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Health economics

in the Irish healthcare setting

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A thesis submitted for the degree of Doctor in Philosophy

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SUMMARY

Economic analysis plays a key role in deciding which healthcare interventions should be made available in collectively funded healthcare systems. The aim of this thesis is to examine the application of health economics in the Irish healthcare setting.

The contribution made by this thesis include the development of:

- A cost-of-illness analysis to estimate cardiovascular disease costs from the Irish health service perspective;
- A cost-effectiveness model for the eradication of Helicobacter pylori using proton pump inhibitor (PPI) triple therapy in the Irish community setting;
- A cost-effectiveness and cost-utility model of statin therapy for the primary prevention of coronary heart disease (CHD) in Ireland; and,
- Extensive sensitivity analysis to address uncertainty in the primary prevention statin therapy model.

In chapter 2, a cost-of-illness analysis was developed to estimate disease-specific treatment costs from the perspective of the Irish health service. The cost of treating cardiovascular disease was estimated at €648m in 2005. This consisted of €426m for hospital costs, estimated from the Casemix programme, and €222m for medications prescribed under the CD schemes. More than 83,000 cases and 489,000 bed days were required by Irish public hospitals to treat diseases and disorders of the circulatory system. The analysis developed in this chapter can be updated annually and applied to other disease categories across the Irish healthcare setting.

In chapter 3, the cost-effectiveness of nine PPI triple therapy regimens for Helicobacter pylori eradication in the community setting in Ireland in 2003 was determined. A cost-effectiveness model was used as outcomes were measured in natural units common to the regimens examined, but were achieved to differing degrees. Decision tree modelling was used as a graphical illustration of all possible alternative regimens was required over a single time period. The overall effectiveness of therapy, in terms of no further maintenance anti-secretary therapy during the one-year follow-up period was 40%-46% depending on the PPI regimen prescribed. Rabeprazole (Pariet®) was the most cost-effective regimen at a cost of €502 per asymptomatic patient. This thesis recommended only prescribing the

most cost-effective preparation under the CD schemes following the identification of €8.7m of potential savings for PPI therapy under the General Medical Services (GMS) scheme alone.

In chapter 4, a cost-effectiveness and cost-utility analysis of statin therapy for the primary prevention of CHD in Ireland in 2005 was undertaken. Markov modelling, which facilitated the representation of the natural history of the disease in terms of a succession of states, each of which was associated with certain costs and outcomes was used. Primary prevention statin therapy increased survival rates by 6%. Incremental cost-effectiveness ratios (ICERs) for the statins prescribed under the GMS and Drugs Payments (DP) schemes compared favourably with recent economic evaluations of other public health interventions in Ireland, although, the cost-effectiveness of individual statins varied greatly. Atorvastatin (Lipitor®), with an ICER of €14,165 per life year gained (LYG), was found to be the most cost-effective statin for Irish males with an average CHD risk of 1.5% per annum. Atorvastatin also had the most favourable cost-utility results. The generic statin preparations were not the most cost-effective preparations.

In chapter 5, sensitivity analysis was used to address uncertainty on the primary prevention statin therapy model by examining the effects of changes in the key model parameters. Simple, scenario and probabilistic sensitivity analysis were conducted. Statin therapy was deemed cost-effective 97% of the time at an ICER threshold of €45,000/LYG, and 90% of the time at the current guideline Irish ICER threshold of €45,000/QALY. A 1% decrease in the cost of statin therapy decreased the ICER by 0.79%. A similar decrease in statin effectiveness increased the ICER by 5%. The probabilistic sensitivity analysis produced an ICER of €14,499/LYG for atorvastatin under the GMS scheme.

In chapter 6, key findings, recommendations and future research arising from the analysis undertaken in this thesis were presented. Recommendations were made regarding the development of data sources and health economic capacity in Ireland. Calls were made to apply the types of economic evaluations developed in this thesis to other disease categories and therapeutic areas. A number of recommendations promoting cost-effective prescribing under the CD schemes were also made. Finally, areas for future research highlighted by this thesis were identified.

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LIST OF ABBREVIATIONS

A&E	Accident and Emergency
ACE	Angiotensin Converting Enzyme
AFCAPs/ TexCAPS	Airforce/Texas Coronary Artherosclerosis Prevention Study
AICD	Arthythmia Implantable Cardioverter Defibrillator
ALOS	Average Length of Stay
AMI	Acute Myocardial Infarction
ATC	Anatomical Therapeutic Classification
Bn	Billion
C&AG	Comptroller and Auditor General
CABG	Coronary Artery Bypass Graft
CARDs	Collaborative Atorvastatin Diabetes Study
CARE	Cholesterol and Recurrent Events Study
CBA	Cost Benefit Analysis
CCOHTA	Canadian Co-ordinating Office for Health Technology Assessment
CD	Community Drugs
CEA	Cost Effectiveness Analysis
CEO	Chief Executive Officer
CHD	Coronary Heart Disease
CI	Confidence Interval
CMA	Cost Minimisation Analysis
CSO	Central Statistics Office
CUA	Cost Utility Analysis
CVD	Cardiovascular Disease
DDD	Defined Daily Dose

DG	Day Case Group
DoF	Department of Finance
DoHC	Department of Health and Children
DP	Drug Payment scheme
DRG	Diagnosis Related Group
ERHA	Eastern Regional Health Authority
EU	European Union
EUnetHTA	European Network for Health Technology Assessment
GDP	Gross Domestic Product
GIST	Gastro-intestinal stromal tumour
GMS	General Medical Services
GMSPB	General Medical Services Payments Board
GP	General Practitioner
H.pylori	Helicobacter pylori
H_2RA	H_2 Receptor Antagonist
HB	Health Board
HIPE	Hospital In-Patient Enquiry
HIQA	Health Information and Quality Authority
HMG CoA	Hydroxy Methyl Glutaryl Coenzyme A
HPS	Heart Protection Study
HSE	Health Service Executive
HTA	Health Technology Assessment
ICD-10- AM	International Classification of Diseases 10 – Australian Modification
ICER	Incremental Cost Effectiveness Ratio
IPHA	Irish Pharmaceutical Healthcare Association

LDL	Low Density Lipoprotein
LIPID	Long Term Intervention with Pravastatin in Ischaemic Disease Study
LTI	Long Term Illness
LYG	Life-Year Gained
M	Million
mRCC	Metastatic Renal Cell Carcinoma
MDC	Major Diagnostic Category
MI	Myocardial Infarction
MIMs	Monthly Index of Medications
MRC/BHF/ HPS	Medical Research Council /British Heart Foundation/ Heart Protection Study
NCEP ATP 111	National Cholesterol Education Programme Adult Treatment Panel 111
NCPE	National Centre for Pharmacoeconomics (Ireland)
NHO	National Hospitals Office
NHS	National Health Service
NICE	National Institute for Health and Clinical Excellence
No	Number
NSAIDS	Non-Steroidal Anti Inflammatory Drugs
OECD	Organisation for Economic Co-operation and Development
PCCC	Primary, Community and Continuing Care
PCI	Percutaneous Coronary Intervention
PCRS	Primary Care Reimbursement Service
PHIS	Public Health Information System
PPI	Proton Pump Inhibitor
PROSPER	Prospective Study of Pravastatin in Elderly Individuals at Risk of Vascular Disease

PSA	Probabilistic Sensitivity Analysis
PTCA	Percutaneous Transluminal Coronary Angioplasty
QALY	Quality-Adjusted Life-Year
SD	Standard Deviation
4S	Scandanavian Simvastatin Survival Study
UK	United Kingdom
USA	Untied States of America
VAT	Value Added Tax
VFM	Value for Money
WHO	World Health Organisation
WOSCOPs	West of Scotland Coronary Prevention Study

Chapter 1

An introduction to health economics

in the Irish healthcare setting

Chapter 1

1.1 Introduction

Economic analysis plays a key role in deciding which healthcare interventions should be made available in collectively funded healthcare systems. The aim of this thesis is to examine the application of health economics in the Irish healthcare setting.

