulation runs for a population of 125,000 for each of the secondary prevention drugs are shown in Table 8.7.2, with the results scaled to a population of one million. The cost effectiveness estimates are from a run of 40 years and the other outcomes are from a run of 20 years (Table 8.7.3).

Table 8.7.2 Results for a population of one million for an average year

	CHD patients	Life years saved	All deaths	All cause deaths prevented
Baseline	35 010		3200	
Statins	35 513	504	3150	50
ACE	35 386	376	3162	37
Aspirin	35 066	56	3194	6
Beta Blockers	35 222	212	3181	19

Table 8.7.3 Cost effectiveness (£/LYS) of the individual secondary prevention drugs; discounted results are 3% for costs and benefits

	Discounted	Un-discounted	Discounted	Un-discounted
	20 years		40 years	
Statins	5400	5560	4230	4500
ACE	3080	3150	2470	2600
Aspirin	690	680	660	670
Beta Blockers	740	740	770	770

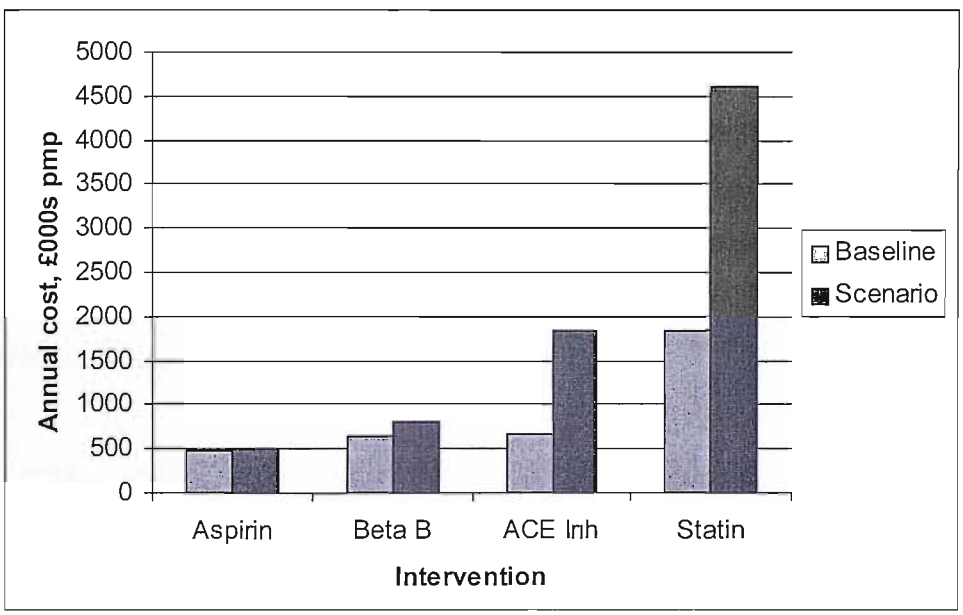

Figure 8.7.5 Annual drug costs (£000s) for a million population averaged over 20 years,

Each of the individual drugs increases the number of CHD patients in the population and reduces the number of cardiac and all cause deaths (Table 8.7.2). The benefits of each of the drugs are similar (Table 8.3.1). The absolute benefits gained are higher for statins and ACE inhibitors as these drugs have the largest increase in uptake compared to the baseline. These drugs are more expensive as well and the extra cost for these drugs are considerable (Figure 8.7.5). Furthermore the cost effectiveness of the individual drugs (Table 8.7.3) is better for the cheaper drugs, for example aspirin. The cost effectiveness of the drugs for different time horizons are shown in Table 8.7.4.

According to the guidelines for cost effectiveness, aspirin and beta blocker present excellent value for money (see section 3.1.2) and ACE inhibitors and statins present very good value for money. However, despite this the implementation of the CHD NSF guidelines for the increase in secondary prevention drugs will put considerable strain upon the NHS. According to the results in this section the increased annual spending for drugs will be in the order of £250 million above pre-NSF spending for the UK.

8.8 Discussion

In this chapter, Markov and simulation models were built to evaluate secondary prevention drug interventions for coronary heart disease. Using these models, the costs and benefits of increased secondary prevention provision was estimated. The models were used as case studies to investigate the choice of modelling technique for chronic (long-term) treatment interventions. Some of the conclusions from chapter 5 for the simple experimental models were tested in a more complex and realistic model to see if they still held true.

It was estimated that the additional annual cost of expanding the use of secondary prevention drugs according to the National Service Framework for Coronary Heart Disease would be about £250 million for the UK. The secondary prevention drugs would save an estimated 6000 lives per year and 60 000 patient life years. Increasing aspirin and beta blocker usage would be excellent value for money with ICER of £690 and £740 respectively. Increasing ACE inhibitor and statin use would also be good value for money with ICER of £3080 and £5400 respectively.

As reported in earlier chapters, the population based approach provided a more comprehensive summary of the value of the intervention for the health care planner than a cohort analysis (Assumption 1 and 2). In addition, the cost effectiveness measure from a population analysis relates more realistically to the population and time period studied. In the analysis in this chapter the cohort model underestimated the discounted cost effectiveness by about 10%. However, the population models built in this chapter

were more complicated and took longer to build than the cohort models. The time horizon chosen was shown to be critical to the cost effectiveness outcome. For shorter time periods, the cost effectiveness will be significantly worse for the population and cohort models. For example, in an analysis of the combined cost effectiveness of all the drugs, the discounted cost effectiveness for the 10 year run was 50% higher than for the 40 year run.

The differences between the Markov and simulation model results were small and were not large enough to lead to different conclusions from each of the models. The time to build each of the models was similar and consequently the choice of preferred model was based on the perceived simplicity and transparency of the models and so the Markov model was the preferred model. In order to make the models more realistic so that the prevalence of drug users increased over time, some more assumptions (and states) were introduced. The number of states in the Markov model would have increased by a factor of 16. In this case it was considerably simpler to use the simulation model. Therefore in the first instance for simple models with a small number of health states, the Markov model should be used. At some point, as the complexity of the model and the number of health states increases it becomes considerably easier and more practical to use a simulation model. The threshold for selecting the appropriate model will be explored in the next chapter.

Chapter 9

Resource-Constrained Interventions: Models for Revascularisation

Abstract

In this chapter Markov and simulation cohort and population models are built to evaluate the costs and benefits from coronary artery bypass grafting (CABG) and percutaneous transluminal coronary angioplasty (PTCA) for coronary heart disease patients. The choice of modelling technique is explored for resource-constrained treatment interventions. Resource-constrained interventions are those for which resources are limited and there may be some decision rules concerning the allocation of resources. These are typified by the referral and subsequent waiting of patients for elective hospital procedures.

CABG is more cost effective for more severe coronary disease (ie triple vessel disease and left main stem) and PTCA is more cost effective for less severe coronary disease (ie single and double vessel disease). Compared to medical treatment, CABG and PTCA are good value for money with ICER of £4900 for PTCA for 1 VD, £6100 for CABG for 3 VD and £5300 for CABG for left main stem. Increasing the provision of revascularisation according to the National Service Framework would cost an additional £180 million per year and would gain over 22 000 QALY per year for UK.

Traditionally, discrete event simulation has been regarded as the technique of choice for modelling resource-constrained queuing systems. However, using these models it was concluded that the results were not significantly affected by modelling the resources without using queues and concluded that DES is not necessarily the most appropriate technique. As in chapter 8, the choice of model was determined by the overall complexity of the model in terms of ease of development and the DES model became the most appropriate when the number of states in the model became sufficiently large.

Chapter 9 Resource-Constrained Interventions: Models for Revascularisation

9.1 Introduction

In this chapter, the modelling of resource-constrained interventions is investigated. Resource-constrained interventions are those for which resources are limited and there may be some decision rules concerning the allocation of resources. These are typified by the referral and subsequent waiting of patients for elective hospital procedures. These differ from those interventions modelled in chapters 7 and 8. In chapter 7, all patients who had a MI would have been eligible for emergency ambulance and thrombolytic treatment. Similarly, in chapter 8, for secondary prevention medication, all patients in each health state were equally eligible for the medication. Simple models were developed for resource-constrained interventions in Chapter 5. A resource-constrained intervention was modelled without the use of queuing and it was concluded that systems with a queue system could be modelled effectively without the need for DES.

In this chapter revascularisation procedures are modelled, using Markov and simulation models. The following hypotheses are examined: firstly whether for dynamic systems which involve constraints or where patients compete for scarce resources, DES is the more appropriate technique (H5). Secondly if the Markov assumption forces the creation or proliferation of states, or if using a homogeneous population is likely to materially bias the results, DES should be considered (H6).

Initially a simple example is modelled comparing medical treatment, coronary artery bypass surgery (CABG) and percutaneous transluminal coronary angioplasty (PTCA) using Markov cohort and simulation models for patients with more serious coronary disease, as in Yock et al. (2003). Then the complexity of the models is increased in order to make the models more realistic and intuitive. The Markov and simulation models are compared and a decision is taken on the preferred model to build at various stages. Finally a more realistic population model is described to assess the likely costs

and benefits of increasing the capacity of revascularisation in the UK from its current level as recommended by the National Service Framework for CHD (Department of Health 2000).

Unless indicated otherwise, the results for the models are shown in terms of cost (£), effectiveness (QALYs gained) and cost effectiveness (incremental cost effectiveness ratio, ICER, £/QALY gained)). The incremental cost effectiveness ratio is shown as the difference in cost between the treatment scenario and baseline divided by the difference in effectiveness between the treatment scenario and baseline.

9.2 Bypass surgery and angioplasty for coronary heart disease

The models built in this chapter are based upon research completed by the author as part of the UK Coronary Heart Disease Policy Model working team (Appendix I). In particular much of the data have been collected by other members of the group and is described in more detail in the Stable Angina Working paper (Chase et al. 2003a). Furthermore the modelling work here was done in consultation with other members of the group.

Patients with angina pectoris suffer from recurring pain or discomfort in the chest. Revascularisation procedures such as coronary artery bypass grafting (CABG) and percutaneous transluminal coronary angioplasty (PTCA) improve the symptoms of angina. A coronary artery bypass graft (CABG) is an operation that bypasses blockages in the heart arteries with veins removed from the leg or chest. Percutaneous transluminal coronary angioplasty (PTCA) is a method which uses a tiny balloon to reduce the arterial narrowings (stenoses) by inserting a catheter in the upper leg and moving it until it is in the heart. Often a metal mesh cage, called a stent, is embedded into the artery wall and holds the artery open.

Patients are categorised by their symptom severity and their clinical classification. Symptom severity is assessed by the use of exercise electrocardiogram (ECG) and is measured. There are several classifications of the severity of the symptoms, for example

the Canadian Cardiovascular Society classification (2002) and the New York Heart Association classification (1994). Patients with more severe symptoms may then be referred for an angiogram, which is able to give an accurate assessment of the severity of the arterial stenoses. Unfortunately symptom severity is not a perfect indication of poor clinical classification and so not all those with poor clinical prognosis will be referred for an angiogram. Similarly many patients with less severe clinical classification will be referred for an angiogram. Clinical classification is defined as the number of major vessels with significant narrowings (0-3 vessels). In addition, if the left main stem (LMS) vessel is stenosed the prognosis is particularly bad. The current guidelines suggest that patients with lower severity of vessel disease (1 or 2 VD) receive angioplasty, whilst patients with more severe vessel disease (3 VD or LMS) receive CABG (SIGN 1998; European Society of Cardiology 1997).

Revascularisation is useful for relieving patients' angina symptoms and thereby improving their quality of life. There are risks of revascularisation, including death or myocardial infarction (MI). After the revascularisation, patients may develop angina again and require further revascularisation. The repeat revascularisation rate for PTCA is particularly high in the first year although this has been improved by the advent of stents.

9.2.1 Other modelling studies of revascularisation

Other modelling studies for revascularisation have been reviewed in detail in section 3.4. Several studies have looked at the benefits and cost effectiveness of revascularisation (Cohen et al. 1994; Wong et al. 1990; Schwicker and Banz 1997; Cleland and Walker 1997; Kwok et al. 2001; Cleland and Walker 1998; Williams 1985; Weinstein et al. 1982; Yock et al. 2003), see Table 3.4.1. Several of the studies were before large scale trials had been completed, (Williams 1985; Wong et al. Weinstein and Stason 1982) and the results may have to be treated with caution. The studies for CABG used a decision tree combined with long term life expectancy (Weinstein and Stason 1982), a Markov model (Kwok et al. 2001), state transition model (Cleland and Walker 1997; Cleland and Walker 1998) and simple calculation methods (William 1985) and the studies for angioplasty and stenting used a Markov cycle model (Wong et al. 1990; Yock et al. 2003) or a decision tree with a Markov model (Cohen et al. 1994;

Schwicker and Banz 1997). The studies found that CABG was suitable for patients with more severe symptomatic and anatomical disease whilst angioplasty was more suitable for less severe indications. Stents were a reasonably cost effective alternative to balloon angioplasty.

9.2.2 Parameters used in the revascularisation models

Many of the parameters used for the revascularisation model have been derived in consultation with other members of the UK Coronary Heart Disease Policy Model working team. Furthermore much of the data for these parameters have been collected by other members of the group and is described in more detail in the Stable Angina Working paper (Chase et al. 2003a).

As mentioned in section 9.2, patients with more severe vessel disease have a worse prognosis. This is represented as a relative risk of suffering a MI or cardiac death compared to patients with single vessel disease (Table 9.2.1). These relative risks are obtained from the death rates of the medical arms of trials comparing CABG against medical treatment in a meta-analysis by Yusuf et al. (1994). The mortality rates in Yusuf et al. were for all cause mortality. The rates were adjusted by subtracting the deaths from non cardiac causes, assuming that non CHD deaths in the UK population were distributed in a similar way to the Yusuf trial for the same age group. This adjustment provided the CHD death rates for each of the vessel disease subgroups, which was used to estimate the relative risk.

Table 9.2.1 Relative risks for patients with different vessel disease (Data from Yusuf et al. 1994; Table from Cooper et al. 2003)

Vessel disease (VD)	Relative risk
1 VD	1
2 VD	1
3 VD	1.78
LMS	4.19

Patients undergoing bypass surgery and angioplasty are at risk of immediate events from the procedure. The mortality and non fatal MI rates for bypass surgery and angioplasty are taken from national audits (Keogh and Kinsman 1998; de Belder 1998) and are shown in Table 9.2.2. Although event rates vary widely according to age, prior intervention and other factors, average event rates have been assumed.

Table 9.2.2 Event rate of patients undergoing surgical procedures (Data from Keogh and Kinsman1998 and de Belder 1998; Table from Cooper et al. 2003)

	CABG, %	**PTCA, %**
MI	5	3.2
Death	2.3	0.9

There are some anomalies between the clinical evidence for angioplasty and CABG. In trials comparing PTCA with medical treatment (Rita 2 1997), there was no significant difference in prognostic benefit between the groups. In trials comparing PTCA with CABG (Pocock et al. 1995), there was no significant difference between the groups. Finally, in trials comparing CABG with medical treatment there was a significant benefit in the CABG group (Yusuf et al. 1994). Based on the available studies the CHD working team decided there was no prognostic benefit for PTCA compared to medical treatment (Chase et al. 2003a). Further, there was prognostic benefit for patients with multi-vessel disease but not those with single or double vessel disease. A recent health technology assessment (Hill et al. 2004) reached the same conclusion after analyzing the results from several recent CABG vs PTCA trials. They commented that

> '*Although none of these results is individually significant, the trend is clearly consistent with a steady shift in the balance of mortality risk in favour of CABG after an initial disadvantage*'.

Over the longer term, revascularisation may provide prognostic benefits, as well as symptomatic relief. Table 9.2.3 shows the relative risks of each of the vessel disease classifications compared to patients on medical treatment. The relative risks describe the risk of a future MI. Thus a patient with triple vessel disease would have their risk of a

further MI reduced by 42% by a successful CABG procedure. The relative risks for CABG are taken from the Yusuf et al. meta analysis. There is little evidence that PTCA provides a prognostic benefit compared to medical treatment (Rita 2 1997; Bucher et al. 2000). PTCA was assumed to provide symptomatic relief but no long term prognostic benefits on survival.

In the trials for CABG versus medical treatment, patients had an increased survival rate after CABG for multi-vessel disease for the first 12 years compared with the medical group. The survival benefit of the CABG operation diminishes after about five years. This diminishing of benefit is probably due to patients returning to angina (stable or unstable), or having events such as MI and death. Patients were assumed to have prognostic benefits from the bypass surgery until they suffer a coronary event, such as unstable angina or MI, but no benefits thereafter.

Table 9.2.3 Relative risks of revascularisation compared to medical treatment (Data from Yusuf et al. 1994; Table from Cooper et al. 2003)

Vessels stenosed	CABG Relative risk	PTCA Relative risk
0	1	1
1	1	1
2	1	1
3	0.58	1
LMS	0.32	1

Revascularisation is primarily used to treat the symptoms of angina. However often the angina recurs and the patients may need to be referred for repeat revascularisation. This is especially common for patients receiving a PTCA who have a high risk of angina recurrence within the first four to six months after a PTCA, although with the advent of stents and new drugs, the restenosis rate has fallen by about 40%. The repeat recurrence rates estimated by Yock et al. (2003) from the BARI trial (1996) and more recent stent trials, for example the Stent restenosis Study (SoS 2002) and the Belgian Netherlands Stent Study (Serruys et al. 2001), for PTCA using stents are shown in Table 9.2.4. In the

BARI trial 8% of patients, who had an initial CABG, had repeat revascularisation within five years and after this time the annual rate of repeat revascularisation was 5%.