This chapter has 3 aims:

- First, to introduce the health economic concepts used in this thesis;
- Second, to provide an overview of the Irish healthcare setting and the main Irish data sources used in the economic evaluations undertaken in this thesis; and,
- Third, to examine the current application of health economics in the Irish healthcare setting.

1.2 Health economic concepts

Economics deals with scarcity and how best to allocate scarce resources to maximise welfare. It is the study of how society decides what gets produced, how, and for whom[1]. The main aim of economics is to define the most efficient use of our limited resources, recognising the costs associated with the choices made. Health economics applies the principles of economics to health[2]. Health economics treats healthcare as an economic commodity, whilst acknowledging the fact that there are significant differences between healthcare and other conventional economic commodities[3]. Over the last decade or so, there has been a pronounced change in how economic analysis has been used in healthcare policy with an increasing number of health systems now using economic analysis as a formal input into healthcare decision making[4].

The increased demand for health, coupled with finite resources available to supply healthcare, is driving the demand for health economic analysis[5]. This has lead to the increasing importance of health economics with an exponential growth in such studies[6]. Escalating costs have stimulated moves towards scarce healthcare resources being directed to the most cost-effective interventions[7] with economic analysis playing a key role in deciding which healthcare interventions should be made available in collectively funded health systems[8]. The health economic concepts used in this thesis are now discussed.

1.2.1 Economic evaluation

Economic evaluation has been widely used to inform decisions about the allocation of healthcare resources[9]. Economic evaluation can assist decision makers when choices have to be made. It involves drawing up a list of the consequences, versus the costs associated with each option. Each approach involves the systematic identification, measurement, and, where appropriate, valuation and comparison of all the relevant costs and consequences of the options under review.

There are a number of elements to a good economic evaluation. The Drummond *et al.* check-list suggests that a good economic evaluation should address the majority of the questions posed in Figure 1.1.

Figure 1.1 Economic evaluation check-list

1. Was a well-defined question posed in answerable form?
2. Was a comprehensive description of the competing alternatives given?
3. Was the effectiveness of the programmes or services established?
4. Were all the important and relevant costs /consequences for each alternative identified?
5. Were costs /consequences measured accurately in appropriate physical units?
6. Were costs /consequences valued credibly?
7. Were costs /consequences adjusted for differential timing?
8. Was an incremental analysis of costs /consequences of alternatives performed?
9. Was allowance made for uncertainty in the estimates of costs /consequences?
10. Did the presentation and discussion of the study results include all issues of concern to the users?

Source: Drummond *et al.* Methods for the economic evaluation of healthcare programmes[10].

Economic evaluation is used as a generic term for a range of techniques. The consideration of the alternatives, and the treatment of the costs and consequences define the healthcare evaluation. The distinguishing characteristics of healthcare evaluations are presented in Figure 1.2.

Figure 1.2 Distinguishing characteristics of healthcare evaluations

		Are both costs and consequences examined?		
		No		**Yes**
Is there a comparison of two or more alternatives?		Examines only consequences	Examines only costs	
	No	**1A Partial evaluation 1B** Outcome description	Cost description	**2 Partial evaluation** Cost-outcome description
	Yes	**3A Partial evaluation 3B** Efficacy or effectiveness evaluation	Cost analysis	**4 Full economic evaluation** Cost-effectiveness analysis Cost-utility analysis Cost-benefit analysis

Source: Drummond *et al.* Methods for the economic evaluation of healthcare programmes[10].

In cells 1 and 2, there is no comparison of alternatives. In cell 1A only the consequences of the strategy under review are examined. This is called an outcome description. Cell 1B is a cost description and does not involve any comparison of alternatives. Cost-of-illness, or burden-of-illness studies fall into this category. In chapter 2, a cost-of-illness study of cardiovascular disease from the Irish health service perspective in 2005 is undertaken.

Cell 2 is a partial evaluation which examines both the costs and consequences of the strategy, however, it does not compare alternative strategies. Cell 3A and 3B, are also only partial economic evaluations, as the costs and consequences of each alternative are not examined simultaneously.

Full economic evaluations can be used to answer questions regarding efficiency as they compare alternative strategies, and examine both costs and consequences, as illustrated in cell 4. There are three types of full economic evaluations, depending on how the consequences are identified and measured. Table 1.1 provides a description of each of these.

Table 1.1 Description of full economic evaluations

Type of study	Alternatives examined	Costs measurement	Identification of consequences	Consequences measurement
Cost-effectiveness analysis	Yes	Monetary units	Single effect of interest, common to both alternatives, but achieved to different degrees	Natural units (e.g. life-years gained, disability-days saved)
Cost-utility analysis	Yes	Monetary units	Single or multiple effects, not necessarily common to both alternatives	Healthy years (e.g. quality-adjusted life-years)
Cost-benefit analysis	Yes	Monetary units	Single or multiple effects, not necessarily common to both alternatives	Monetary units

Source: Drummond *et al.* Methods for the economic evaluation of healthcare programmes[10].

Cost-effectiveness analysis (CEA) measures consequences or outcomes in natural units, which are common to the various interventions. A CEA usually involves developing a model of the outcomes of alternative treatments, selecting published data on the probabilities of the outcomes to enter in the model, identifying the costs associated with each therapy, and, comparing the results with those of various benchmark therapies[11]. The therapy, which produces the greatest benefit to the individual relative to the costs incurred, is the preferable alternative.

A key advantage of CEA is that it can be performed on alternatives, which have a common effect. In chapter 3, a CEA of proton pump inhibitor (PPI) triple therapy regimens for Helicobacter pylori (H. pylori) eradication in Ireland in 2003 is undertaken. In chapter 4, a CEA of statin therapy for the primary prevention of coronary heart disease (CHD) in Ireland in 2005 is undertaken.

Cost-utility analysis (CUA) incorporates quality-of-life measures for differing treatments while, at the same time, comparing the costs and outcomes of those treatments. Individuals seek to maximise their utility by consuming goods, including healthcare. If the utility gained from one intervention is higher than another, and the costs of the two are equal, then the former intervention is the more efficient. Programmes using CUA approach

are usually measured in terms of quality-adjusted life-years (QALYs), the main measure of health outcome[12]. QALYs are calculated by adjusting the length of time gained as a result of the intervention using a utility value, on a scale of 0 to 1. In chapter 4, a CUA of statin therapy for the primary prevention of CHD in Ireland in 2005 is undertaken.

Cost-benefit analysis (CBA) compares both costs and benefits of alternative programmes using monetary measurements. This allows for comparison not only with healthcare programmes designed to achieve the same result, but also programmes designed to achieve different results. A major concern with this approach, however, is the inability of many outcomes to be measured in monetary terms and, the ethical concerns which this approach raises such as the value of a statistical life. For these reasons, a CBA was not undertaken in this thesis.

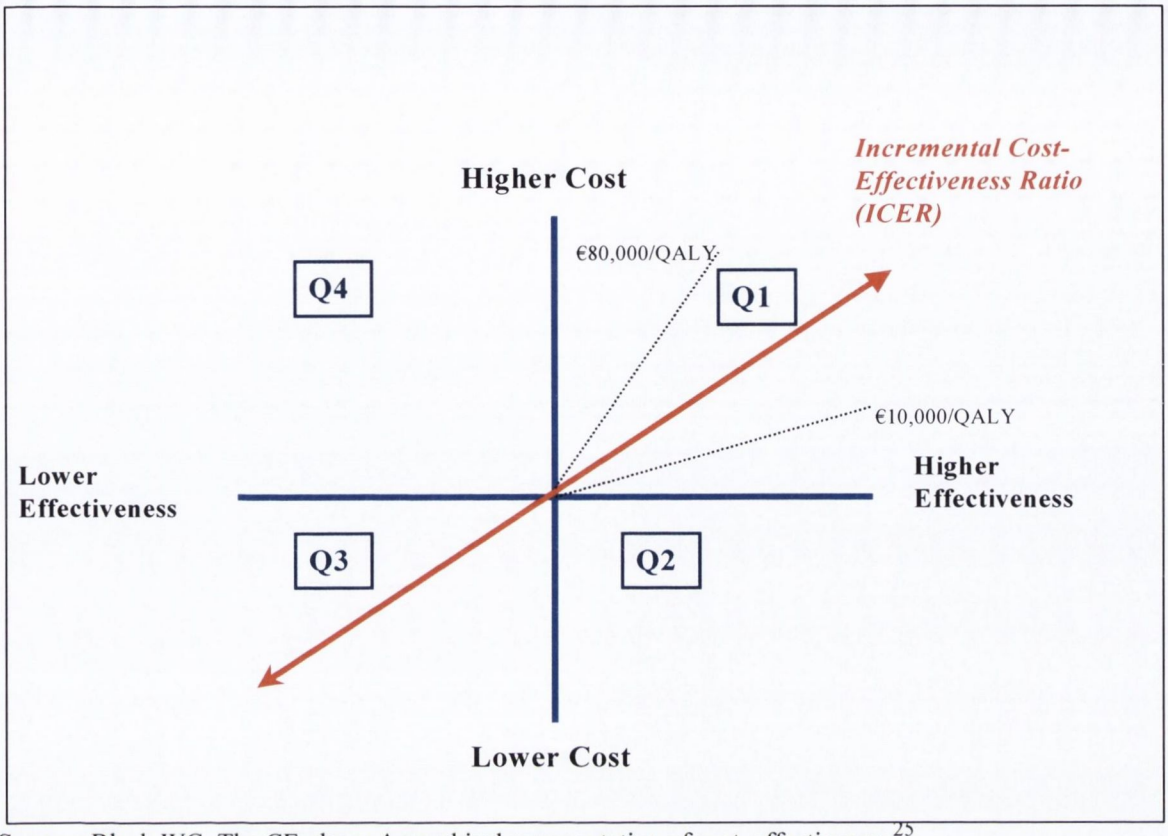
1.2.2 Decision analytic models

Decision analytic models provide a framework, which can represent decision problems explicitly, combining evidence from a range of sources and facilitating the extrapolation of costs and effects over time[13]. They are widely used as a means of establishing the most cost-effective intervention from alternatives strategies[14, 15]. The use of decision analytic models for the purpose of optimum allocation of healthcare resources has increased dramatically in recent years and are now well established in formal decision making processes[16, 17, 18, 19, 20, 21, 22].

Decision analysis has two key components. First, is the gathering of evidence relating to the treatment programme[23]. This may be sourced from a number of primary or secondary studies providing data on epidemiological factors, natural history, effectiveness, costs, quality-of-life measures, and, the impact of alternative treatments. The second component, relates to the formal synthesis of that evidence within an analytical framework. Thus, decision analytic models provide an explicit 2-way bridge between primary data and the decisions they inform.

Decision rules are required to assist policy makers in interpreting decision models[24]. The most frequently used rules involve the cost-effectiveness plane, which is presented in Figure 1.3.

Figure 1.3 The cost-effectiveness plane



Source: Black WC. The CE plane: A graphical representation of cost–effectiveness[25].

The cost-effectiveness plane is incremental in nature. The old or standard therapy is represented by the origin, and the horizontal and vertical axes relate to the effectiveness and cost differences between the new and the old intervention, respectively. In quadrants 2 and 4, one intervention is simultaneously cheaper and more effective than the other and, therefore, is the treatment of choice. In quadrant 2, the new treatment dominates. In quadrant 4, the old treatment dominates. When an intervention is both more costly and more effective, as in quadrants 1 and 3, further analysis is required to determine the strategy of choice. In quadrant 1, a decision needs to be made whether the additional cost is justified by the additional effectiveness associated with that therapy. In quadrant 3, a decision needs to be made whether the lower cost and lower effectiveness of the intervention is acceptable.

In order to assist with this decision, an incremental cost-effectiveness ratio (ICER) can be calculated which summarises the cost-effectiveness of one intervention relative to the other.

The ICER can be defined as:

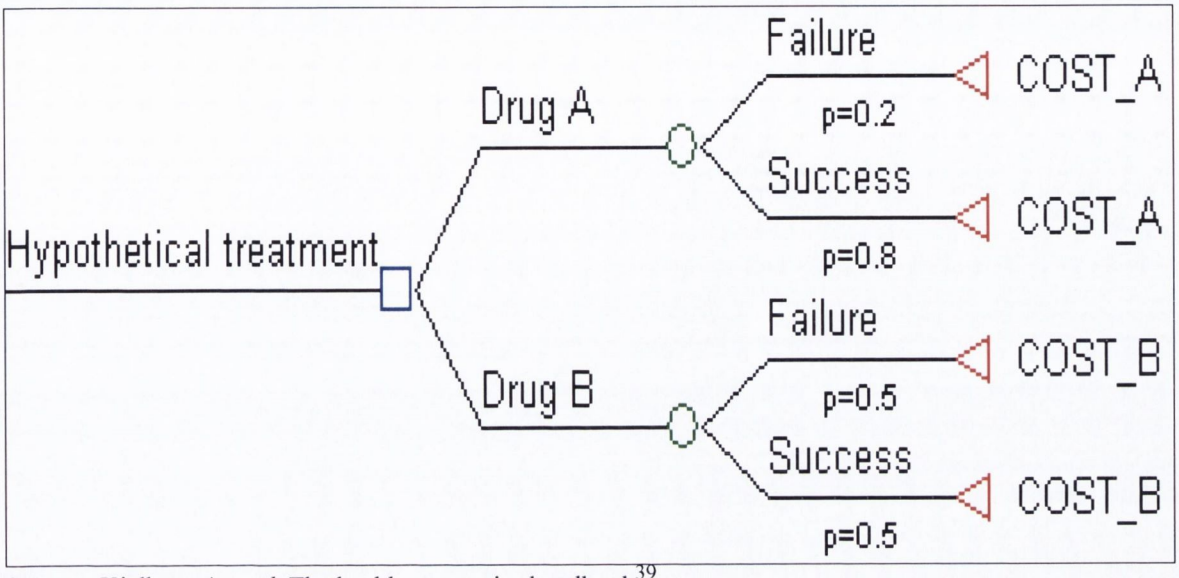
$$\text{ICER} = \frac{\text{Cost new therapy} - \text{cost old therapy}}{\text{Effectiveness of new therapy} - \text{effectiveness of old therapy}}$$