Table 9.2.4 Probability of repeat revascularisation using stents estimated by Yock et al. (2003)

	0 – 6 months after PTCA	**6 – 12 months after PTCA**	**12 – 48 months after PTCA**	**Each year after 48 months**
Probability	0.19	0.09	0.16	0.05

Not all patients whose anginal symptoms recur have immediate revascularisation. The proportion of patients receiving repeat revascularisation was estimated using a survey by the British Cardiac Society (see Table 9.2.5), consultation with a cardiologist at Southampton General Hospital and data from the Scottish Health Service (Table 9.2.6). Combining these data it was estimated that around 20% of patients with non fatal MI and 60% of patients with unstable angina received repeat revascularisation. There is a high proportion of repeat revascularisation in the first year after a PTCA over and above the natural recurrence of angina through acute coronary incidents (ACI) (see Table 9.2.4). It was estimated that in addition to the recurrence through ACI, 23% of patients who have PTCA receive repeat PTCA within the first year.

Table 9.2.5 Acute referrals for diagnostic tests for patients with unstable angina or MI (Survey from British Cardiac Society)

%	**As inpatients**	**Within 6 weeks of discharge**	**Never receive one**
Patients with non fatal MI who have exercise ECG*	55	25	20
Patients with unstable angina who proceed to angiogram	55	25	20

*Of those receiving exercise testing, 45% go on to have angiography

Table 9.2.6 Proportion of patients referred from angiography to revascularisation for different vessel disease (Scottish Health Service data)

	1 or 2 VD	3 VD	LMS
Patients with stable angina or MI	60	55	70
Patients with unstable angina	85	70	70

9.2.3 Quality of life (QoL) measures

As mentioned above, revascularisation often improves the quality of life of patients. Several studies have attempted to quantify the level of quality of life for CHD patients but the values used vary widely. For a more extensive list of QoL scores from which the studies below are obtained see Bell et al. (2001). These studies have used quality of life analyses and in some cases adapted them for their own uses or derived them from a panel of experts. The QoL estimates can be calculated using several methods, including the rating scale, standard gamble and time trade off (section 2.2.4).

There is a wide variation between the utility methods described. Kuntz et al. (1999) described how they used the Nease et al. (1995) study results for the standard gamble method to give the following scores: No chest pain 0.87, mild angina 0.81, and severe chest pain 0.67. This is in general agreement with other studies; some of the ranges are also shown.

Good quality of life: Asymptomatic (history of CHD) 0.902 (Stinnett et al. 1996), NYHA functional class II angina 0.9 (Levin et al), stable and asymptomatic after surviving an MI 0.9 (Hummel et al. 1997), Post MI with no angina, no congestive heart failure 0.93 (Kuntz et al. 1996). Mild chest pain 1.0 (Doubilet et al. 1985), NYHA functional class I angina 1.0 (Levin et al. 1992).

Intermediate quality of life: Mild angina 0.8 (Hummel et al. 1997), mild angina in sedentary person 0.8 (Pliskin et al. 1981), CHD 0.8 (Halziandreu et al. 1988), angina (no congestive heart failure) 0.84 (Stinnett et al. 1996). Angina 0.75 (Danese et al. 1996), angina 0.9 (Salkield et al. 1997).

Poor quality of life: Severe angina 0.7 (Wong et al. 1990), severe chest pain 0.7 (Doubilet et al. 1985), severe angina (Cohen et al. 1994), NYHA functional class II/IV angina 0.7 (Levin et al. 1992). Severe angina 0.0 (Pliskin et al. 1981), Post MI with severe angina, no congestive failure 0.82 (Kuntz et al. 1996).

Table 9.2.7 Studies that have used QoL scores (1) Standard gamble – SG, time trade off – TTO, author/clinical judgement A/CJ (Table from Davies et al. 2003a)

Study	Definition	Pref. score	Method
Levin et al. 1992	NYHA functional class I angina	1.0	-
Kuntz et al. 1999	No chest pain	0.87	SG
Stinnett et al. 1996	Asymptomatic (history of CHD)	0.902	TTO
Levin et al. 1992	NYHA functional class II angina	0.9	
Hummel et al. 1997	Stable and asymptomatic after surviving MI	0.9	ACJ
Kuntz et al. 1996	Post MI with no angina, no congestive heart failure	0.93	TTO
Kuntz et al. 1999	Mild angina	0.81	SG
Doubilet et al. 1985	Mild chest pain	1.0	ACJ
Hummel et al. 1997	Mild angina	0.8	ACJ
Pliskin et al. 1981	Mild angina in sedentary person	0.8	SG
Hatziandreu et al. 1988	CHD	0.8	ACJ
Stinnett et al. 1996	Angina (no congestive heart failure)	0.84	TTO
Danese et al. 1996	Angina	0.75	ACJ
Salkeld et al. 1997	Angina	0.9	TTO
Wong et al. 1990	Severe angina	0.7	-
Doubilet et al. 1985	Severe chest pain	0.7	ACJ
Cohen et al. 1994	Severe angina	0.7	TTO/ ACJ
Levin et al. 1992	NYHA functional class III/IV	0.7	
Pliskin et al. 1992	Severe angina	0	SG
Kuntz et al. 1996	Post MI with severe angina, no CHF	0.82	TTO
Kuntz et al. 1999	Severe angina	0.67	SG

Most of the studies shown in Table 9.2.7 have derived their QoL scores from different studies. Several of these studies, for example Kuntz, cite Nease et al. (1995). This study investigated attitudes towards their angina symptoms in a representative sample of 220 patients using the rating scale, time trade off and standard gamble utility methods.

The patients were categorised by Canadian Cardiovascular Society (CCS) class (I – IV) according to the severity of their symptoms assessed by his or her cardiologist, with class I being the least severe. Table 9.2.8 shows the patient utilities for each of the utility methods.

Table 9.2.8 Median patient utilities by measurement metric and Canadian Cardiovascular Society class (CCS) (Data from Kuntz et al. 1999; Table from Davies et al. 2003a)

	Class I	**Class II**	**Class III/IV**
Proportion in class, %	18	51	31
Rating scale	0.89	0.78	0.59
Time trade off	1	0.997	0.929
Standard gamble	0.965	0.97	0.875

Table 9.2.9 Patient utilities by measurement metric and selected criterion measure (Data from Kuntz et al. 1999; Table from Davies et al. 2003a)

How would you describe your angina discomfort on average?	**Rating scale**	**Time trade off**	**Standard gamble**
Very mild, mild or moderate	0.832	0.999	0.878
Severe or very severe	0.558	0.967	0.833

Melsop et al. (2003) measured the quality of life in patients who had previously received revascularisation as part of the Bypass Angioplasty Revascularisation Investigation (BARI) Study of Economics and Quality of Life. They measured quality of life measures, such as Duke Activity Status Index and angina class, together with a time trade off utility assessment on average of 7.3 years after random assignment. Of

those 458 questioned, 400 did not have angina after 7.3 years. Those without angina had median TTO scores of 9.95 (mean = 8.7) and those with had median TTO scores of 8.5 (mean = 7.03). Some of the results are shown in table 9.2.10.

Table 9.2.10 Patient utilities by measurement metric and Canadian Cardiovascular Society class (CCS) (Data form Kuntz et al. 1999; Table from Davies et al. 2003a)

	Class I	**Class II**	**Class III**	**Class IV**
Number in class	14	29	11	4
Median	9.79	9	8.5	0.5
Mean	8.18	7.4	6.7	1.25

The study by Melsop et al. (2003) shows that the quality of life of people after revascularisation is excellent. Indeed the majority were still free from angina after over 7 years. The mean quality of life utility for Melsop et al. (2003) was similar to those reported in Kuntz et al. (1999).

On the basis of the study shown here for quality of life measures, it was assumed that the major benefits to quality of life are seen after revascularisation and these will remain whilst the angina symptoms are controlled. The CHD modelling team used the mean TTO scores for those with and without angina after revascularisation from Melsop et al. (2003), i.e. the quality of life scores vary in the range of 0.7 to 0.87 (Davies et al. 2003a) and the same values are used in the models in this chapter.

9.2.4 Costs

A more detailed discussion of the data for coronary heart disease costs can be found in the UK Coronary Heart Disease Policy Model Working paper on costs (Raftery et al. 2003). A full list of the derived costs for coronary heart disease are shown in Appendix VI. The estimated cost per patient is £368 per year, which includes GP and cardiology appointment and non secondary prevention drugs costs (such as nitrates and calcium channel blockers). The estimated cost per MI admission is £1,465, which includes the cost of the hospital stay, coronary care unit, thrombolysis and the ambulance. The

estimated cost per unstable angina admission is £741. The estimated cost for CABG and PTCA is £6215 and £3346 and these include the cost of angiogram.

9.3 Description of the revascularisation models

The Markov and DES models in this chapter are developed, as far as possible, to be identical to each other. Accordingly they use the same parameters for transitions between states and costs. The initial models constructed are cohort models for patients with previous history of MI.

9.3.1 Markov model

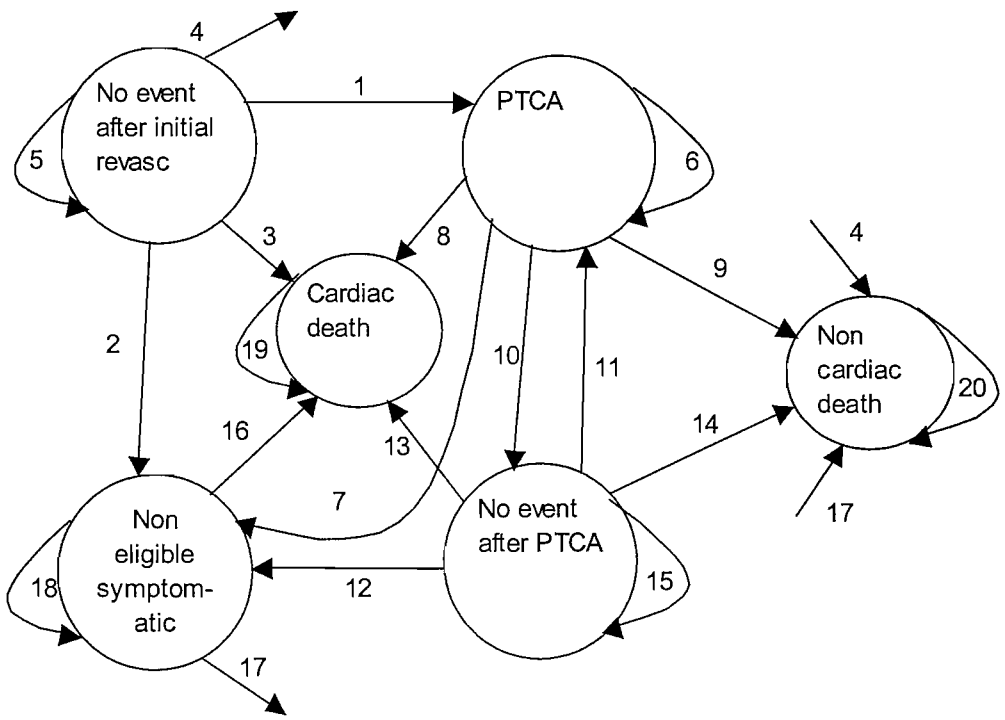

Figure 9.3.1 Simple revascularisation Markov cohort model

A simple Markov cohort model for revascularisation is shown below in Figure 9.3.1. It consists of six states: *No event after initial revasc, PTCA, no event after PTCA, Non eligible symptomatic, Cardiac death* and *Non cause death.* The model has a cycle length of one year. A cohort of patients begins with an initial revascularisation and will start in the *No event after initial revasc* state. A proportion of these patients will have angina recurrence and these will either have further revascularisation (*PTCA*), or will be *Non*

eligible symptomatic. PTCA has an increased repeat revascularisation rate in the first year as shown in Table 9.2.4; those surviving this year will enter the *No event after PTCA state*. Patients may die from any state.

In this model, it is assumed that angina recurrence is as a result of acute coronary events, such as unstable angina and MI. The recurrence of angina symptoms is also related to the severity of vessel disease and the individuals with more severe vessel disease are more likely to have a recurrence of angina symptom as shown by their relative risks in Table 9.2.1. The risks of unstable angina and MI have been derived in section 6.4.5 and 6.4.6 and Appendix IX. The risk of unstable angina is $0.0141 R \exp^{0.0156x}$ where x is the age of the individual and R is the relative risk as shown in Table 9.2.1. The risk of MI is $0.006 R \exp^{0.03x}$ where x is the age of the individual and R is the relative risk as shown in Table 9.2.1.

Those with the more severe vessel disease have a higher risk of long term mortality and morbidity according to the relative risks shown in Table 9.2.1. Thus, patients with triple vessel disease are almost twice as likely to experience a MI as those with single vessel disease. There are also greater benefits from CABG for the more severe vessel disease, while patients remain in the state *No event after initial revasc,* and these are shown in Table 9.2.3. Thus those with triple vessel disease have their risk of a MI almost halved after a CABG. The operative risks for the procedures are incorporated in the model for PTCA and CABG and these are shown in Table 9.2.2. For each vessel disease classification, the proportion of those with recurrent symptoms who have repeat revascularisation is assumed to be the same.

Not all patients whose anginal symptoms recur have immediate revascularisation. The proportion of patients receiving repeat revascularisation was 20% of patients with non fatal MI and 60% of patients with unstable angina received repeat revascularisation. There is a high proportion of repeat revascularisation in the first year after a PTCA over and above the natural recurrence of angina through acute coronary incidents (see Table 9.2.4). It was estimated that in addition to the recurrence through ACI, 23% of patients who have PTCA receive repeat PTCA within the first year.

Those who have repeat revascularisation are assumed to have 3 months of anginal symptoms until they are relieved. In addition those patients in state *Non eligible symptomatic* are assumed to have the lower quality of life. The model was constructed in Treeage and run with a population of age 60 years with long term MI.

The transitions in the model (numbered on diagram) are as follows:

From *No event after initial revasc*

1) Patient has ACI and is referred for repeat revascularisation (PTCA)
2) Patient has ACI but is not eligible for repeat revascularisation
3) Patient has cardiac death
4) Patient has non cardiac death
5) Patient has no ACI after initial revascularisation

From *PTCA*

6) Patient has ACI after repeat PTCA and is referred for further PTCA
7) Patient has ACI after repeat PTCA but is not eligible for repeat revascularisation
8) Patient has cardiac death
9) Patient has non cardiac death
10) Patient has no event after repeat PTCA

From *No event after PTCA*

11) Patient has ACI and is referred for repeat revascularisation (PTCA)
12) Patient has ACI but is not eligible for repeat revascularisation
13) Patient has cardiac death
14) Patient has non cardiac death
15) Patient remains event free

From *Non eligible symptomatic*

16) Patient has cardiac death
17) Patient has non cardiac death
18) Patient ineligible for revascularisation does not die

19) Cardiac death (absorbing state)

20) Non cardiac death (absorbing state)

Table 9.3.1 Transition probabilities for the Markov model for the revascularisation model. Values for patient of age 60 with triple vessel disease for the CABG scenario. (ONS = Office of National Statistics (Table 6.4.3); p(NFMI) = probability of non fatal MI; p(UA) = probability of unstable angina; RRp is prognostic relative risk for vessel disease (Table 9.2.1); RRb is surgical benefit for vessel disease (Table 9.2.3); PTCA_mort = probability of mortality from PTCA, Death rate DR in or out of hospital from UKHAS, (Table 6.4.4)).

Transition	Data source / derived equation	Value for age 60
1)	(0.2*p(NFMI) + 0.6*p(UA))*RRb	0.027
2)	(0.8*p(NFMI) + 0.4*(UA))*RRb	0.035
3)	$0.0066\exp^{0.03x}$*RRp*RRb*(DR in out hosp)	0.016
4)	ONS	0.007
5)	1 – T1 – T2 – T3 – T4	0.915
6)	0.23 + 0.2*p(NFMI) + 0.6*p(UA)	0.277
7)	0.8*p(NFMI) + 0.4*(UA)	0.06
8)	$0.0066\exp^{0.03x}$*RRp* (DR in out hosp) + PTCA_mort	0.037
9)	ONS	0.007
10)	1 – T6 – T7 – T8 – T9	0.619
11)	0.2*p(NFMI) + 0.6*p(UA)	0.047
12)	0.8*p(NFMI) + 0.4*(UA)	0.06
13)	$0.0066\exp^{0.03x}$*RRp* (DR in out hosp)	0.028
14)	ONS	0.007
15)	1 – T11 – T12 – T13 – T14	0.858
16)	$0.0066\exp^{0.03x}$*RRp* *(DR in out hosp)	0.028
17)	ONS	0.007
18)	1 – T16 – T17	0.965
19)	1	1
20)	1	1

9.3.2 Results

The simulation model was constructed in a similar way to the Markov model and run for 100 runs of 40 years. The results from the runs of the Markov and simulation models are shown in Table 9.3.2 and 9.3.3. Both of the CABG and PTCA strategies are compared to medical therapy. The results from each of the models are similar. The mean absolute errors between the two models for cost, QALY and ICER are 1.8%, 0.7% and 5.5% respectively. In both cases, CABG is most cost effective for the more severe vessel disease and PTCA for the less severe vessel disease.