The ICER can be used to decide which treatment should be adopted. One approach, involves creating a league table of interventions by ranking all possible uses of the resources by their ICER. Decision makers can then implement the most cost-effective treatments (the smallest ICER) until the budget is exhausted[26, 27, 28, 29]. The league table can also be used in a revealed-preference type approach, where an intervention is considered cost-effective on the basis that less cost-effective interventions are already widely used.

A third approach, which is used in the CEA and CUA developed in chapter 4, involves defining a cut-off value of the maximum acceptable ICER appropriate for decision making. This can be represented by the slope of the line in Figure 1.3. This line divides the cost-effectiveness plane, such that points to the right of the line indicate that the intervention is cost-effective, and points to the left of the line indicate that the intervention is not cost-effective. As the cost per QALY increases, the likelihood of the technology being cost-effective decreases. The exact value of the ceiling ICER for cost-effective interventions is, however, not always clear. In the US, it has been proposed that an ICER less than $50,000/QALY (€35,000/QALY) be considered cost-effective[30]. In the U.K., the National Institute for Health and Clinical Excellence (NICE) does not specify a cost-effectiveness threshold. However, many approved technologies have an ICER less than £30,000/QALY (€43,000/QALY)[31, 32]. In Ireland, it would appear that the threshold is in the region of €45,000/QALY[33, 34, 35, 36, 37, 38].

The choice of decision analytic model used depends on the structure of the disease, the impact of the technology and data availability. The decision analytic models used in this thesis include decision tree and Markov transition probability models. A decision tree is a graphical illustration of all possible alternative strategies being compared, beginning with a clinical choice or decision. The probabilities of each strategy are used to reflect uncertain events. The sum of costs, weighted by the probability of occurrence, for each treatment strategy is used to determine the expected or average cost per patient. Expected costs and outcomes of the alternative strategies can then be compared as illustrated in Figure 1.4.

Figure 1.4 Decision tree for two hypothetical treatments



Source: Kielhorn A *et al.* The health economics handbook[39].

Decision trees should only be used over a single time period otherwise the decision tree may become too complex and difficult to interpret. Decision tree analysis is used in chapter 3 to undertake a CEA of PPI triple therapy regimens for H. pylori eradication in Ireland in 2003.

Markov transition probability models are analytic structures that represent key elements of a disease and are frequently used in economic evaluation[40]. They are used to evaluate diseases in which certain events occur repeatedly over time. Markov models are routinely used to represent the natural history of a disease in terms of a succession of states, each of which may be associated with certain costs and utilities in the form of LYG or QALY adjustments[41]. Each person in the model resides in one and only one health state at any point in time. At fixed increments of time, known as the Markov cycle length, individuals transit between the health states according to a set of transition probabilities. These probabilities can either be constant or time-dependant. There are three types of health states:

- transient with persons revisiting the state at any time;
- temporary with persons staying in the state for only one cycle; or,
- absorbing with persons never exiting that state i.e. death.

All persons in a particular health state are indistinguishable from one another. Transition probabilities depend only on the patients' current health state, and, not how long they have been in that health state or, how they got there.

Markov modelling has been used in health evaluation studies including extrapolation studies, progression of disease studies and, screening and prevention studies[42, 43, 44]. A Markov model is developed in chapter 4 to estimate the cost-effectiveness and cost-utility of statin therapy for the primary prevention of CHD in Ireland in 2005.

1.2.3 Sensitivity analysis

Over the last decade or so, there have been many developments in the methods to handle uncertainty in cost-effectiveness studies[45]. It is widely accepted that the systematic handling of uncertainty in economic evaluations is an important area that remains methodologically underdeveloped[46, 47]. When patient-level data are available, uncertainty can be addressed by standard statistical methods. However, such methods can not be applied to data that are synthesised from a number of sources, which is usually the case in decision analytic models. The recommended method for handling this type of uncertainty is sensitivity analysis.

Sensitivity analysis involves systematically examining the influence of the variables and assumptions employed in the evaluation[48]. There are three key steps when conducting any sensitivity analysis. First, the parameters used in the economic evaluation should be examined. These parameters may be uncertain due to reasons such as inadequate data sources or differing timeframes. Second, upper and lower boundaries for these parameters should be selected, based on clinical trials, existing research, or expert opinion. Third, the results of the evaluation must be re-calculated using the new parameters. If the variation between the estimates and the original results is small, then we can say with confidence that our original results appear valid. If large variations exist, then more effort is needed to reduce the uncertainty in the variables.

There are a number of types of sensitivity analysis. Simple sensitivity analysis involves varying one or more evaluation parameter. With one-way simple sensitivity analysis, each parameter is varied one at a time while the other parameters remain constant. This is the

most common form of sensitivity analysis, though it is well recognised that, considering the effects of parameters individually, is likely to under-estimate overall uncertainty.

A more sophisticated approach is multi-way simple sensitivity analysis, which involves varying a number of parameters at one time. This is more realistic than the one-way approach. However, if there are a large number of uncertain parameters the number of potential combinations will increase making the results more difficult to interpret. Both one-way and two-way simple sensitivity analysis is conducted on the cost-effectiveness model for H. pylori eradication in chapter 3.

Scenario analysis examines a series of hypothetical scenarios. Typically, the scenarios may include a base case, best case and worst case scenario. The analyst may also apply a scenario that he feels could possibly apply. Scenario analysis, however, does not consider the probability of these alternative scenarios occurring and can tend to over-estimate or under-estimate uncertainty.

Probabilistic sensitivity analysis (PSA) involves applying probability distributions to the specified ranges for the key parameters. Samples are then drawn, at random, using Monte Carlo simulation techniques, from these distributions to generate an empirical distribution of the ICER[9]. The variation observed is purely a result of the alternative pathways through the model and is similar to the population variability of outcomes in a clinical trial[49]. PSA handles uncertainty in data inputs and, allows for the incorporation of expert opinion in the formation of the parameter distributions[50]. By analysing parameters collectively, variations between the parameters are more likely to be captured.

Probabilistic information is often presented in terms of cost-effectiveness acceptability curves as these curves summarise the evidence in favour of the strategy being cost-effective[51, 52]. Recently, the use of PSA has increased significantly with NICE requiring that PSA be used in all cost-effectiveness models submitted to them[53]. Chapter 5 applies these three types of sensitivity analysis to the statin therapy primary prevention analysis developed in chapter 4.