Table 9.3.2 Costs, life expectancies and cost effectiveness ratios for CABG and PTCA for different severity of disease for the Markov model

	1 or 2 VD			3 VD			LMS		
	Medical	**CABG**	**PTCA**	**Medical**	**CABG**	**PTCA**	**Medical**	**CABG**	**PTCA**
Cost	6862	14463	12667	6209	14234	12342	5233	13712	11664
QALY	11.0	12.4	12.6	8.8	11.2	9.8	5.4	8.6	5.8
ICER		5114	3585		3266	5876		2667	15517

Table 9.3.3 Costs, life expectancies and cost effectiveness ratios for CABG and PTCA for different severity of disease for the simulation model

	1 or 2 VD			3 VD			LMS		
	Medical	**CABG**	**PTCA**	**Medical**	**CABG**	**PTCA**	**Medical**	**CABG**	**PTCA**
Cost	6821	14400	12496	6182	14058	12120	5137	13329	11213
QALY	10.9	12.5	12.6	8.8	11.2	9.9	5.5	8.6	6.0
ICER		4914	3473		3293	5620		2685	12965

As mentioned above, there is some debate as to whether there is the same prognostic benefit from CABG as that from PTCA. In the case where there is no prognostic benefit from CABG, similar to PTCA, the cost effectiveness ratio for 3 vessel disease is £7800 and for left main stem is £18 000. In this case, PTCA would be the preferred treatment for all treatments.

9.3.3 Modelling revascularisation for patients with angina

The models were expanded to estimate the cost effectiveness of patients without a history of MI. In this case the number of states in Figure 9.3.1 increase from six to ten. Each of the non death states would be either angina only or MI. Patients can pass from the angina states to the MI states if they have a non fatal MI. Patients with angina only had a risk of MI of $0.0089\text{Rexp}^{0.0155x}$ where R is the relative risk of the individual's vessel disease and x is their age.

Table 9.3.4 Costs, life expectancies and cost effectiveness ratios for CABG and PTCA for different severity of disease for the Markov model with angina and MI patients

	1 or 2 VD			3 VD			LMS		
	Medical	**CABG**	**PTCA**	**Medical**	**CABG**	**PTCA**	**Medical**	**CABG**	**PTCA**
Cost	7677	15494	13540	7201	15450	13809	6168	14957	13312
QALY	12.7	14.6	14.8	10.8	13.6	12.3	7.1	10.7	7.9
ICER		4136	2832		2946	4319		2415	8505

Table 9.3.5 Costs, life expectancies and cost effectiveness ratios for CABG and PTCA for different severity of disease for the simulation model with angina and MI patients

	1 or 2 VD			3 VD			LMS		
	Medical	**CABG**	**PTCA**	**Medical**	**CABG**	**PTCA**	**Medical**	**CABG**	**PTCA**
Cost	7641	15393	13540	7144	15207	13510	6071	14496	12769
QALY	12.8	14.7	14.9	10.9	13.6	12.4	7.2	10.6	7.9
ICER		3975	2814		2927	4247		2491	9245

The results from the runs of the Markov and simulation models are shown in Table 9.3.4 and 9.3.5. The results from each of the models are similar for all analyses. In both cases, CABG is most cost effective for the more severe vessel disease and PTCA for the

less severe vessel disease. In each analysis, the procedures are more cost effective for angina patients (Table 9.3.4 and 9.3.5) than MI only patients (Table 9.3.2 and 9.3.3).

9.3.4 Discussion

The models in this section took a similar time of roughly three weeks to build and the results from the Markov and simulation models were simulation. Consequently the choice of preferred model was based on the perceived simplicity and transparency of the models and so the Markov model was chosen as the optimal model to build. Thus a resource based intervention has been modelled without using queues.

The results from this model show the cost effectiveness of revascularisation techniques using cohort analyses. In previous chapters the advantages were shown of population based analyses in order to estimate the likely costs and benefits for a population. In the next section the models are extended and built as population based models. Based on the experiences building population models in chapter 8, it was decided that it would be more difficult to build a Markov population model than extend the simulation model and so the population based model is built as a simulation model.

9.4 A population-based simulation model for revascularisation

In this section, a population-based simulation model is built. In order to do this, some new parameters are introduced which describe the proportion of the CHD population with different vessel disease.

9.4.1 Parameters for the population-based model

In the population-based model, the vessel distribution amongst CHD patients needs to be used. This is needed in order to estimate the need for revascularisation for each of the severity of heart disease. The vessel disease distribution for prevalent patients was determined from a 1970s observational study by Jones (1972). The data were broken down by whether or not patients suffered a previous MI. This study was the only one

found to be a survey of all patients with CHD, rather than those selected for angiography (Table 9.4.1).

In practice, patients' vessel disease will change as they age. However, in this model, as with the UK CHD Policy model (Davies et al. 2003a), it is assumed that patients keep the same vessel disease throughout the simulation. As those with more severe vessel disease have shorter life expectancies the numbers of patients with more severe vessel disease would decrease as the simulation progresses. In order to avoid this and keep the proportions of patients with different vessel disease constant over time, the vessel disease profile of incident patients was adjusted. The vessel disease make-up of unstable angina patients was taken from the FRISC II study (1999) (Table 9.4.2).

Table 9.4.1 Vessel disease make-up of prevalent CHD patients (Data from Jones 1972; Table from Cooper et al. 2003)

No. of vessels stenosed	Stable angina % of patients	Previous MI % of patients
0	52.0	5 .0
1	16.5	24.2
2	8.0	14.1
3/2+LAD	20.7	50.5
LMS	2.8	6.2

In any group of people, the risk of LMS is assumed to be proportional to the number of vessels diseased. Thus in groups with more triple vessel disease, there would be a subsequent higher number with left main stem. Using this assumption, the likely proportion of the CHD population with LMS was calculated for the patients in the Yusuf et al. meta analysis (1994), see Appendix VII. Yusuf et al. (1994) showed that the prognosis for persons with 2 vessel disease (VD) and left anterior descending disease (LAD) is similar to that of persons with 3 VD whilst for persons with 2 VD and no LAD the prognosis was similar to that for person with 1 VD. Those with 2 VD and LAD will be treated the same as those with 3 VD, and those with 2 VD and no LAD

will be treated the same as those with 1 VD. Yusuf (1994) showed that half of 2 VD patients had LAD, thus half of 2 VD patients were categorised as 3VD patients within the model.

Table 9.4.2 Vessel disease make-up of incident CHD patients (Stable angina and previous MI values adjusted as described above) (Data from FRISC II 1999; Table from Cooper et al. 2003)

No. of vessels stenosed	Stable angina % of patients derived*	Post MI % of patients derived*	Unstable angina % of patients
0	44.5	1 .0	14.0
1	13.0	16.2	29.0
2	7.5	12.0	13.0
3/2 +LAD	28.5	58.0	36.0
LMS	6.5	12.8	8.0

* The parameters in these columns have been derived in order to keep the vessel disease stable at the prevalent proportion shown in 9.4.1

The simulation was run for prevalent and incident patients of a particular vessel disease. The number of patients with that disease is proportional to the vessel disease make-up described in Table 9.4.1 and 9.4.2 and the prevalent and incident rates described in Table 6.4.1 and 6.4.2. As with the previous models, the model in this section was not run with patients with zero vessel disease.

In this model, (but not in the UK CHD policy model) it is assumed that none of the prevalent patients have had a previous CABG or PTCA operation and will only be eligible for a PTCA if they have a non fatal ACI. New incident MI and unstable angina patients have the same revascularisation rate as that reported above, ie 60% of unstable angina patients and 20% of MI patients have revascularisation respectively. In a similar manner, 50% of new stable angina patients will have revascularisation.

Patients who have survived an MI are at a higher risk of further MI in their first year after MI. The risk of MI is $0.013 R \exp^{0.0337x}$ where x is the age of the individual and R is the relative risk as shown in Table 9.2.1.

9.4.2 Results

The simulation model was run for a population of 125,000 for 40 years with 100 iterations. Table 9.4.3 shows the results for the costs, life expectancies and cost effectiveness ratios. Table 9.4.4 shows these results discounted at 3% for costs and benefits. As seen in earlier results, PTCA is more cost effective for 1 or 2 vessel disease, and CABG more cost effective for 3 vessel disease and left main stem.

Table 9.4.3 Average annual costs, life expectancies and cost effectiveness ratios for CABG and PTCA for different severity of disease for the simulation model

	1 or 2 VD			3 VD			LMS		
	Medical	**CABG**	**PTCA**	**Medical**	**CABG**	**PTCA**	**Medical**	**CABG**	**PTCA**
Cost (£000s)	550	902	824.8	717.1	1230.7	1125.7	112.5	216.2	194.6
QALY	831	889	892	939	1034	1003	105	127	111
ICER		6044	4463		5423	6419		4701	13259

Table 9.4.4 Average annual discounted costs, life expectancies and cost effectiveness ratios for CABG and PTCA for different severity of disease for the simulation model; costs and benefits discounted at 3%

	1 or 2 VD			3 VD			LMS		
	Medical	**CABG**	**PTCA**	**Medical**	**CABG**	**PTCA**	**Medical**	**CABG**	**PTCA**
Cost (£000s)	322.6	529.8	484.3	416.2	719	658.6	65.6	126.7	114.5
QALY	487	519	520	544	594	579	61	73	65
ICER		6609	4916		6059	6919		5271	13740

As shown in previous chapters, one of the advantages of running a population model is that it produces estimated total costs and benefits of introducing the intervention. If the results are scaled up to a population of one million, then Table 9.4.5 shows the number of operations for each category. Thus if the optimal procedure is chosen in each case about 510 CABG and 1170 PTCA will be performed per million population (Table 9.4.5). This policy will save 1425 quality adjusted life years per year at an extra cost of £7.1 million per million population, compared with treating patients with medical treatment only. This corresponds to an undiscounted and discounted cost effectiveness ratio of £5000 and £5560 per QALY gained.

Table 9.4.5 Number of operations for CABG and PTCA for different vessel disease for a scaled population of one million

	CABG			PTCA		
	1 VD	**3 VD**	**LMS**	**1 VD**	**3 VD**	**LMS**
Initial procedure	306	429	84	306	429	84
Subsequent PTCA	274	426	87	346	544	111

Table 9.4.6 shows the CHD prevalence and coronary events for the medical and optimal revascularisation scenarios. For the revascularisation scenario there will be a marginal increase in the CHD prevalence and a small decrease in the number of coronary events between the scenarios.

Table 9.4.6 Average number of coronary events and CHD prevalence for medical treatment and optimal revascularisation policy for the simulation runs for a scaled population of one million

	Medical	**Revasc**	**% Diff**
Alive	21425	21649	1.0%
MI ad	1788	1735	-3.0%
UA	1681	1581	-6.0%

9.4.3 Sensitivity analysis

In the simulation model described in this section the number of people who received repeat revascularisation has been constrained by merely allocating a set proportion of the patients to the procedure. There is no queuing process explicitly modelled. In practice patients with stable angina would be referred by their GP to a cardiology clinic where, after assessment, they may be referred for angiography and thereafter for revascularisation. At each stage, there would be a waiting list of some kind which would influence the time that it takes for an appointment. This is also the case for patients who experience acute coronary events, although their referral process may differ slightly in priority for treatment and waiting time.

In this section we investigate whether this method of allocating resource instead of the use of queues leads to erroneous results:
H5) For dynamic systems which involve constraints or where patients compete for resources, DES is the more appropriate technique.

The simulation model was modified to include a queue for patients who are referred for a repeat PTCA. The runs were completed for patients with triple vessel disease for the CABG procedure scenario. Patients are added to the queue when they are referred to have a repeat PTCA. At the beginning of each simulated month, patients are taken from the front of the queue according to the number of procedures to be completed each month. The results are shown for three possible resource levels: four, five and six PTCA per month. This results in average waiting times of 1.24 years, 0.46 years and 0.19 years for each of the resource levels. In the comparative model without queues, patients will wait for a set time period equivalent to the average queuing time from the queuing model before they have the repeat PTCA procedure.

The results from the runs are shown in Table 9.4.7 and the average error between the two models is shown in Table 9.4.8. There is little difference between the results from the two model runs with less than 1.4% 'error' between the cost, QALY and cost effectiveness ratios. Certainly the inclusion of queues has not materially affected the results. However, in this case the results were largely unaffected by the increase in waiting time. For example the cost and QALY are only 2% and 1% lower for the

longest waiting time scenario (4 PTCA / month) compared to the shortest waiting time scenario (6 PTCA / month) and the cost effectiveness ratio is only 2.4% better. The number of repeat PTCA completed is 47.8 and 55 per year for the longest and shortest waiting time scenario respectively.

Table 9.4.7 Average annual costs, life expectancies and cost effectiveness ratios for CABG with triple vessel disease for the simulation models with and without PTCA queue

		4 PTCA / month		5 PTCA / month		6 PTCA / month	
	Medical	**Queue**	**No queue**	**Queue**	**No queue**	**Queue**	**No Queue**
Cost £000s	717.1	1212.3	1198.2	1230	1222.8	1238.9	1233.2
QALY	938.8	1029.1	1027.4	1033.1	1032.3	1036.3	1033.9
ICER		5484	5430	5444	5411	5353	5430

Table 9.4.8 Error between simulation runs with and without PTCA queue, %

	PTCA / month		
%	**4**	**5**	**6**
Cost	1.2	0.6	0.5
QALY	0.2	0.1	0.2
ICER	1.0	0.6	-1.4

9.4.4 Discussion

The results from the population based simulation model show the cost effectiveness and likely costs and benefits of revascularisation. The resource-constrained interventions have been modelled without queues and unconstrained. Thus for a dynamic system involving constraints or where patients compete for resources, DES is not necessarily the most appropriate technique (Hypothesis 5).

One assumption that is made is that patients receive revascularisation, irrespective of their need. For example, 60% of patients with unstable angina receive revascularisation, irrespective of whether they have 1 VD or left main stem. In practice, those with the more serious vessel disease are treated with greater urgency while those with less serious vessel disease will wait much longer. Furthermore it was assumed that patients with recurrent symptoms will receive a repeat PTCA. In practice it would be possible for patients to receive CABG as treatment for recurrent symptoms. However patients will not be able to have more than two CABG operations. In a simulation model this constraint can be easily incorporated by recording the number of CABG procedures completed for each patient and ensuring that it does not exceed two. In a Markov model, this would require extra states according to the number of CABG procedures completed, eg zero CABG, one CABG, two CABG, and the number of states would expand appropriately.

In order to estimate the likely costs and benefits of increasing the revascularisation rates from the pre-NSF rates to NSF targets, the benefits can be estimated more accurately by including this information in the modelling process. The UK CHD policy model used queues to model revascularisation. In the next section the costs and benefits of greater revascularisation are estimated using this model.

9.5 Parameters for the UK CHD Policy model

The UK CHD policy model simulates individual patients through their elective and acute treatment pathways (see Figure 9.5.1). Patients who present with new disease usually present at their GP for stable angina symptoms and hospital for MI or unstable angina. The model describes the referral of stable angina patients to their GP, to cardiology consultation for initial investigation, such as exercise ECG, to angiography and finally revascularisation. Acute patients with unstable angina and myocardial infarction follow a similar (but more urgent) referral process. Patients who are referred to angiography and revascularisation join queues and then must wait their turn for the procedures. There is different priority given according to the severity of the patients'

condition. In this modelling exercise the effect of increasing the volume of revascularisation from the pre-NSF rates to the NSF targets is estimated.

9.5.1 Referral to angiogram for patients with stable angina patients

In general, there is a large variation in the treatment of patients according to their age, and the CHD modelling team (Davies et al. 2003a) attempted to build this variation into the referral pathways. Referral to angiogram was derived from a trial of incident and prevalent patients, Gill et al. (1999), which reported a referral to outpatients of incident patients of 59% in three years. Bucher et al. (2000) reported that approximately 10% of medically treated patients experienced sufficient worsening of symptoms to require revascularisation over a year. Martin et al. (2002) extrapolated these data to allow for the interest in referrals rather than revascularisations and used 15% as the annual proportion of prevalent patients who present for hospital investigations.

The CHD modelling team combined these three studies. If patients do not get referred initially (ie within 3 years) they will be subject to an annual referral probability of 15%. Dudley et al. (2002) and Macleod et al. (1999) have shown that there is a strong bias for referral according to age. Furthermore Macleod showed that patient referral from acute MI in hospital over two years was heavily influenced by age but the referral process from angiogram to revascularisation was much less influenced by age.

Clarke (1994) reported that 28% of incident stable angina patients were referred to angiogram from GP within 3 years. However this study dates from 1994 and the referral rates have increased since it was written. The CHD modelling team assumed a higher rate of 36% to account for this increase in the number of angiograms performed in the intervening years.