1.3 The Irish healthcare setting

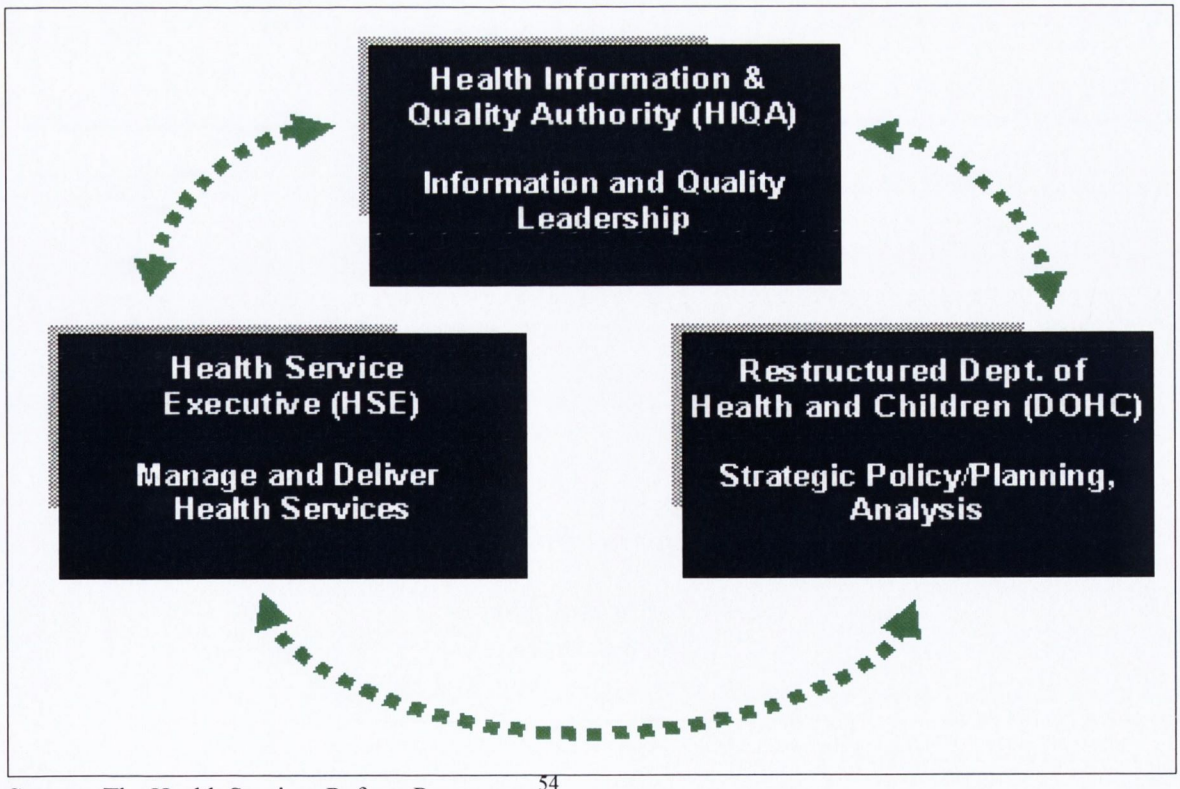
1.3.1 Background

The Irish health service is currently undergoing the largest structural reform ever undertaken by any organisation in the country. The Health Service Reform Programme was announced in June 2003[54]. Key elements of the programme include:

- a major rationalisation of the existing health structures to reduce fragmentation;
- the reorganisation of the Department of Health and Children (DoHC) to ensure improved policy development;
- the establishment of a Health Service Executive (HSE) to manage the health service as a single national entity; and,
- the establishment of a Health Information and Quality Authority (HIQA) to ensure that quality of care is promoted throughout the system.

An overview of the restructured health service is shown in Figure 1.5.

Figure 1.5 The restructured health service



Source: The Health Services Reform Programme[54].

The HSE is responsible for managing and delivering health and personal social services in Ireland. Its fundamental purpose is to enable people live healthier and more fulfilled

lives[55]. It is the largest employer in the State, employing over 70,000 staff directly and funding a further 36,000 staff[56]. The HSE provides thousands of different acute (hospital) and non-acute services. These services are wide ranging and include:

- treating older persons in the community;
- caring for children with challenging behaviour;
- performing highly complex surgery;
- controlling the spread of infectious diseases;
- educating people to live healthier lives; and,
- planning for potential major emergencies.

The HSE has three clearly defined service delivery mechanisms:

1. Primary, Community and Continuing Care (PCCC) delivering non-acute services in the community through 32 Local Health Offices across the country;
2. National Hospitals Office (NHO) providing acute hospital and ambulance services throughout the country; and,
3. Population Health promoting and protecting the health of the entire population[57].

In 2006, the HSE had a budget of €12.4bn, the largest of any public sector organisation in Ireland. The majority of this budget was for PCCC including the provision of the CD schemes. The 2006 budget for the HSE is detailed in Table 1.2.

Table 1.2: HSE budget 2006

Service Delivery Mechanism	**€m**	**%**
Primary, Community & Continuing Care	6,689	56.5%
National Hospitals Office	3,956	33.5%
Population Health	69	0.6%
Support Services and generated income	1,117	9.4%
Total Revenue	**11,831**	**100%**
Capital Services	**558**	
Total Estimate Provision	**12,389**	

Source: Annual report and financial statements[56].

In 2005, total healthcare expenditure in Ireland accounted for 7.5% of GDP, less than the Organisation for Economic Co-operation and Development (OECD) average of 9.0%[58]. In the same year, life expectancy in Ireland stood at 79.5 years, nearly one year above the OECD average. Ireland had 2.8 physicians and 2.8 acute hospital beds per 1,000 population in 2005, versus an OECD average of 3.0 and 3.9 respectively. Ireland spends less on pharmaceutical products than most other OECD countries at 10.9% of its total health expenditure, versus an OECD average of 17.4%[58]. However, prescribing trends are increasing rapidly in Ireland, with the average annual growth rate in pharmaceutical expenditure now exceeding that of most other European member states[59].

1.3.2 Casemix hospital programme

Casemix is the most internationally accepted performance-related acute hospital activity programme[60]. It compares hospital activity, costs, and complexity. It also facilitates hospital performance, making it possible to measure, fund, and manage resources[61]. Casemix classifies and categorises hospital outputs contributing towards equity, efficiency and transparency. Clinically meaningful cases, that use a similar level of resources in the treatment of a particular case, are grouped together to facilitate this comparison. Patients are categorised depending on the type of procedure performed and the intensity of resources used.