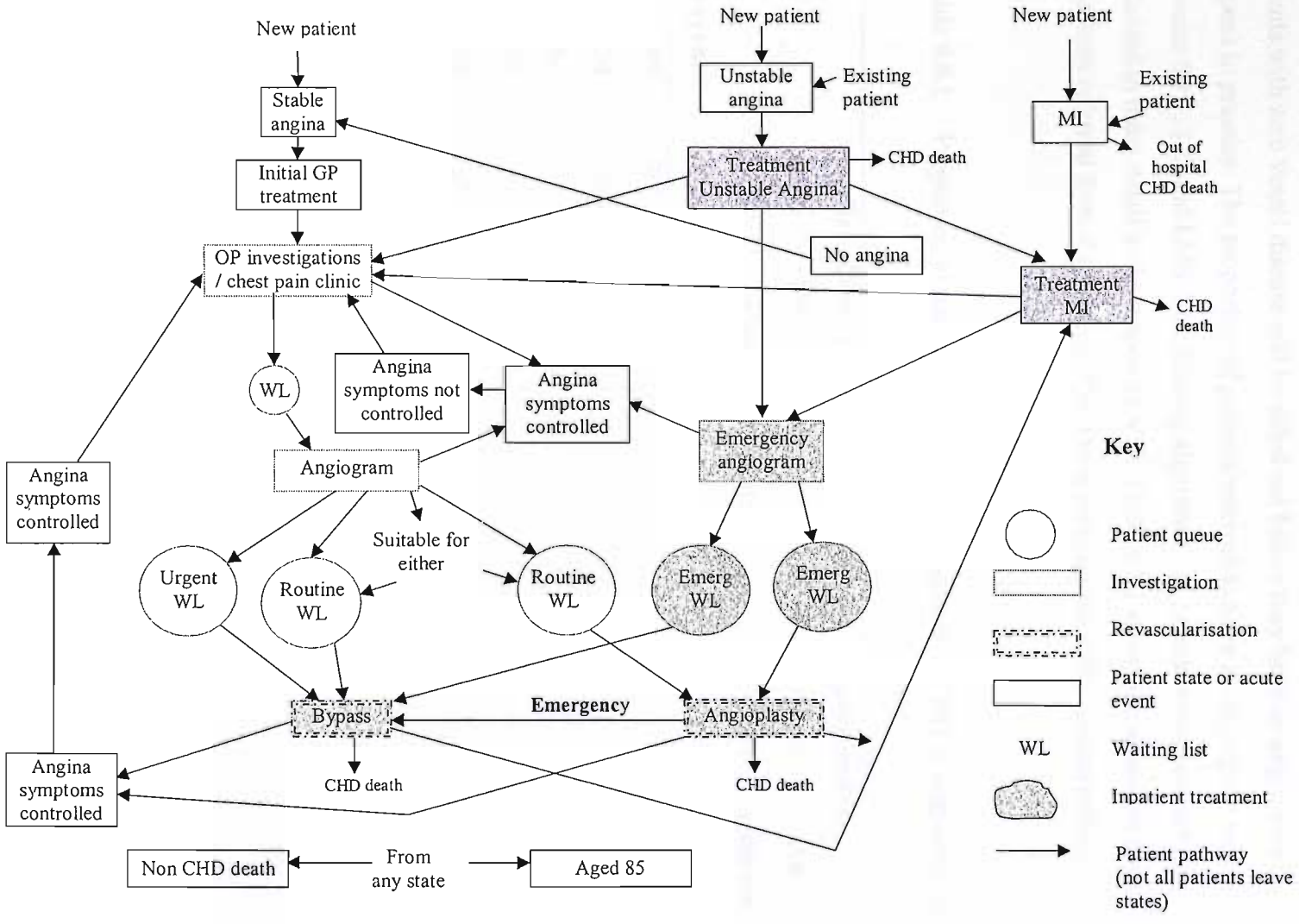

Figure 9.5.1 Elective and acute treatment pathways of the CHD Policy Model (Cooper et al, 2002)

In the UK CHD policy model, there is a two stage referral process for patients with stable angina. They will be referred from initial diagnosis at the GP state to cardiac clinic or rapid chest pain clinic (for exercise ECG) and from there to angiogram. Patients will be referred on the basis of both age and clinical vessel disease. Many of the patients with zero vessel disease will be sifted out before they have an angiogram as happens in practice. The proportion of patients referred to have an angiogram will be the same for 1, 2, 3 and LMS. The filtering algorithm and referral rates used are explained in more detail in the Appendix VIII. Table 9.5.1 shows the actual proportion of patients referred from diagnosis of CHD to angiogram for stable angina patients.

Table 9.5.1 Proportion of patients referred from diagnosis of CHD to angiogram by age

	Base Case (Pre – NSF)			**Target scenario**		
Age (years)	**0 VD**	**Other vessel disease**	**All patients**	**0 VD**	**Other vessel disease**	**All patients**
35 – 45	20%	82%	51.0%	29%	96%	62.5%
45 – 54	20%	82%	51.0%	29%	96%	62.5%
55 – 64	20%	82%	51.0%	29%	96%	62.5%
65 – 74	11%	43%	26.5%	22%	68%	45.1%
75 – 84	2%	9%	5.3%	7%	23%	15.0%

9.5.2 Referral to angiogram for patients with unstable angina and MI

In a similar way, patients who experience unstable angina or non fatal MI events often receive an exercise ECG during their hospital stay and many of these who have positive exercise ECG will have an inpatient angiogram and go on to have a non elective revascularisation.

For the base case, the PRAIS (Collinson 2000) observational dataset was used for the referral of patients with acute unstable angina to inpatient angiogram. PRAIS estimated that 10% of patients who had an unstable angina event had an inpatient angiogram. For the target scenario, a British Cardiac Society survey on resource use after acute MI and unstable angina was used (see Table 9.2.5). Fewer older patients are referred to inpatient angiogram than younger patients based on the study by Macleod et al. (1999).

The UK CHD policy model refers unstable angina patients for an inpatient angiogram according to table 9.5.2. All remaining patients are referred for an outpatient appointment within 6 weeks and these patients will be referred for angiogram in the same way as those for stable angina referred from outpatient clinic to angiogram.

Table 9.5.2 Proportion of unstable angina patients in hospital who have inpatient angiogram, % (Data from PRAIS 2003; Table from Cooper et al. 2003)

Age band (years)	**45 – 54**	**55 – 64**	**65 - 74**	**75 – 84**	**Total**
Base case	20	15	7.5	1.5	10
Target scenario	90	70	40	8	55

As for unstable angina, the British Cardiac Society Survey was used for the target scenario for the referral of patients with non fatal MI to inpatient angiogram (Table 9.2.5). UKHAS (Norris 1998) was used for the base case. UKHAS estimates that 8% of patients have an inpatient angiogram. Fewer older patients will be referred to inpatient angiogram than younger patients, based on the study by Macleod et al. (1999).

The model refers surviving MI patients to inpatient angiogram according to table 9.5.3, with roughly 20% receiving an inpatient angiogram. A further 40% are referred to outpatient appointment within 6 weeks.

Table 9.5.3 Proportion of MI patients in hospital who have inpatient angiogram, % (Data from Norris 1998; Table from Cooper et al. 2003)

Age band (years)	45 – 54	55 – 64	65 - 74	75 – 84	Total
Base case	20	15	7.5	1.5	10
Target scenario	60	45	25	5	20

9.5.3 Allocation of revascularisation resources after angiogram

As mentioned in the previous section, patients with more severe vessel disease who have had an angiogram are likely to be referred for revascularisation. Patients are referred to either urgent or elective waiting lists, depending on the severity of their disease. Acute MI and unstable angina patients may also be referred to emergency waiting lists.

In the UK CHD policy model, emergency and urgent waiting lists have priority over elective waiting lists. People on emergency and urgent waiting list will receive revascularisation as soon as the resources become available. They would in practice remain in hospital until the revascularisation could be performed. Those patients on an elective waiting list will wait considerably longer.

Older patients may have different referral rates to younger patients and those who have acute unstable angina may have different referral rates to stable angina patients or those who have acute MI.

The referral pathways to revascularisation for post MI patients are similar to those of stable angina patients, but different for post unstable angina patients, who are assumed to have more PTCA resources. The CHD modelling team expected that fewer older patients would be referred from angiogram to receive revascularization; however the data do not seem to support this assumption. Tables 9.5.4-9.5.7 show revascularisation data from Scotland (Smith 2004). In the model runs in this section it is estimated that a third of those with triple vessel disease and two thirds of those with left main stem are seen urgently.

Table 9.5.4 Allocation of revascularisation resources after angiogram for stable angina and post MI patients under the age of 70 (Smith 2004)

Treatment, %	**Vessels stenosed**				
	0	**1**	**2**	**3**	**LMS**
CABG queue	4	6	17	31	56
PTCA queue	13	59	44	24	12
Medical treatment	83	35	39	45	32
Total	100	100	100	100	100

Table 9.5.5 Allocation of revascularisation resources after angiogram for stable angina and post MI patients over age of 70 (Smith 2004)

Treatment, %	**Vessels stenosed**				
	0	**1**	**2**	**3**	**LMS**
CABG queue	14	11	27	41	45
PTCA queue	17	51	34	16	15
Medical treatment	69	38	39	43	40
Total	100	100	100	100	100

Table 9.5.6 Allocation of revascularisation resources after angiogram for unstable angina patients under age of 70 (Smith 2004)

Treatment, %	**Vessels stenosed**				
	0	**1**	**2**	**3**	**LMS**
CABG queue	4	4	14	36	64
PTCA queue	20	78	66	40	19
Medical treatment	76	18	20	24	17
Total	100	100	100	100	100

Table 9.5.7 Allocation of revascularisation resources after angiogram for unstable angina patients over age of 70 (Smith 2004)

Treatment, %	Vessels stenosed				
	0	**1**	**2**	**3**	**LMS**
CABG queue	6	6	27	35	48
PTCA queue	28	79	55	35	23
Medical treatment	66	17	18	30	29
Total	100	100	100	100	100

9.5.4 Resources available

In the UK CHD policy model the maximum number of resources is set. Each week this will be the maximum number of patients who can receive angiogram, PTCA and CABG procedures, if there are patients on the waiting lists. Those patients on the waiting lists will continue to wait until the procedures become available. If more resources are made available, the waiting lists will decrease and more patients will have their angina symptoms controlled by revascularisation.

The base case usage of angiogram, CABG and PTCA was based on the British Cardiovascular Intervention Society (de Belder 1998) and The Society of Cardiothoracic Surgeons of Great Britain and Ireland, London 1998 (Keogh and Kinsman 1998), Table 9.5.8.

In the UK CHD policy model, patients who have CABG are given a different vessel disease from their original and would take the prognosis of that different vessel disease category. Furthermore, these patients' vessel disease also changes when the angina recurs or if the patient has an unstable angina attack or MI. According to Bottner et al. (1989), there is little evidence that the vessel disease of PTCA patients changes and thus for PTCA, patients vessel disease remains unchanged after PTCA and when their angina recurs.

Table 9.5.8 Resources available (Data from Keogh and Kinsman 1998, De Belder 1998; Table from Cooper et al. 2003)

Resources, no. per year (per million)	Base case (pre- NSF)	NSF targets
Angiogram	2385	3200*
CABG	435	750
PTCA	437	750

* No target set in NSF; this is suggested value.

9.5.5 Results

The simulation was run for a population of 500,000 for 40 years with 50 iterations. The following scenarios were compared. The referral rates and revascularisation resources are shown in Tables 9.5.1, 9.5.2, 9.5.3 and 9.5.8.

1) Medical treatment only. No angioplasty or revascularisation procedures.
2) Base case. Pre – NSF revascularisation rates.
3) NSF Target revascularisation rates.
4) NSF Target revascularisation rates (Increased PTCA). Increased number of angioplasty procedures to 1000 per million population, number of CABG operations remains at pre-NSF level.

Table 9.5.9 shows the results for the simulation runs for a population of one million averaged for the first 20 years for the Pre-NSF scenario compared to no revascularisation. The Table shows that revascularisation only has slight improvements in patient survival with only 30 life years saved per year and 7 deaths prevented per million population. If the cost effectiveness is only calculated on the basis of life years saved, the cost effectiveness ratio is over £250,000 per life year saved which would not be considered cost effective. However, as mentioned before the main benefit of revascularisation is the improvement in quality of life. Indeed there will be 779 QALYs saved per year per million population and revascularisation will be considered cost effective.

Table 9.5.9 Annual results for a population of one million per year averaged over 20 years; discounted cost effectiveness ratios at 3% for cost and benefits

Scenario	CHD patients	All cause deaths	Cost / year (£000s)	QALY	ICER (£/LYS)	ICER (£/QALY gained)
Medical treatment	30,781	2,312	12,213	21,861		
Base case: Pre-NSF	30,811	2,305	18,135	22,640	251,000	8100

Table 9.5.10 shows the results for the simulation runs for the NSF scenarios compared to the Pre-NSF base case. In this case, the NSF target with equal revascularization rates for CABG and PTCA results in increased patient survival and reduced all cause deaths compared to the base case. In contrast the NSF target with increased PTCA results in reduced patient survival and increased all cause deaths. Interestingly, the PTCA scenario has a negative cost effectiveness ratio for life years saved but is still slightly more cost effective than the NSF target with equal CABG and PTCA rates for QALYs saved. The increased annual cost for the NSF target and increased PTCA NSF target are £3 million and £2 million per million population compared to the base case (Pre-NSF).

Table 9.5.10 Annual results for a population of one million per year averaged over 20 years; discounted cost effectiveness ratios at 3% for cost and benefits

Scenario	CHD patients	All cause deaths	Cost / year (£000s)	QALY	ICER (£/LYS)	ICER (£/QALY gained)
Base case: Pre NSF	30,811	2,305	18,135	22,640		
NSF Target	30,829	2,302	20,994	23,014	191,000	8200
NSF: Inc PTCA	30,796	2,306	20,147	22,938	-149,000	7100

9.5.6 Discussion

The models built in section 9.3 and 9.4 did not use queues for patients waiting for revascularisation resources, in contrast to the UK CHD policy model described in section 9.5. The UK CHD policy model was able to simulate a more realistic flow of patients and would have been able to identify bottlenecks in the system and constrain resource use by only allowing a maximum number of procedures in any time period. For example Davies (1994) and Hilton (2001) show that angiography is a bottleneck. In order to build the patient flows in the UK CHD policy model, much data for patient referral needed to be collected and referral algorithms derived. In fact the models in section 9.3 and 9.4 were able to constrain the level of revascularisation procedures completed by the proportion of patients referred for repeat revascularisation after acute coronary events. For example in the example in section 9.4, 1700 procedures were completed per million population; if fewer procedures were expected the referral rates could be reduced. In this example a national scenario was modelled with event rates and resources available according to a national average. In this case, the use of queues is not as necessary for evaluating the resource-constrained intervention.

In the preceding sections in this chapter models were built for revascularisation and investigated whether systems which involve constraints or where patients compete from resources, should use DES and conclude that there may be many instances where it is not necessary.

In section 9.3, simple Markov and simulation cohort models were built to investigate the cost effectiveness of revascularisation procedures for patients with different vessel disease. It was concluded that the models gave similar results and that the Markov model would have been easier to build and so is the preferred model. In section 9.4, this model was extended to a population based approach in order to estimate the actual costs and benefits from the population. Based on our experiences in chapter 8 it was decided that simulation would be the preferred model to build. However, this decision was not made on the basis of constraints or competition for resources but on the complexity of the model and the ease and time taken to develop the models. As mentioned in the section above, resources may be modelled without the use of queues and this may not still answer our research question without making compromising assumptions.

However, it is certainly the case where dynamic systems are modelled which involve interactions between individuals, such as infectious disease modelling, or where it was desired to describe the patient flow through the system, for example to identify any bottlenecks DES would be more appropriate. In the cases where patients compete for resources, modellers should identify whether the variability of the system is likely to materially affect the results. However, as for a local scenario where the variability in the system would benefit from the use of queues, for example Davies (1994) used a simulation model to describe a local cardiology unit.

An example of this is a local system where the resources are allocated according to highly variable demand. Davies and Davies (1994) concludes that

> *'DES is particularly suitable for problems at an operational level where the use of resources is dependent on decisions about individuals'.*

9.6 Complex systems: Dimensionality

The Markov model forces the creation of extra states as the model becomes more complicated. As more and more parameters are introduced the number of states can proliferate. As an example consider the model built by Weinstein et al. (1987). This is a state transition model for coronary heart disease developed in FORTRAN in the 1980s. It consists of the development of heart disease in the healthly population and their subsequent survival.

The disease progression of people in the Weinstein model is dependent on their risk factors parameters (50 ages, 2 sexes, 2 smoking statuses, 3 blood pressure levels, 3 cholesterol levels, 3 relative weights). Thus the model is stratified into a total of 5400 sub groups. A simulation model is also able to generate the same model with these risk factors, however the total number of parameters increase in an additive way rather than multiplicative (Table 9.6.1). The authors comment that one of the biggest problems with the model was dimensionality:

'Constraints on computing time and costs forced us to restrict the number of risk factors and disease history states and to make numerous independence assumptions. We are currently struggling with the issue of how to incorporate coronary angioplasty into the model without doubling the size of the disease history model' (Weinstein et al. 1989).

Table 9.6.1 Number of states needed for the Markov and simulation models as modelled by Weinstein et al. (1987)

	Markov	**Simulation**
Age (50)	50	50
Gender (2)	100	52
Smoking (2)	200	54
Blood pressure (3)	600	57
Cholesterol (3)	1800	60
Weight (3)	5400	63

DES is ideal for modelling complex systems of this type as it is able to model individuals who carry a very large number of physical and clinical attributes with them. For example a similar model to Weinstein's was developed for coronary heart disease prevention by Babad et al. (2002). It consisted of a population described in terms of sex, smoking (3 categories), and a continuous range of age, blood pressure and cholesterol. As a comparison to Weinstein, suppose that a state transition model modelled the continuous variables to the nearest whole number. Then in order to have a similar accuracy as the simulation model the following parameters are needed: Sex (2), age (60), smoking (3), blood pressure (140), cholesterol (12), which consists of over 600 000 sub groups. The prevention model was linked to a treatment model (Cooper et al. 2002) which consisted of a further 60 sub categories.

Improvements in computing power since 1987 may now make the dimensionality of Weinstein's model less of a problem. Indeed Thomas et al (1995) built a model with 81,000 states. These systems with large numbers of states have been modelled using

sophisticated matrix multiplication software or written in computer languages such as FORTRAN or C although there is little evidence of their use for disease modelling. The case studies in this thesis have used widely available and popular software such as EXCEL and TREEAGE. As Thomas et al. (1995) discusses there are still problems with the 'curse' of dimensionality which restricted their ability to formulate and solve problems quickly and efficiently. As shown in Table 9.6.1 the number of states for the Markov models will increase much more dramatically than for the DES as the complexity of the model increases (in terms of constraints and competing for resources etc). And thus we have shown:

H6) For complex systems where the Markov assumption forces the creation or proliferation of states, DES should be considered.

9.7 Model complexity

In section 4.3, the choice of modelling technique was discussed. It was stated that the choice of modelling technique will depend upon factors such as acceptance by model users, ease and speed of model development, type of intervention, and the complexity of the system. Some of these factors have been explored in subsequent chapters. Other factors also influence this decision such as the experience and expertise of the modeller and the software available. In this section the choice of model is examined with regard to the complexity of the model.