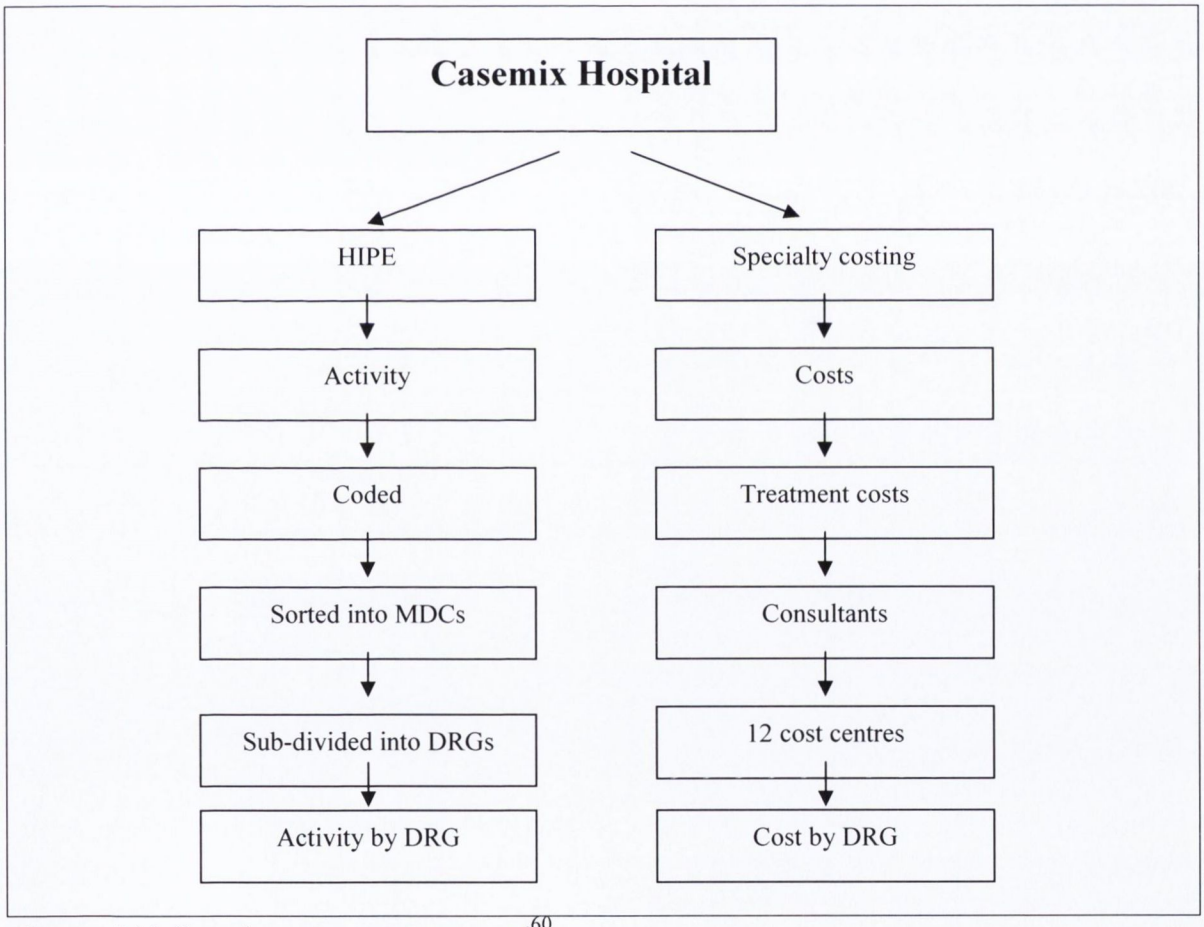
The Casemix programme has been operational in Ireland since 1993. The programme incorporates four hospital peer groups:

- Teaching hospitals (8 hospitals);
- Non-teaching hospitals (24 hospitals);
- Maternity hospitals (3 hospitals); and,
- Paediatric hospitals (2 hospitals).

Inpatient, day case, accident and emergency (A&E), dialysis and acute psychiatry admissions are included in the Casemix database. The 2007 Casemix programme uses 2005 activity data and 2006 costs. Nearly 1.6 million patient episodes are captured in the 2007 Casemix model[62].

In 2007, 50% of the hospitals' budget is peer group performance related having increased incrementally from 20% in 2004. Therefore, in determining the cost per case, half the tariff is set by each hospital's actual cost per case, and the other half is determined by the peer group. The Minister for Health and Children and the HSE remain committed to the use of performance related funding, via the Casemix programme and, has made provision for the incremental broadening of the programme over the coming years. The Irish Casemix framework incorporating the Hospital Inpatient Enquiry (HIPE) programme and the speciality costing programme is presented in Figure 1.6.

Figure 1.6 The Casemix framework



Source: Irish Casemix programme user manual[60].

1.3.2.1 Hospital Inpatient Enquiry programme

The HIPE programme collects an abstract of clinical and demographic activity data in 60 Irish hospitals[63]. In 2006, the programme recorded 594,000 inpatient admissions, 543,000 day case procedures, 1,269,000 A&E department attendances, 2,779,000 out patient attendances and nearly 63,000 births[63].

Patients' details are coded and imported into the HIPE database system on discharge. Each HIPE record represents one episode of care, and patients may be admitted to hospital(s) more than once, with the same or different diagnosis. Data recorded in HIPE can be logically grouped to demographic, clinical, or, administrative. The clinical data includes up to six diagnosis and four procedures. HIPE codes diagnosis by the International Classification of Diseases (ICD), developed by the World Health Organisation (WHO)[64]. Diagnosis is sorted into 23 Major Diagnostic Categories (MDCs) which, in turn, are sub-divided into 665 Diagnostic Related Groups (DRGs).

The coding system used in Ireland, since 2005, is ICD-10-AM (4th edition) which allows for over 15,000 diagnosis and 8,000 individual procedures. ICD-10 is fast becoming the standard for diagnostic coding, though many countries, including Ireland, have adapted their own country-specific DRGs to better reflect local circumstances.

1.3.2.2 Speciality costing programme

The speciality costing programme uses costs from the hospitals' annual financial statements to categorise costs by hospital speciality. Information on costs is supplied by the individual hospitals, submitted to the DoHC and, is subject to audit. Today, a total of 37 hospitals are involved in the speciality costing programme accounting for 95% of all acute hospital admissions and more than €4bn of costs[56].

The speciality costing programme categorises inpatient and day case costs to a particular speciality and consultant. Costs are predominately allocated by DRG. They can also be allocated on the basis of daily costs for services primarily influenced by length of hospital stay. Superannuation and capital costs are excluded from the model. However, other costs such as work performed by another hospital for patients coded in the initial hospital are added back into the model. The twelve cost centres used in the speciality costing programme are shown in Table 1.3.

Table 1.3 Speciality costing programme cost centres

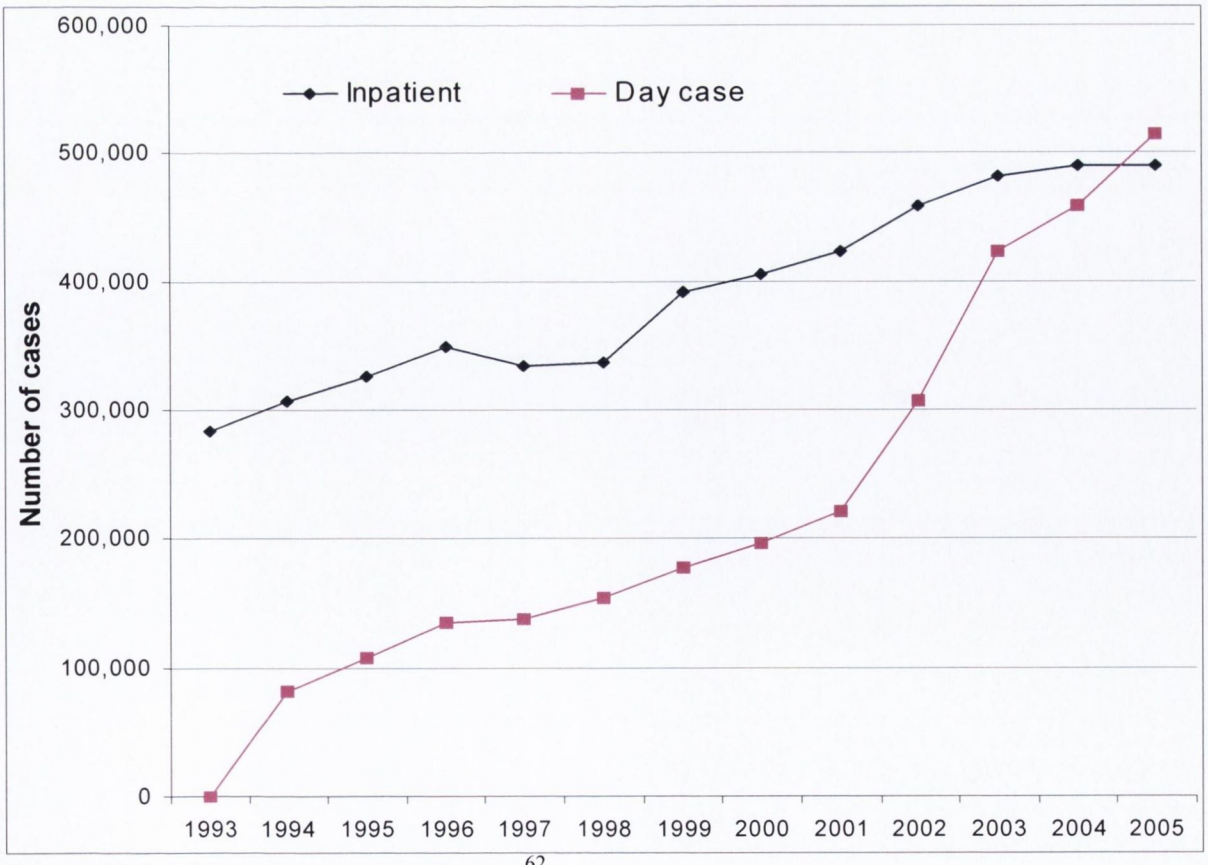
Allied health professionals	Imaging	Pharmacy
Intensive care unit	Medical pay	Theatre
Cardiac care unit	Nursing	Bloods
Accident and emergency	Pathology	Prosthesis

The two largest speciality cost centres are pay-related with nursing consuming approximately one-third of all resources and medical pay consuming a further 16%.

1.3.2.3 Some Casemix results

Activity captured by the Irish Casemix programme has increased significantly in recent years. The 2007 Casemix programme, which refers to 2005 activity data, includes 1,002,000 cases (489,000 inpatient and 513,000 day cases) as illustrated in Figure 1.7.

Figure 1.7 Growth in activity captured by the Irish Casemix programme from 1993 to 2005



Source: National Casemix programme database[62].

The Irish Casemix programme is used as part of the budgetary process. It aims to fund hospitals for the patients they actually treat. Ireland operates a unique budget-neutral policy which rewards efficiency by rebalancing funding based on a Casemix review of the patient workload of the hospital. Overall acute hospital funding is not affected by the programme. Some hospitals, however, lose funding while others gain, via the Casemix programme. The financial adjustments used as part of the HSE's 2007 hospital budget allocations are displayed in Table 1.4.

Table 1.4 Casemix financial adjustments by hospital in 2007

Hospital	Positive Adjustment €	Negative Adjustment €
St.James	1,818,662	
Waterford Regional	1,168,007	
Longford/Westmeath	1,037,140	
UCH Galway	990,361	
Letterkenny	927,724	
St.Vincents	872,444	
Wexford General	845,872	
South Infirmary Royal Victoria	844,566	
Merlin Park	659,837	
James Connolly	621,764	
Cork University	609,548	
Louth General	578,806	
Limerick Regional	439,200	
Coombe	174,515	
Portiuncula	111,694	
Beaumont	103,470	
OLHSC, Crumlin	35,777	
National Maternity		-22,046
Mallow		-29,486
Temple Street		-35,777
Croom		-43,411
Tullamore		-109,999
Mercy		-150,440
Rotunda		-152,468
Portlaoise		-314,034
St Marys Orthopaedic		-331,573
Tralee		-404,045
Lourdes Drogheda		-448,666
Sligo		-542,951
Cavan		-579,234
Mayo		-787,888
Navan		-793,246
St Lukes Kilkenny		-899,596
St. Colmcilles		-1,178,280
Mater		-2,150,877
Tallaght AMNCH		-2,865,372
TOTAL	**0**	**0**

Source: National Casemix programme database[62].

Not all activity captured by the Casemix programme is included in the Casemix budgetary model. The 2007 Casemix budgetary model included 896,000 cases which is lower than the total activity captured by the programme. The majority of the acute hospital activity is provided by the non-teaching hospitals, though the more complex inpatient cases are undertaken by the teaching hospitals. Table 1.5 highlights key activity and base price by peer group from the 2007 Casemix model.

Table 1.5 Key hospital activity and prices in 2005

Hospitals	Total no. of cases	No. of inpatient cases	No. of day cases	Average inpatient price €	Average day case price €
Teaching Hospitals	356,000	153,000	203,000	4,637	587
Non-Teaching Hospitals	449,000	272,000	177,000	4,114	588
Maternity Hospitals	56,000	51,000	5,000	4,194	-
Paediatric Hospitals	35,000	19,000	16,000	5,356	-
Total for all Hospitals	**896,000**	**495,000**	**401,000**	**4,403**	**588**

Source: National Casemix programme database[62].
Note: Costs relate to 2006, activity to 2005.

The average cost of an inpatient procedure undertaken in Irish teaching hospitals is €4,637, with a range of plus or minus 6%. The average cost of a day case procedure for these hospitals is €587, with a wider range of plus or minus 20%. The average cost of inpatient cases is highest for the paediatric hospitals at €5,356. The average day case price is similar in both the teaching and non-teaching hospitals. Day case prices for the maternity and paediatric hospitals have yet to be incorporated in the model.

Activity can also be examined by disease and disorder category. Table 1.6 shows the top five inpatient MDCs by bed day in the 2007 Casemix model, with diseases and disorders of the circulatory and respiratory systems consuming 12.7% and 12.2% of all inpatient bed days, respectively.

Table 1.6 Top five inpatient Major Diagnostic Categories by bed day in 2005

MDC	Diseases and disorders of the:	No. of bed days	% of total bed days
5	Circulatory system	489,000	12.7
4	Respiratory system	470,000	12.2
6	Digestive system	443,000	11.5
1	Nervous system	416,000	10.8
8	Musculoskeletal system	373,000	9.7
	Total for top five MDCs	**2,191,000**	**56.9%**
Total	**All MDCs**	**3,862,109**	**100%**

Source: National Casemix programme database[62].