In section 8.6.2 it was noted that there was a point at which the complexity of the model was such that the author preferred the use of DES to a Markov model on the basis of a shorter development time. For each of these models developed in this thesis a judgement was made for the preferred model based on the model's complexity and the expected or actual development time. In this section, the judgement for each of these models is discussed and an attempt is made to quantify the complexity of the models so that this measure can be used as a basis for choosing between the Markov and simulation models. In this context, the complexity of the model includes the number of states and transitions and whether the model is a cohort model or population.

The number of states and transitions for each of the models built in the thesis are shown in Table 9.7.1. The number of transitions relates to the number of non zero transition probabilities between the states. It is estimated that by building a population model, the complexity of the model increases in proportion to the number of starting states. In the secondary prevention drugs model in chapter 8, there were three prevalent starting states for *angina only, Post MI 1st year* and *Post MI subsequent years*. In addition there were two incident states: new angina and new MI. The incident patient cohorts are calculated from the prevalent starting cohort models of *angina only* and *Post MI subsequent years*. Thus, in order to calculate the total number of patients in the Markov model, individual cohort models are needed for each of the starting states. In this case the statins cohort model has a total of five states. It is estimated that the population model has an additional complexity equivalent to 15 states where 5 is the number of states in the cohort model and 3 is the number of prevalent starting states. The number of transitions between the states for the population model can also be estimated in a similar manner.

In Table 9.7.1 the complexity of the models has been estimated by incorporating the number of states or transitions in the cohort model together with the number of prevalent starting states in the population model. In each of the chapters 7 - 9, comparative models were built for each intervention. The results were compared and in each case the results were found to be sufficiently similar to choose the simplest and easiest model to build. In chapter 7, a cohort model for ambulance and thrombolysis interventions was developed. The model consisted of only 4 states and in this case the decision tree model was the easiest model to build. In chapter 8, a simple population model was built for secondary prevention drug interventions. Although it took longer to build the Markov model than the simulation model, this was mainly due to the similarity of the simulation model to the UK CHD Policy model (Cooper et al. 2002) and was it not for this, the Markov model would have been simpler and easier to build. However for a more complex secondary prevention model with 16 times the number of states, the extra complexity would have been much simpler to incorporate with the simulation model than the Markov model. This was also the case with the revascularisation model built in chapter 9.

Table 9.7.1 Summary of models built and preferred modelling technique chosen based on ease of development

Intervention	Markov states		Markov transitions		Model type	'Preferred' model
	Cohort	Popn	Cohort	Popn		
1) Ambulance and thrombolysis	4	0	10	0	Cohort	Decision tree or Markov
2) Secondary prevention simple	5	15	14	42	Population	Markov
3) Secondary prevention complex	50	150	194	582	Population	Simulation
4) Revascularisation simple	14	0	52	0	Cohort	Markov
5) Revascularisation complex	14	42	52	156	Population	Simulation

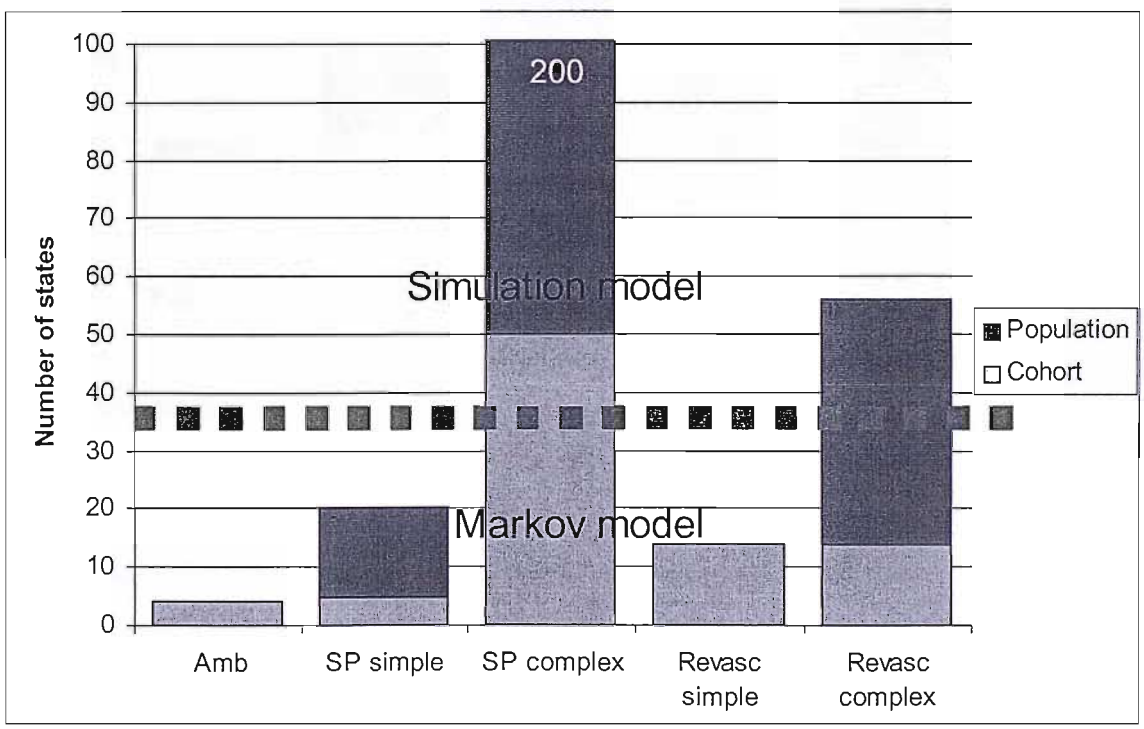

Figure 9.7.1 Number of states for each of the models built

Based on the information shown in Table 9.7.1, a level of complexity is chosen above which the simulation would be chosen in preference to the Markov model. This level of complexity is in the range of 20 to 56 states and 56 to 208 transitions. If the mid point of these ranges is chosen then the modeller would be advised to choose to use a simulation model once the total number of Markov states exceeds about 35 or the total number of Markov population transitions exceeds about 140 based on the ease of development. These recommendations are illustrated graphically in Figures 9.7.1 and 9.7.2.

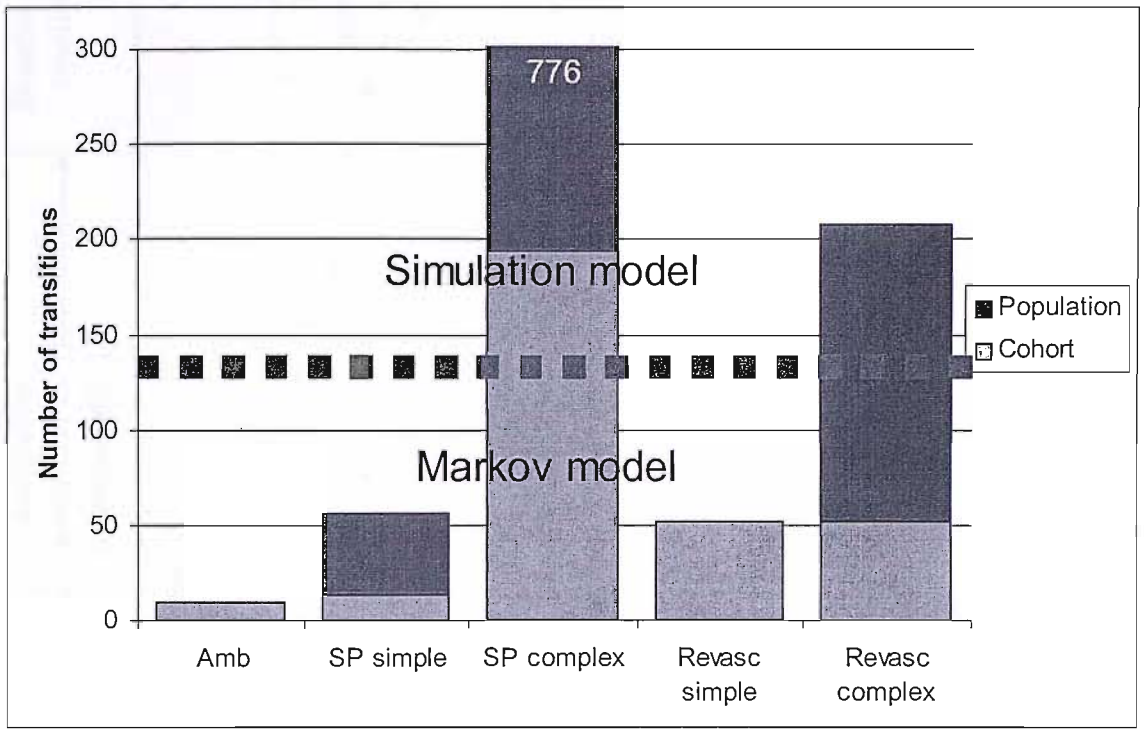

Figure 9.7.2 Number of transitions for each of the models built

9.7.1 Discussion

The suggestions on model complexity were a subjective assessment based on a small number of models for coronary heart disease interventions. Clearly the complexity threshold may vary for other modellers and disease applications. As the number of different studies and modellers grow so this threshold will become more objective, nevertheless it may be used as a guide to choose between the model types on the basis of complexity.

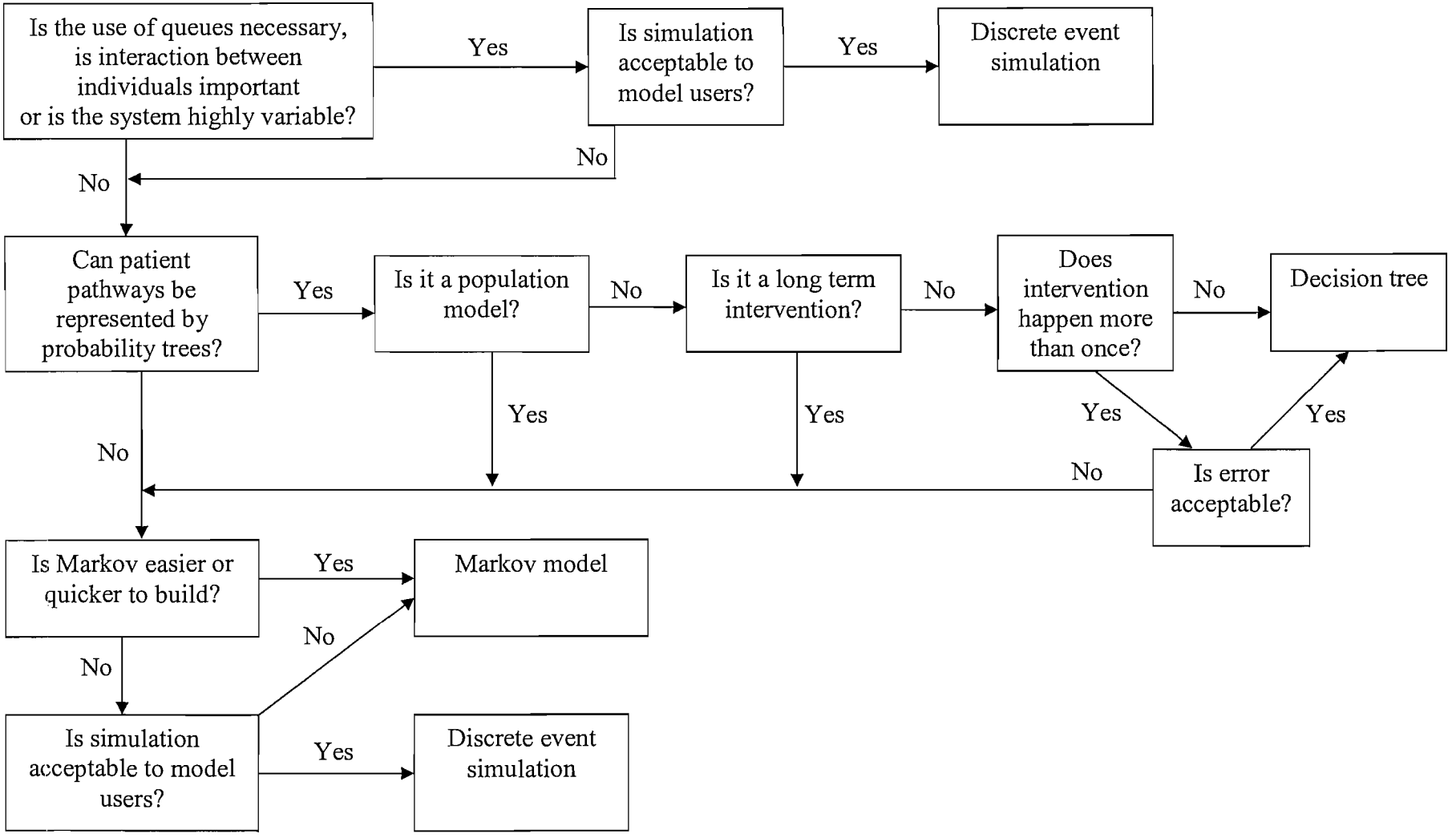

Figure 9.7.3 Schematic of choice of model type for evaluating health care interventions

The suggestions on model complexity refer to disease models. It has been shown how resource-constrained models can be built without the need for queues. We have not considered the effects of variability in these systems or the interaction between individuals such as in infectious disease modelling. These factors are likely to be more significant in organisational planning and complex problems of this nature lend themselves well to DES (Davies et al. 1985; Davies and Davies 1994; Fone et al. 2003).

The guidelines for selection for model type are shown in Figure 9.7.3. As indicated in this thesis, the choice of model type will be influenced by model appropriateness, model error, model acceptance and ease and speed of model development.

9.8 Conclusions

In this chapter the choice of modelling technique was explored for resource-constrained treatment interventions. Resource-constrained interventions are those for which there may be some decision rules concerning the allocation of the resources and these are typified by the referral and subsequent waiting of patients for elective hospital procedures. Markov and simulation cohort and population models were built to evaluate the costs and benefits from coronary artery bypass grafting (CABG) and percutaneous transluminal coronary angioplasty (PTCA) for coronary heart disease patients.

CABG is more cost effective for more severe coronary disease (ie triple vessel disease and left main stem) and PTCA is more cost effective for less severe coronary disease (ie single and double vessel disease). Compared to medical treatment, CABG and PTCA are good value for money with ICER of £4900 for PTCA for 1 VD, £6100 for CABG for 3 VD and £5300 for CABG for left main stem. Increasing the provision of revascularisation according to the National Service Framework would cost an additional £180 million per year and would gain over 22 000 QALY per year for UK.

Using these models it is concluded that the results were not significantly affected by modelling the resources without using queues and concluded that DES is not necessarily

the most appropriate technique. As in chapter 8, the choice of the preferred model was determined by the ease and speed of model development. As the overall complexity, in terms of the number of states, became sufficiently large the DES model became the preferred model. For model choice based on ease and speed of development time, a relationship was developed between the complexity of the model in terms of number of states and the preferred model to build.

Chapter 10

Summary of results and conclusions

The final chapter reviews the results from the coronary heart disease analyses, discusses the aims and findings of this research, considers limitations to this research and suggests further research.

The first aim of this research was to develop a variety of models to evaluate coronary heart disease interventions. These models were developed to evaluate faster ambulance and thrombolysis response times, secondary prevention drugs and revascularisation. In addition to evaluating the cost effectiveness of each of the interventions, analyses have also been carried to estimate the likely costs and benefits of improving treatment for these interventions according to guidelines suggested by the National Service Framework for Coronary Heart Disease.

The second aim of this research was to examine the appropriate modelling technique to be used to evaluate a given health care intervention. This question was addressed for a variety of types of health care intervention. The research aims were achieved by constructing many health care models for different health care intervention types. A set of hypotheses were tested by the analysis of these models. A framework for choosing between the models according to the complexity of the models and the health care intervention characteristics was then developed.

Chapter 10 Summary of results and conclusions

10.1 Introduction

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10.2 Results for the Coronary heart disease interventions

In chapter 7 models were built to evaluate faster ambulance and thrombolysis response times for out of hospital MI. In chapter 8 models were built to evaluate secondary prevention drugs for CHD patients. In chapter 9 models were built to evaluate revascularisation for CHD patients. In this section the results from each of the interventions are reviewed.

A comparison of these results demonstrates the difficulties of comparing modelling results from different studies. For example the ambulance response and thrombolysis interventions used cohort models, whilst those for secondary prevention drug and revascularisation interventions used population models. The differences in results between the cohort and population models have been discussed in previous chapters in this thesis. It was concluded that although cohort models are more commonly used in the health care modelling literature, population models provide a more comprehensive evaluation of the intervention. For comparison purposes, the cohort based models were compared with population model runs of 40 years, as this represents a reasonable estimate to the average life time of the combined cohorts. As noted earlier, the time horizon chosen is critical to the results of the model, and 20 year run results are also shown as these are likely to be of greater interest to health care providers.

The results from all the model runs are shown in Table 10.2.1 and 10.2.2 and Figures 10.2.1 - 10.2.4. They show the cost, benefits and cost effectiveness ratios of each of the interventions for 20 and 40 years.

Table 10.2.1 Average annual results for the CHD interventions for 40 years for a population of one million

	ICER (£/LYS)	**ICER (£/QALY)**	**Increased cost (£M)**	**LYS**	**QALY gained**
Ambulance	5000	6300	0.395	105	84
Thrombolysis	22 000	27 500	0.461	25	20
Statins	4500	5600	3.837	906	725
ACE Inhibitor	2600	3200	1.616	673	539
Aspirin	700	800	0.04	115	92
Beta Blocker	800	1000	0.211	320	256
PTCA 1VD	-59 300	4900	2.19	-56	491
CABG 3VD	72 800	6100	4.11	158	758
CABG LMS	10 300	5300	0.83	120	177
NSF Revasc	108 500	6800	2.8	31	445

Table 10.2.2 Average annual results from the CHD interventions for 20 years for a population for one million

	ICER (£/LYS)	ICER (£/QALY)	Increased cost (£M)	LYS	QALY gained
Statins	5600	7000	2.79	504	403
ACE Inhibitor	3200	3900	1.17	376	301
Aspirin	700	900	0.02	56	45
Beta Blocker	700	900	0.16	212	170
PTCA 1VD	-45 100	5900	2.31	-42	420
CABG 3VD	33 800	7500	4.28	70	609
CABG LMS	8000	6600	0.85	82	140
NSF Revasc	190 600	8200	2.9	18	375

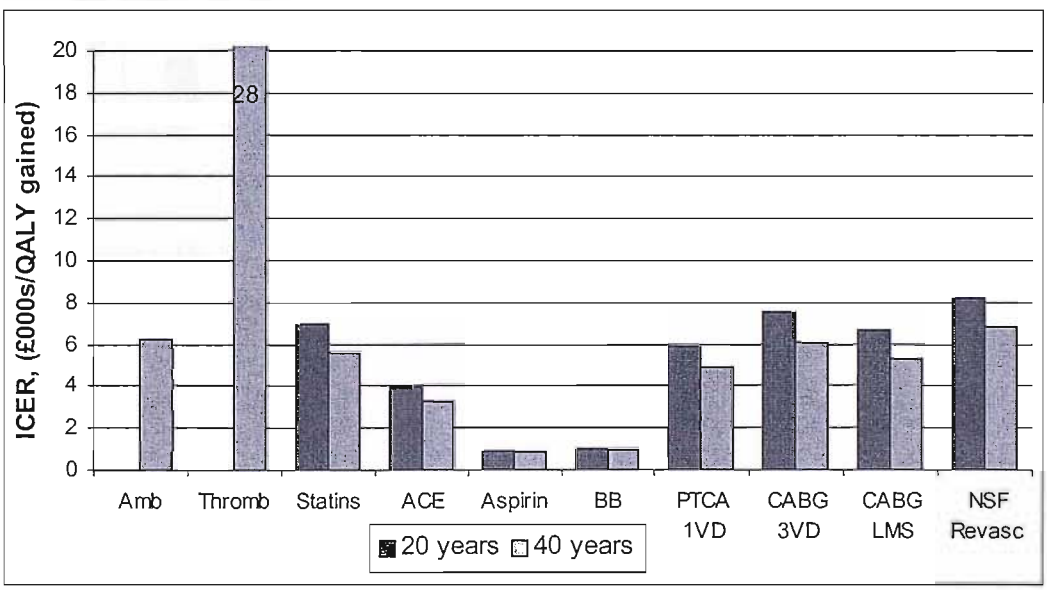

Figure 10.2.1 Discounted cost per QALY gained for the interventions with costs and benefits discounted at 3%

Revascularisation is primarily concerned with increased quality of life; the results have been synthesized by comparing the cost effectiveness as cost per QALY gained rather than cost per life year saved. The average quality of life score is assumed to be 0.8 for the CHD population for the ambulance and thrombolysis and secondary prevention

interventions. The ambulance, thrombolysis, secondary prevention and NSF revascularisation scenarios represent the costs and benefits of increasing from health levels and resource levels before the NSF to the NSF targets for each of these interventions whereas the revascularisation scenarios (PTCA 1VD, CABG 3 VD, CABG LMS) show the cost and benefits of these interventions compared to medical treatment only.

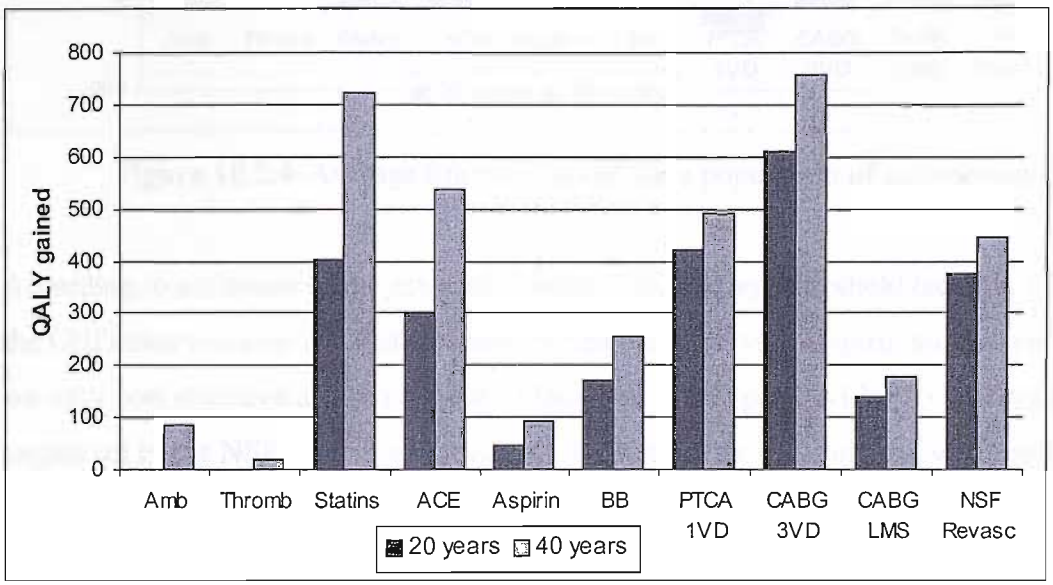

Figure 10.2.2 Average annual QALY gained for a population of one million

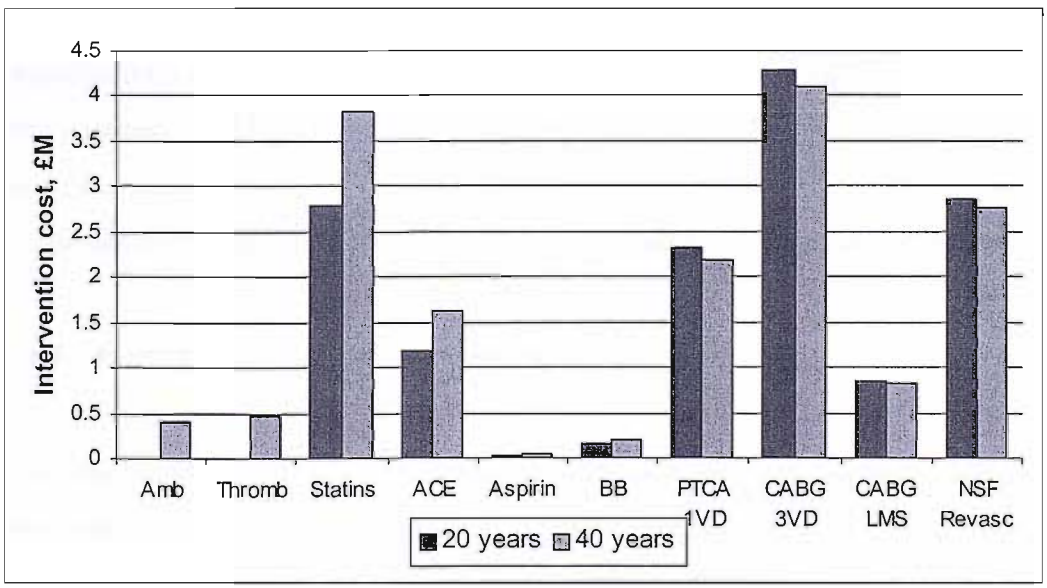

Figure 10.2.3 Average increased intervention cost for a population of one million

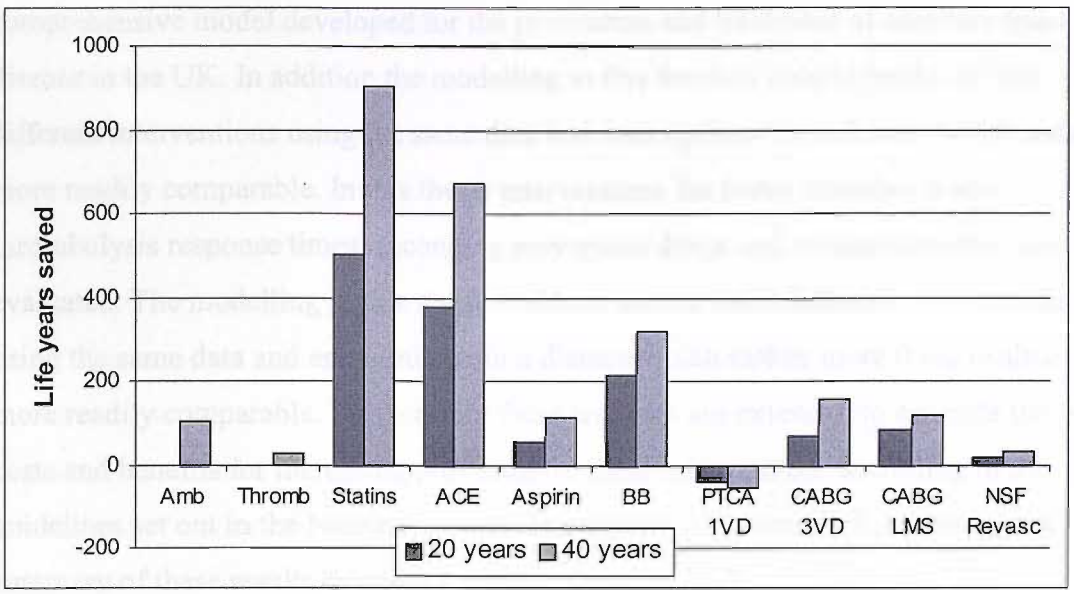

Figure 10.2.4 Average life years saved for a population of one million

According to estimates of the estimated 'willingness to pay' threshold (section 3.1.2) all the CHD interventions are cost effective except thrombolysis. Aspirin and beta blockers are very cost effective and have ICER of less than £1000 per QALY. To achieve the targets set in the NSF, statins and revascularisation are the most expensive to implement and would each cost an extra £3 million per million population per year. Aspirin and beta blocker targets are very cheap to implement and would only cost an extra £20 000 and £160 000 per million population per year. The most QALY gained would be from the statins and revascularisation interventions. There would be little QALY gained from the ambulance, thrombolysis or aspirin scenario.

Implementing each of the NSF scenarios for England over the next 20 years for these interventions would result in an average annual extra cost of £400 million and will result in a saving of 65,000 life years and 70,000 QALYs each year. Statins and revascularisation account for about 80% of the costs and 60% of the benefits (QALY).

10.3 Conclusions from the research

This dissertation has developed a variety of models to evaluate coronary heart disease interventions. This research advanced the knowledge in coronary heart disease modelling because the UK Coronary Heart Disease Policy model is the most

comprehensive model developed for the prevention and treatment of coronary heart disease in the UK. In addition the modelling in this thesis is able to model several different interventions using the same data and assumptions for a disease which makes more readily comparable. In this thesis interventions for faster ambulance and thrombolysis response times, secondary prevention drugs and revascularisation are evaluated. The modelling in this thesis is able to model these different interventions using the same data and assumptions for a disease which makes more these evaluations more readily comparable. Furthermore these analyses are extended to estimate the likely costs and benefits for increasing provision for these interventions according to the guidelines set out in the National Service Framework for coronary heart disease. A summary of these results have been shown in section 10.2.

In general the interventions have been shown to be good value for money according to a willingness to pay threshold of £30,000 per QALY gained. Aspirin and beta blockers are the most cost effective and have ICER of less than £1000 per QALY gained. Improving thrombolysis response times is the least cost effective with ICER of almost £30,000 per QALY gained. In order to achieve the targets from the National Service Framework, the increased spending (and consequent health benefits) would be greatest for statins and revascularisation. Implementing each of the NSF scenarios for England over the next 20 years for these interventions would result in an average annual extra cost of £400 million and will result in a saving of 65,000 life years and 70,000 QALYs each year.

This dissertation has contributed to existing knowledge on appropriate model selection for health care interventions. The primary contribution of this research is an examination of the theory of model selection using the case study approach. This approach was a useful method of investigating the current theory in a practical way, for example by building models using each of the techniques it is possible to gain insights into the comparative ease of development and results of the models. The insights gained from this research have been used to develop a framework for choosing between the models according to the complexity of the models and the health care intervention characteristics.

From a review of the health care modelling literature in Chapter 3, it was apparent that the two most commonly used modelling techniques are decision tree and Markov models. Generally decision tree models have been used to evaluate acute health care interventions and Markov models have been used to model chronic health care interventions. Models for resource-constrained interventions were also modelled without queuing using Markov models. A small number of studies used simulation models for complex and resource-constrained interventions.

According to the review of the modelling literature, the modeller should strive for simplicity and transparency although this should not be achieved by making restrictive and unrealistic assumptions of the disease condition or health care system. The choice of the preferred model will depend on the likely ease and speed of development, the complexity of the model in terms of the number of states, and the interconnectedness of the system. The modeller will need to judge whether interactions between individuals is a significant issue in the health care system and whether queuing for resources and resource constraints are relevant to the research question. The modeller will need to judge whether the preferred modelling techniques will be most acceptable to the users of the model. Finally the use of population-based models and the provision of health care outcomes for the likely cost, health benefits and cost effectiveness of the interventions was recommended.

A set of hypotheses concerning the modelling techniques were examined using the case study approach. Initially hypothetical simple models were constructed to examine the hypotheses and then they were further examined using more complex and realistic health care models for CHD. It was concluded that decision tree models are an appropriate technique for modelling the cost effectiveness of acute interventions. However when the intervention happens more than once in a patient's lifetime, decision trees underestimate the total costs and health benefits incurred compared to the other modelling techniques. For more accurate costs and benefits for the intervention, a Markov or simulation model should be used.

When modelled using the same data and assumptions, the Markov and simulation models give similar results which converge as the cycle time of the Markov model decreases. It was shown that the cohort and population-based approaches yield different

results, and the population-based approach gives a worse cost effectiveness ratio compared to the cohort-based approach. The population-based model was more complex to build than the cohort model. The appropriate choice of time horizon for the model is critical to the obtaining suitable results and conclusions.

Traditionally, discrete event simulation has been regarded as the technique of choice for modelling resource-constrained interventions. However, in the literature review and also through constructing models, it was concluded that the results were not significantly affected by modelling the resources without using queues and thus DES is not necessarily the most appropriate technique. These suggestions on model complexity refer to disease models. We have not considered the effects of variability in these systems or the interaction between individuals such as in infectious disease modelling. Several authors in literature suggested that these factors are likely to be more significant in organisational planning and complex problems of this nature lend themselves well to DES (Davies et al. 1985; Davies and Davies 1994; Fone et al. 2003).

Finally the choice of the preferred model was determined by the overall complexity of the model in terms of the number of states and transitions. For each of the models built in the case studies, the results from the models were similar and the preferred choice of model was based on the ease and speed of model development. This complexity was related to the number of states and transitions in the models and whether the model was a cohort or population model.

10.4 Limitations of the research

As with all modelling, the models built for coronary heart disease in this thesis have been based on a number of assumptions. These have been necessary to simplify the real world situation or where there is an absence of data. Often the data were difficult to obtain and it would have been preferable to have the individual datasets so that individuals' risk factors could be examined to determine the quantitative relationship between their risk factors. For example, the models would have been more credible if the relationships between age, gender, vessel disease, previous CHD and other patient

characteristics and risk factors were better understood. Furthermore although severity of vessel disease is recognised as being a major factor for prognosis, the underlying theory into the development of vessel disease and evidence for its prevalence for different health states was poor. This required a series of assumptions about vessel disease distribution in different states and the effect of vessel disease on prognosis. The secondary prevention model has assumed that the secondary prevention drugs act independently of each other and that individuals who fail to take the drugs because of side effects, or other reasons, are independently distributed for each drug. In practice, individuals who have problems with taking one drug are likely to have problems with another and therefore there will be some correlation. The models do not include stroke as a disease outcome and the benefits of secondary prevention will be underestimated. (Davies et al. 2003)

The models in this thesis have answered national policy questions for treatment interventions. In this case, local variations are not considered rather an aggregated average approach has been assumed. For example in chapter 7, the ambulance and thrombolysis models assume an average effect across England and Wales. Clearly there will be wide variation in the ability of individual ambulance services to achieve the NSF targets. The figures presented here assume that hospital units will achieve the targets based on the extra NHS spending allocated whereas it may be the case that it is not feasible for some urban ambulance services to meet this target. The recommendations on model selection from these analyses may be different for smaller scale models for example for the individual ambulance services where the variability of the system is a larger factor.

The recommendations in this dissertation for preferred model selection have been based partly on a review of the literature and partly by examining the theory using the case study approach. Only the most commonly used techniques for disease modelling were used, namely decision tree, Markov and discrete event simulation. Other models such as system dynamics and semi-Markov were used more rarely and were not evaluated in this thesis due to the time constraints of this thesis.

The model choice for the threshold of complexity for choosing between Markov and simulation models has been based upon the ease and speed of building the coronary heart disease models. This was a subjective judgement made according to a low number of different interventions. This judgement was made according to the expertise of the author and was influenced by the suitability, flexibility and usefulness of the modelling software used. The case studies in this thesis have used widely available and popular software such as EXCEL and TREEAGE. For example the judgement of ease of development was biased towards Markov modelling as the software, TREEAGE, had been built especially for health care modelling whereas the simulation software, SIMUL8 had not and had certain limitations for example the modelling of concurrent activities.

The more realistic models in this dissertation have been built for the treatment of coronary heart disease. Whilst these models have backed the conclusions from the simple model analyses in chapter 5, it may be these conclusions may have been biased or influenced by the nature of a disease such as coronary heart disease.

10.5 Further research

This thesis has made recommendations for the choice of models for short term, long term and resource constrained interventions for disease treatment. More research is needed on the choice of modelling techniques for evaluating other interventions, for example prevention interventions such as screening. The suggestions on model complexity refer to disease models and the interventions in this thesis have answered national policy questions. Further research is needed for the choice of modelling technique for organisational planning for health care. In this thesis, local variations are not considered rather an aggregated average approach is taken. Further research is needed on interventions for small scale operations such as individual hospitals or health clinics where the variability in the system is likely to be significant.

More research is needed to test the generalisability of the conclusions of this research for different health conditions. The suggestions on model complexity were a subjective

assessment based on a small number of models for coronary heart disease interventions. Furthermore these suggestions have been based upon the ease of development of building the models according to the author's expertise and his perception of the suitability, flexibility and usefulness of the modelling software used. These conclusions would be more objective if more research were completed by authors with varying backgrounds and expertise.

The acceptance of modelling technique has been identified as an important factor in the selection of the modelling technique. More research is needed to examine the perception of users on the modelling techniques of the advantages and disadvantages of these techniques. Finally this research has compared decision tree, Markov and simulation models. Research is needed for other modelling techniques such as system dynamics.

Appendix I Summary of shared work for the Coronary Heart Disease Simulation Project and agreement of work to be used in the PhD thesis (Davies. 2003)

Coronary Heart Disease Simulation Project				
Topic	**Who did the work**	**Who wrote what**	**Use in PhD**	**Actual use**
Model structure	Ruth, Paul, Keith all contributed to the structure. Keith did the coding with suggestions and advice from Ruth. Ruth sketched the diagrams with help from the group and Keith drew in Excel or Ruth in other software.	Ruth wrote the Final Report section.	Will need to describe in own words, making it clear that it is joint work. Diagrams should be acknowledged as being joint work and where relevant referenced (e.g. Final report).	Model structure described in my own words and referenced accordingly.
HCMS paper (Cooper et al. 2002)	Mainly Keith, Ruth, Paul	Keith wrote initial version. All contributed. Ruth largely rewrote the whole paper.	Can be referenced and quoted from but not cut and pasted.	Referenced
Data sources	Debbie, Paul and Marcus did most of the work.	Paul did final versions of working papers.	Can be referenced.	Referenced
Parameter	Keith did much of this work –	Keith wrote most of working	Can use text from earlier version of	Parameter derivation

derivation	which was substantial – with advice from Ruth and Paul. Ruth and Keith did maths on Gompertz and redid derivations for time to death.	paper for Phase 1 and initial draft for Phase 2. Ruth rewrote much of it for Phase 2. Ruth wrote section in Final Report.	relevant working paper but will need to adapt to needs of PhD subject (i.e. will need to be shortened!). Gompertz and its implementation can be referenced from HCMS paper.	described in thesis from original text written by Keith. Gompertz referenced from Final report.
Screens	Keith designed them and edited them after feedback from Ruth and others. Ruth and Keith discussed batch runs and Keith implemented them.	Instructions handbook written by Keith. Criticism and suggested edits by Ruth.	Can be used but unlikely to be relevant.	Not used
Variance reduction	Ruth and Keith discussed these based on Ruth's earlier work. Keith implemented it in code.	Ruth wrote section in Final Report.	Can be referenced in Final Report if needed.	Not used
Sensitivity analysis	Keith did univariate analyses. Ruth and Marcus did multivariate with help from Keith and Paul.	Ruth and Marcus wrote section in Final Report.	Could use univariate analysis but if discussing multivariate analysis would need almost to start again as there is a lot of interesting work to do here and we barely scratched the surface. Would need to acknowledge	Not used

			Marcus's contribution	
Ambulance and thrombolysis	Keith worked on logic and decided how to implement in program with help from group. Keith produced results.	Debbie wrote paper with help from everyone. Keith wrote appendices – with advice from Ruth and James.	Can use description of calculations. Can not cut and paste from BMJ paper but can use appendices.	Description of calculations used from appendices written by Keith.
Validation	Mainly Keith.	Final report chapter – written by Keith, edited by Ruth.	Could use.	Validation used
Costs	Mainly James. Both Keith and Marcus spent some time on deriving and listing costs. Keith implemented structure in program.	James wrote working paper with help from Marcus, Ruth and Keith.	Could reference Cost Working paper.	Final report referenced
QALYs	Keith reviewed literature and made initial suggestions for implementation. Group made further suggestions Ruth worked out how to implement them. Keith implemented them for some scenarios.	Mainly Ruth. Keith wrote short paper about literature.	Could build on this. Would have to acknowledge method currently used as being developed by group and would have to write own text.	New method used for QALY. Original review written by Keith used.
Results	Keith designed spreadsheets for	Keith drafted material and Ruth	Would need to write in the context	Results produced from

	the analysis. Keith produced results after discussion with group.	rewrote material to go in Final Report.	of PhD theme.	models built for PhD.
Linkage	Keith in discussion with Ruth designed linked structure. Keith implemented code and made program work.	Ruth wrote section in Final Report.	Scope for PhD to develop this.	Not used
Cloning	Mainly Colin	Colin	Might need to relook at cloning issues if discussing linkage.	Not used
Discussion		Paul and Ruth wrote section in Final Report – mainly Paul.		Not used

Appendix II Mid-1999 population estimates for England and Wales (Office of National Statistics, 1999)

	MEN		WOMEN	
	England	**Wales**	**England**	**Wales**
0-4	1557400	87800	1480700	83500
5-9	1671400	97400	1590100	93100
10-14	1640600	101500	1556400	96300
15-19	1564700	96700	1478300	93100
20-24	1496600	85900	1425500	77300
25-29	1843000	97900	1742600	90700
30-34	2074500	107800	1973800	103900
35-39	2021700	107500	1935800	106100
40-44	1698500	95700	1673000	95800
45-49	1589600	95300	1585200	95800
50-54	1678900	101200	1685600	102000
55-59	1306600	82300	1323400	83900
60-64	1168800	74300	1209400	76900
65-69	1029300	66700	1126300	73300
70-74	878900	58500	1063300	70900
75-79	710000	46400	1017000	66700
80-84	349700	22900	630300	41800
85+	262600	15900	713200	44200
All Ages	**24542900**	**1441700**	**25210000**	**1495300**

Appendix III Deaths by cause, sex and age, 1998, United Kingdom (Office of National Statistics, 1999)

		All ages	Under 35	35-44	45-54	55-64	65-74	75 & over
All causes	Men	298,767	10,860	6,822	15,720	33,518	75,390	156,457
	Women	327,384	5,547	4,283	10,381	20,730	53,927	232,516
	Total	626,151	16,407	11,105	26,101	54,248	129,317	388,973
Coronary heart	Men	74,542	148	1,004	3,971	9,795	21,622	38,002
disease	Women	62,611	40	180	837	3,080	11,167	47,307
(410-414)	Total	137,153	188	1,184	4,808	12,875	32,789	85,309

Appendix IV MI and sudden death with relation to age (Cooper et al. 2003)

The risk of death and MI was assumed to increase with age. Furthermore, the relative risk of death increases exponentially with age.

The annual probability of death or MI can be represented by the Gompertz distribution in which $f(t) = \exp(at + b)$, where $f(t)$ is the annual probability of death or MI of a person of age t and a and b are constants.

Calculating the age gradient

Suppose that a person of age 50 years has an event risk of 0.0718 and that a person of age 70 years is 1.562 times more likely to have event than one of age 50 years.

$f(t) = 0.0718$ at age 50 and
$f(70) = 1.562\ f(50)$.

These equations can be solved, $f(t) = at + b$

For age 50, $f(50) = \exp(50a + b) = 0.0718$ (1)

For ages 50 and 70, $f(70) = 1.562\ f(50)$

so $\exp(70a + b) = 1.562 \exp(50a + b)$

$\exp(70a - 50a) = 1.562$

$a = 0.0223$ (2)

Now if (2) is substituted into (1), $\exp(50a + b) = 0.0718$

$\exp(1.115 + b) = 0.0718$

$b = -3.749$

Thus the Gompertz distribution for post MI re-infarction is $e^{0.022t - 3.749}$.

Appendix V Mathematical model of the risk of MI or death (Cooper et al. 2003)

'We are assuming that the probability of death or MI from CHD causes increases exponentially with age, $g(t) = exp(a(d+t)+b)$, d is age, t is time and a and b are constants. g(t) is the hazard function. In order to find the probability of death at any age, we need to know a and b. The relative risk of k different effects e.g. vessel disease, aspirin are denoted $r_1, r_2, \ldots r_k$. The overall probability of an MI or death at age d (i.e. the hazard function) is $r_1 r_2 \ldots r_k \exp(a(d+t)+b)$. This is:

$g(t) = exp(a(d+t) + b + ln(r_1) + ln(r_2) + \ldots ln(r_k))$

Let $ln(r_1) + ln(r_2) + \ldots ln(r_k)) = R$

These relative risk are not all applied immediately but may be added or removed as time goes by, changing the projected date of MI or death. We need thus to determine how it is to be sampled and re-sampled.

The survivorship function S(t) = 1- F(t), where F(t) is the cumulative distribution function.

$$S(t) = e^{-\int_0^t g(x)dx}$$

$$= e^{-\int_0^t \exp(a(x+d)+b+R)dx}$$

$$= exp(-(1/a)[exp(a(t+d)+b+R) - exp(ad+b+R)]$$

$$= exp((-exp(ad+b+R)/a)(exp(at)-1))$$

Take a random number $u = 1-F(t) = S(t)$

$$ln(u) = (-exp(ad+b+R)/a)(exp(at)-1)$$

$$exp(at) = 1 - a\, ln(u)/exp(ad+b+R)$$

$t = (1/a)\ ln(1-a\ ln(u)/exp(ad+b+R))$

If you were to resample using a new random number, then you would use the same formula but you would have to recaculate with the new R' and the new d'.

The current projected time to death has to be extracted and replaced. However, in order for the patient to have a consistent risk, we want to re-use the same random number. It has to be scaled to take account of the fact that random number values less that F(T) have been 'used up'.

Suppose that u was the last adjusted random number, the new number
$u' = u /(1-F(T))$

T is the current time and F(T) is the distribution value based on the previous risk and age.

$u' = u / (exp((-exp(ad+b+R)/a)(exp(aT)-1))$

This means that each time you change risk, you need to retain information about age and previous risk and the previous random number - 3 attributes. This enables you to calculate the new random number. You then calculate the new time to event using the new risk and age.'

Appendix VI Costs used in the UK CHD policy model (Raftery et al. 2003)

The costs used in the UK CHD Policy model are shown in this appendix as described in Raftery et al. (2003).

'General Practice

All patients in the UK are under the care of a General Practitioner (GP) and CHD patients are likely to be more demanding than most. We have little information about attendance but assumed that: an initial visit by a patient with CHD is likely to comprise both a GP and a nurse consultation (either concurrent or subsequent). Thereafter patients are assumed to see their GP at six monthly intervals and have repeat prescriptions monthly (the recommended period between the issuing of prescriptions).

The cost of drugs is based on Defined Daily Dosages (DDDs). Although BNF/MIMs are often used to calculate drug costs, this requires assumptions on drug dosages. DDDs by contrast use standardised international assumptions on dosage. Data on Net Ingredient Cost (NIC) cost per DDD was obtained from the Prescription Pricing Authority (PPA). The cost of dispensing the drugs is added in.

Outpatient visits

Outpatient visits are related to particular events in the simulation. Most patients are referred from their GP to a chest pain clinic or cardiac outpatient clinic. We assume that the cost will include an exercise ECG and pathology tests. This will be followed up by, on average, two further outpatient appointments. We assume that patients will have a similar set of outpatient appointments after an admission for: an angioplasty, unstable angina, MI or after a patient, formerly without angina, but with a history of MI is referred with a prospective diagnosis of stable angina.

Those having a bypass graft are assumed to attend the cardiothoracic outpatients before the procedure and to have follow-up appointments twice afterwards.

Angiograms and revascularisation

Elective patients receive an angiogram before having revascularisation. Those having angiograms in hospital would normally have an angioplasty at the same time as an angiogram if it were needed.

Inpatient episodes

The inpatient HRG costs are for finished consultant episodes. The assumptions we made are discussed in detail in the working paper (T9). In summary, the cost of the use of a critical care unit or A&E and the cost of any angiograms and/or revascularisation done in hospital following an unstable angina attack or MI are added to the cost or the inpatient stay. The cost of thrombolysis is also added to the cost of an MI, where relevant. '

Table A6.1 Unit costs to be used in CHD treatment model, England 2000/1 (Raftery et al. 2003)

Type of case	*HRG/reference/use*	*Unit cost (£)*	*Comment*
Primary care costs			
GP first consultation (one off)	Netten & Curtis	£30	Assume cost of GP and nurse
Follow-up consultation (continuous)	Netten & Curtis	£20.	Assume all CHD patients have six monthly visit. Includes CHD clinics and providing repeat prescriptions
Drug regimens – GP (all continuous)		*£/pat/year*	
Calcium channel blockers	DDDs	130	Proportion of all patients.
Beta-blockers	DDDs	52	Proportion of all patients for symptoms, of post-MI patients for secondary prevention.
ACE inhibitors	DDDs	95	Proportion of all patients.
Antiplatelet (aspirin)	DDDs	20	Proportion of all patients.
Nitrates	DDDs	78	Proportion of patients
Statins	DDDs	237	Proportion of all patients.
Dispensing cost	All GP prescriptions	24	£2/dispensation, monthly.
Outpatient visits (one off or limited number)			
Assessment visits or chest pain clinic	E09op plus E13op	84	First outpatient visit for assessment, Includes exercise ECG and pathology test.
Follow up Attendance	E16op	54	Use for all follow-ups OP attendances, assume 2 per first visit.
Cardiothoracic surgery first	OPF170	131	Assume prior to CABG

outpatient			
Cardiothoracic surgery follow up attendance	OPFU170	95	Assume two follow up attendances for all CABGs
Day and inpatient episodes- all one off			
Angiogram	E14 day case	657	This figure used for all angiograms (in practice 63% are day case).
CABG	E04 elective	5,483	Add cardiothoracic outpatients above.
	E04 non-elective	5,558	For those with unstable angina or MI.
PTCA	E15 elective	2,428	As for CABG. Includes costs of stents and drugs.
	E15 non-elective	2,689	For those with unstable angina or MI.
AMI	E12 nelip	909	Add one day CCU/AE admission ward for all, plus thrombolysis for proportion and angiogram/ PTCA/CABG (?) where needed
Unstable Angina	E33 nelip	741	Add CCU and angiogram/ PTCA as for AMI. No thrombolysis cost to be included.
CCU/A&E	CC7	298	Assuming all MI and UA admissions via this route. £399 (less thrombolysis cost of £202/2)
Thrombolysis, Streptokinase, alteplase		202	83% streptokinase at £85.45 per dose and 17% alteplase at £770 per dose, as per UKHAS study.
Other services			
Ambulance	Scenario		Ambulance costs have been based on increase in annual funding 1997-2003 of £18m pa
Cardiac Rehabilitation	HTA report	£486 /course	Assume offered to all CHD patients post hospital. Different take up rates for AMI for UA, CABG and PTCA. See working paper T10 for further details.

Appendix VII Calculation of proportion of patients with left main stem disease (Cooper et al. 2003)

We have assumed that the proportion of patients with left main stem is proportional to the number of vessels they have diseased. In a population of patients with vessel disease, if x_1 is the number of patients with 1 VD, x_2 is the number of patients with 2 VD, x_3 is the number of patients with 3 VD where each of these parameters include patients with LMS then the total numbers of patients is $x_1 + x_2 + x_3$.

For one vessel disease patients, a proportion p will have LMS, for two vessel disease patients, a proportion 2p will have LMS, and for three vessel disease, 3p will have LMS.

Thus if the total number of LMS patients within the population is Y then,

$$Y = p(x_1) + 2p(x_2) + 3p(x_3)$$

and so by rearrangement, the proportion of people with 1 VD that have LMS is,

$$p = \frac{Y}{x_1 + 2x_2 + 3x_3}.$$

If we use the Yusuf et al [9] study:

10.2	1 VD
32.4	2 VD
50.6	3 VD
6.6	LMS

$p = 0.029$

Thus we can calculate the proportion of the population who have LMS for the groups with stable angina and post MI.

Appendix VIII Filtering algorithm (Cooper et al. 2003)

'*We have assumed that patients with more severe underlying vessel disease will be referred for angiogram in a greater proportion than those with less severe disease who are more likely to receive medical treatment. This takes account of the association of disease severity with exercise test abnormalities and past history both of which will influence referral to angiography. In general, there is a large variation in the treatment of patients according to age, so we attempted to build this variation into the referral pathways. We have not at this stage modelled referral by gender though it is recognised that the yield of prognostic vessel disease is less in women.*

In the simulation, referral is a two stage process, with patients first going from the initial diagnosis (initial GP state) to cardiac clinic or rapid chest pain clinic and from there to angiogram. The two stage process is influenced both by age and whether patients have significant vessel disease in one or more vessels. Patients with 0 vessel disease are sifted out at both stages of the process but, for simplicity, the age weighting takes place at the second stage only. Tables A8.1 and A8.2 show the individual and combined effects of the first two stages. Prevalent patient, not referred to an outpatient clinic in the first 3 years, were assumed to be referred at a rate of 15% a year.

In devising the "most recent scenario" we assumed that the advent of rapid chest pain clinics and the increase in revascularisation would increase the referral of all patients to angiogram but, in particular, more of those with no vessel disease and more elderly.'

Table A8.1 Proportion of patients referred to cardiac and chest pain clinics and from there to angiogram. Note: all the age difference is taken account of in the second part of the process.

Transition from diagnosis to OP clinic	Base Case			"Most Recent scenario"		
	0 VD	Other vessel disease	All patients	0 VD	Other vessel disease	All patients
All ages	35%	85%	60%	50%	100%	75%
Transition from OP Clinic to angiogram	Base Case			"Most Recent scenario"		
	0 VD	Other vessel disease		0 VD	Other vessel disease	
Age 35 - 45 years	58%	96%		58%	96%	
Age 45 – 54 years	58%	96%		58%	96%	
Age 55 – 64 years	58%	96%		58%	96%	
Age 65 – 74 years	34%	57%		44%	68%	
Age 75 – 84 years	7%	12%		14%	23%	

Table A8.2 Proportion of patients referred from diagnosis of CHD to angiogram, includes both transitions shown in Table A8.1

	Base Case			"Most Recent scenario"		
	0 VD	Other vessel disease	All patients	0 VD	Other vessel disease	All patients
Age 35 - 45 years	20%	82%	51.0%	29%	96%	62.5%
Age 45 – 54 years	20%	82%	51.0%	29%	96%	62.5%
Age 55 – 64 years	20%	82%	51.0%	29%	96%	62.5%
Age 65 – 74 years	12%	48%	26.5%	22%	68%	45.1%
Age 75 – 84 years	2%	10%	5.3%	7%	23%	15.0%

Appendix IX Derivation of probability of myocardial infarction (Cooper et al. 2003)

As mentioned in section 6.4.5, the post MI rate for re-infarction is calculated using the EMMACE dataset. This assumes different rates for first year and subsequent years after infarction. The myocardial infarction rate for stable angina patients is also calculated from the EMMACE data using an adjustment for non MI patients from British Regional Heart Study (Lampe et al. 2000).

The EMMACE dataset (n = 2196) provides post MI mortality rates over 5 years. The cumulative post discharge all cause mortality rates for males and females are similar. Patients in EMMACE were prescribed secondary prevention drugs on discharge; 42% received beta blockers, 38% ace-inhibitors, 86% aspirin and 8% statins. The data were adjusted to estimate CHD mortality, by age group and year. Further adjustments were made using UKHAS data (Table 6.4.4) to estimate the myocardial infarction rate.

The British Regional Heart Study (BRHS) is a study of the natural history of prevalent ischaemic heart disease in middle aged men. It followed a group of 7735 men and recorded the association of the disease groups with coronary heart disease event outcomes over a ten year follow up. It did not provide data related to the time since patients had had a previous MI. Although the BRHS data only related to men, there is no data to suggest that men and women would not have similar survival probabilities and the association between groups of risk of MI was assumed to be similar for men and women.

The risk of myocardial infarction was derived in the following steps (see sections A9.1-9.6):

1) EMMACE data were split into first year and subsequent years data
2) EMMACE data were adjusted to exclude non cardiac death using ONS data (1999)
3) The CHD death rate was adjusted to estimate the cardiac mortality associated with natural history (ie no secondary prevention drugs)

4) A conditional probability was used to estimate the MI infarction rate using UKHAS sudden death data (Norris 1998).

5) The resulting survival data are fit to two probability distributions, one for the probability of a re-infarction in the first year and one for subsequent years

6) The probability of MI for angina only patients was derived from the BRHS data

A9.1 EMMACE data split into first year and subsequent years data

The EMMACE dataset is shown in Table A9.1. It shows the cumulative probability of all cause mortality in the five years following an MI for 10 year age bands, relating to the age of patients when they had the MI. Males and females were grouped together as they had similar survival probabilities.

Table A9.1 Cumulative all cause mortality data from EMMACE for males and females following MI

Years	1	2	3	4	5
35 - 44	0.018	0.036	0.036	0.055	0.055
45 – 54	0.033	0.044	0.055	0.094	0.099
55 – 64	0.085	0.106	0.127	0.160	0.181
65 – 74	0.117	0.184	0.226	0.274	0.323
75 – 84	0.264	0.382	0.463	0.534	0.612

Clearly, for each of the age bands, the probability of death was much higher for the first year than for any of the subsequent years. In the years following the first year, there are small numbers of deaths and in some cases no deaths. In addition the proportion of deaths in any one year (after the first) is similar. Thus it was assumed that the long term probability of death in any year after the first is not related to the time since the MI and aggregated the data for years 2 to 5. For each age group, the smoothed annual long term probability of mortality in years 2 to 5, was thus estimated to be

$$1-\left(\frac{1-m_5}{1-m_1}\right)^{0.25}$$

where m_i is the cumulative probability of mortality at the end of year i. This is shown in Table A9.2.

Table A9.2 All cause mortality data from EMMACE, smoothed so that probabilities of death are equal in years 2 to 5 following MI

Years	1	2	3	4	5
35 - 44	0.018	0.009	0.009	0.009	0.009
45 – 54	0.033	0.018	0.018	0.018	0.018
55 – 64	0.085	0.028	0.028	0.028	0.028
65 – 74	0.117	0.064	0.064	0.064	0.064
75 – 84	0.264	0.148	0.148	0.148	0.148

A9.2 EMMACE data adjusted to exclude non cardiac death using ONS data (1999)

The ONS non CHD death rates were subtracted from the EMMACE data in Table A9.2 by age and sex. The non CHD death rates for the age at the mid point of each age band were subtracted for the year 1 EMMACE death rates in Table A9.2. Similarly the non CHD death rates for the age at the mid point plus two years were subtracted from the death rates for years 2 to 5. The non CHD death rates are shown in Table A9.3. This gave an estimate of the first year and subsequent year CHD mortality probabilities (Table A9.4).

Table A9.3 Non CHD death rates from ONS

Years	1	2 to 5
35 - 44	0.001	0.001
45 – 54	0.003	0.003
55 – 64	0.007	0.009
65 – 74	0.020	0.025
75 – 84	0.053	0.065

Table A9.4 CHD death rates from EMMACE with ONS non CHD deaths excluded

Years	1	2 to 5
35 - 44	0.017	0.008
45 – 54	0.030	0.014
55 – 64	0.078	0.019
65 – 74	0.097	0.041
75 – 84	0.211	0.088

A9.3 The CHD death rate adjusted to estimate natural history (ie in the absence of secondary prevention drugs)

In the EMMACE study, many of the CHD patients used secondary prevention medication to reduce their risk of further coronary events. In order to study the effects of increased secondary prevention medication it is helpful to derive the natural history of patients who do not take any secondary prevention drugs. The CHD rate was adjusted to take account of the level of secondary prevention drug usage in the EMMACE dataset.

For each secondary prevention drug the overall relative risk for the population is

$$1-p(1-r)$$

where p is the proportion of people on that drug and r is the relative risk for a person on that drug. The death rates are adjusted to that of the natural history by dividing by the overall relative risk shown here.

The drugs work in different ways in order to improve a patient's prognosis and thus independence between the benefits of the individual drugs is assumed. The overall effect of the drugs on the population is the product of the relative risk for the individual drugs on the population. In this case, patients in EMMACE were prescribed secondary prevention drugs on discharge; 42% received beta blockers, 38% ace-inhibitors, 86% aspirin and 8% statins. Table A9.5 shows the natural history calculations.

Table A9.5 Natural history (NH) calculations for secondary prevention drugs in the EMMACE dataset

	Aspirin	ACE Inhibitor	Beta blockers	Statins
Prevalence, p	0.86	0.38	0.42	0.08
Relative risk, r	0.75	0.8	0.77	0.73
Overall risk, 1-p(1-r)	0.79	0.92	0.9	0.98
Adjustment for NH	1.27	1.08	1.11	1.02

The adjustment for secondary prevention is the product of the bottom row of Table A9.5, ie 1.56. The EMMACE CHD mortality rates in Table A9.4 were multiplied by this value (Table A9.6).

Table A9.6 Estimated natural history CHD mortality rates from EMMACE

Years	1	2 to 5
35 - 44	0.027	0.013
45 – 54	0.048	0.022
55 – 64	0.121	0.030
65 – 74	0.151	0.063
75 – 84	0.330	0.138

A9.4 Conditional probability used to estimate MI infarction rate

The EMMACE dataset does not give any information on the number of non fatal MI suffered by patients before they died. However for the purposes of the ambulance and thrombolysis model in chapter sever, it is desirable to generate the rate of myocardial infarctions whilst maintaining the correct overall CHD mortality. The MI infarction risk was estimated using a conditional probability.

UKHAS gives values for the probability of dying from a MI for all patients who had an out of hospital MI, ie (P(Death | MI). This information was used to estimate the infarction rate (P(MI)) from the cardiac mortality rate (P(Death)) as shown.

$$P(\text{Death}) = P(\text{MI}) * P(\text{Death} \mid \text{MI})$$

$$\text{By rearranging, } P(MI) = \frac{P(Death)}{P(Death|MI)}$$

Table A9.7 Probability of dying from an out of hospital MI (UKHAS)

Age band	P(Death | MI)
35 - 44	0.22
45 – 54	0.28
55 – 64	0.4
65 – 74	0.54
75 – 84	0.65

The resulting probability of MI is shown in Table A9.8.

Table A9.8 Probability of MI from EMMACE

Years	1	2 to 5
35 - 44	0.121	0.057
45 – 54	0.170	0.079
55 – 64	0.303	0.074
65 – 74	0.280	0.117
75 – 84	0.507	0.212

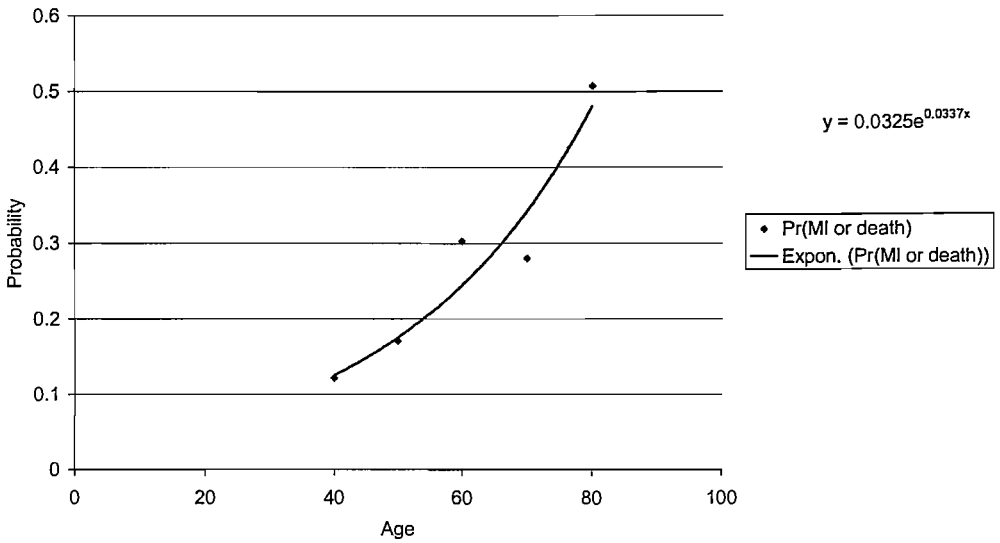

Figure A9.1 Probability of MI in first year after MI as derived from EMMACE

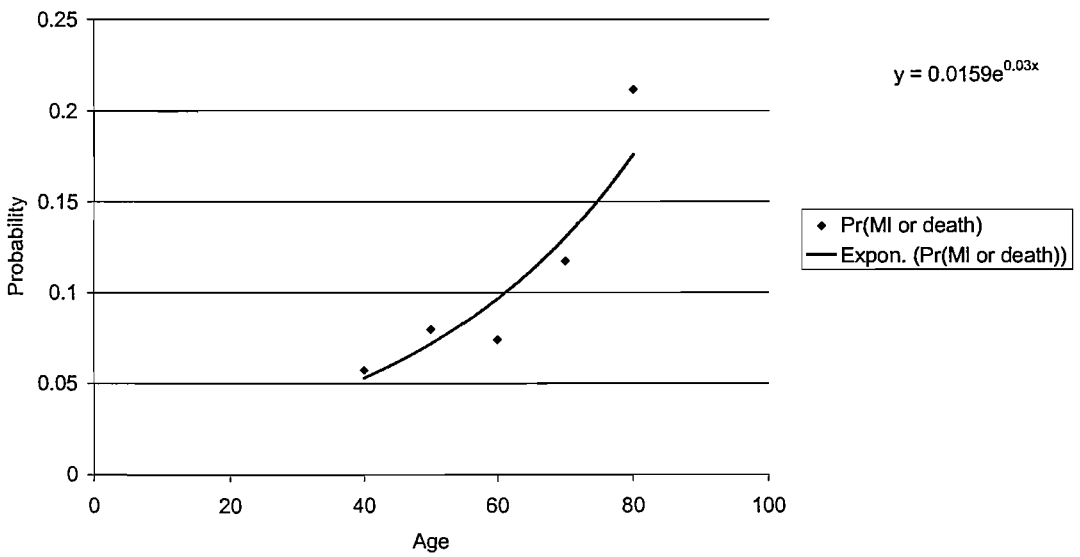

Figure A9.2 Probability of MI in the subsequent years after MI as derived from EMMACE

A9.5 The resulting survival data were fit to two probability distributions, one for the probability of a re-infarction in the first year and one for subsequent years

The probability of MI as shown in Table A9.8 were fitted to exponential distributions across the age groups for the first year and the subsequent years. The Excel exponential distribution fitting function was used and this is shown in Figure A9.1 and A9.2. Thus annual probability rates for MI for patients with history of MI have been derived as shown in Table 6.4.5.

A9.6 The probability of MI for angina only patients was derived from the BRHS data

As mentioned above, The British Regional Heart Study is a study of the natural history of prevalent ischaemic heart disease in middle aged men. The 10 year follow up data for patients with prevalent angina but no previous myocardial infarctions was used.

'The BRHS gives major coronary events related to patients years survived per year. The risk of an event in those with angina was 24.2% in the first 10 years (1980 to 1990) for males, who started with an average age of 53.8 years. It was assumed that the average age during the 10 years was 58 years and that females would have similar rates to males.

The BRHS Newsletter at http://www.ucl.ac.uk/primcare-popsci/brhs/Newsletter/News40.htm indicates that 32% of men who had events before 1985 and 53% who had events between 1985 and 1989 were taking aspirin. The event rate was modified to give the natural history event rate as if patients were taking no drugs. It was assumed that beta blockers had no effect on event rates for patients who had not had an MI, and the multiplying factor was 1.087 (see section A9.3 for more details on natural history conversion). This gave the age 58 event rate to be 26.3% within 10 years.

The patient's risk of death or infarction increases with age. The BARI study (1996) gives mortality rates for a CABG / PTCA trial for younger patients (mean 55.7 yrs) relative to that of older patients (mean 70.6 years). The relative risk for cardiac

mortality was 1.98 for the older versus the younger. ' (Cooper et al. 2003)

However this relative risk for older patients may be partly explained by the fact that there is an age gradient for sudden death in or out of hospital for patients who have an MI. For sudden death in or out of hospital, older patients (mean age 70.6 years) are 1.57 times more likely to die from an MI than the younger patients (mean age 55.7 years). Independence was assumed between the relative risk of infarction and the relative risk of sudden death in or out of hospital for older versus younger patients. The relative risk for older patients compared to younger patients was 1.98/1.57 = 1.26.

The annual probability of death or MI was represented by the Gompertz distribution in which $f(t) = \exp(at + b)$, where $f(t)$ is the annual probability of death or MI of a person of age t and a and b are constants. Using the point estimate for the probability of MI at age 58 and the age gradient between two ages the annual probability of MI for angina only patients was derived to be $0.0107\exp^{0.0155x}$ (see Appendix IV for age gradient calculations).

Glossary of medical terms

ACE inhibitor (Angiotensin-converting enzyme inhibitor) A drug that blocks one of the body's enzymes, causing the blood vessels to relax.

Amlodipine calcium antagonist drug

Angina pectoris Chest pain caused by a lack of blood to the heart due to narrowed arteries

Angiogram Xray examination of the heart and coronary arteries

Aspirin Drug that thins the blood and helps reduce clotting

Atherosclerosis The build up of fatty deposits in the arteries

Beta blocker Drug that slows the heart rate by 'blocking' adrenaline

Calcium antagonist Drugs that relax arteries by reducing calcium in the artery walls

Cardiac arrest A heart attack when the heart stops beating

Clopidogrel Anti-platelet drug similar to aspirin.

Coronary Artery Bypass Graft (CABG) Surgical procedure to bypass narrowed arteries

Defibrillator Equipment to give electric shocks to correct abnormal heart beat or restart the heart after cardiac arrest

Electrocardiogram (ECG) Recording of the electrical activity of the heart

Echocardiogram (ECHO) Pictures of the heart muscle generated by ultrasound waves

Ejection fraction The portion of blood that is pumped out of a filled ventricle as a result of a heartbeat

Heart failure (or congestive heart failure) Damage to the heart muscle such that the heart cannot pump blood as strongly as the body demands it

Ischaemic heart disease Inadequate blood supply usually caused by narrowed arteries

Myocardial infarction (MI) Blockages in the heart arteries (heart attack)

Positron Emission Tomography (PET) Radionuclide test to show pictures of the heart

Percutaneous Transluminal Coronary Angioplasty (PTCA) Procedure to reduce narrowing in arteries

Revascularisation Repair of the coronary arteries using CABG or PTCA procedures

Reperfusion The restoration of blood flow to an organ or tissue

Single photon emission computed tomography (SPECT) Radionuclide test to show pictures of the heart

Statin Cholesterol reducing drug, eg simvastatin

Stenosis Narrowing

Stent Metal cage inserted into the artery during PTCA

Thrombolysis Administration of drug clotting drugs such as tPA or SK

Unstable angina More serious form of angina where chest pain occurs erratically

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