Individual DRGs can also be scrutinised. Tracheostomy or ventilation (DRG A06Z) had the highest total expenditure of any DRG in the 2007 Casemix model. Expenditure of over €123m was recorded for this DRG with a cost per case of €67,437. DRG O60B, vaginal delivery recorded over 32,000 inpatient cases at a total cost of €67.9m. Table 1.7 shows the top 10 inpatient DRGs by total expenditure in 2005.

Table 1.7 Top ten inpatient Diagnostic Related Groups by expenditure in 2005

DRG	Description	No. of cases	Alos (days)	Cost per case €	Cost €m	% total cost
A06Z	Tracheostomy or ventilation	1,825	43.1	67,437	123.0	5.2
O60B	Vaginal delivery	32,236	3.1	2,107	67.9	2.9
O01C	Caesarean delivery	12,191	5.5	4,314	52.6	2.2
I03C	Hip replacement	3,847	12.0	10,869	41.8	1.8
F15Z	Percutaneous coronary intervention w/o AMI w stent	2,847	3.7	8,034	22.9	1.0
B70A	Stroke	849	54.9	26,819	22.8	1.0
G02B	Major small and large bowel procedures	1,654	16.0	13,575	22.5	0.9
O66A	Antenatal & other obstetric admission	19,886	2.5	1,111	22.1	0.9
G67B	Oesophagus, gastro scope & miscellaneous diagnosis	7,916	4.1	2,775	22.0	0.9
G07B	Appendicostomy	5,383	3.9	4,050	21.8	0.9
	Total for top ten DRGs	**88,634**			**419.4m**	**17.7%**

Source: National Casemix programme database[62].
Key: Alos: average length of stay, w: with, w/o: without, AMI: acute myocardial infarction.
Note: Costs relate to 2006, activity to 2005.

1.3.3 Community Drug schemes

The HSE Primary Care Reimbursement Service (PCRS), formerly the General Medical Services Payments Board (GMSPB) manages the reimbursement of medications in the community. In 2005, the PCRS made payments of over €1,881m including €1,189m to pharmacists and €414m to doctors. It also dispensed over 50m prescription items[65]. The largest CD schemes are the GMS, the DP, and, the Long Term Illness (LTI) scheme. Combined, these schemes account for 98% of total payments by the PCRS. An overview of these schemes is presented in Table 1.8.

Table 1.8 Overview of the main Community Drugs schemes in 2005

Community Drug scheme	Prescription items (millions)	Payment to pharmacies (€ million)	Eligibility	Patient co-payment
GMS	37.43	831.44	All below income threshold & all over 70 years	None
DP	10.58	244.49	All who are not eligible for GMS or LTI schemes	€85 per month
LTI	1.93	100.55	Fifteen specific chronic conditions	None
Total for all schemes	**50.56**	**1,189.41**		

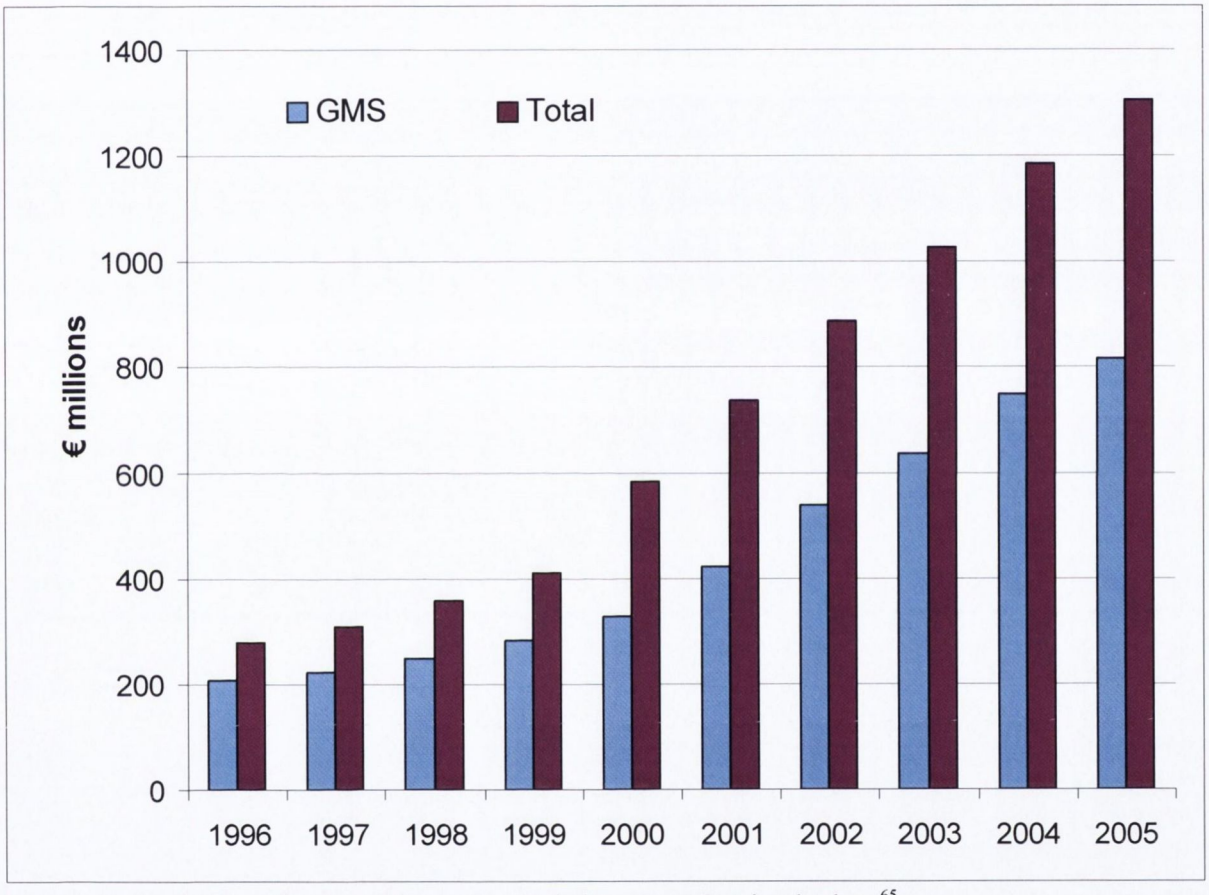
Source: National Shared Services Primary Care Reimbursement Service database[65].

Prescription claims databases have been described as one of the most accurate means of determining drugs dispensed to individuals[66]. They provide drug related information for real-world patients and, therefore, lack the bias towards positive outcomes observed in clinical trials. The PCRS maintains a database to ensure that appropriate payment is made to the pharmacists, general practitioners (GPs), dentists, and opticians participating in the schemes. All medications are coded using the internationally recognised anatomical therapeutic classification (ATC) system. The database contains prescription data by former health board (HB) for each calendar month. Each row of data contains details on one prescribed item, including a pharmacy and GP identifier, the patient's GMS number, sex and age, the prescription claim number, GMS code, and number of dosage units dispensed. Also recorded are the pharmacy fee, cost of prescriptions, and value-added tax (VAT).

1.3.3.1 Some prescribing trends

The CD schemes are one of the fastest growing components of Irish health service expenditure. Drug expenditure increased by nearly 5-fold over the past 10 years as illustrated in Figure 1.8.

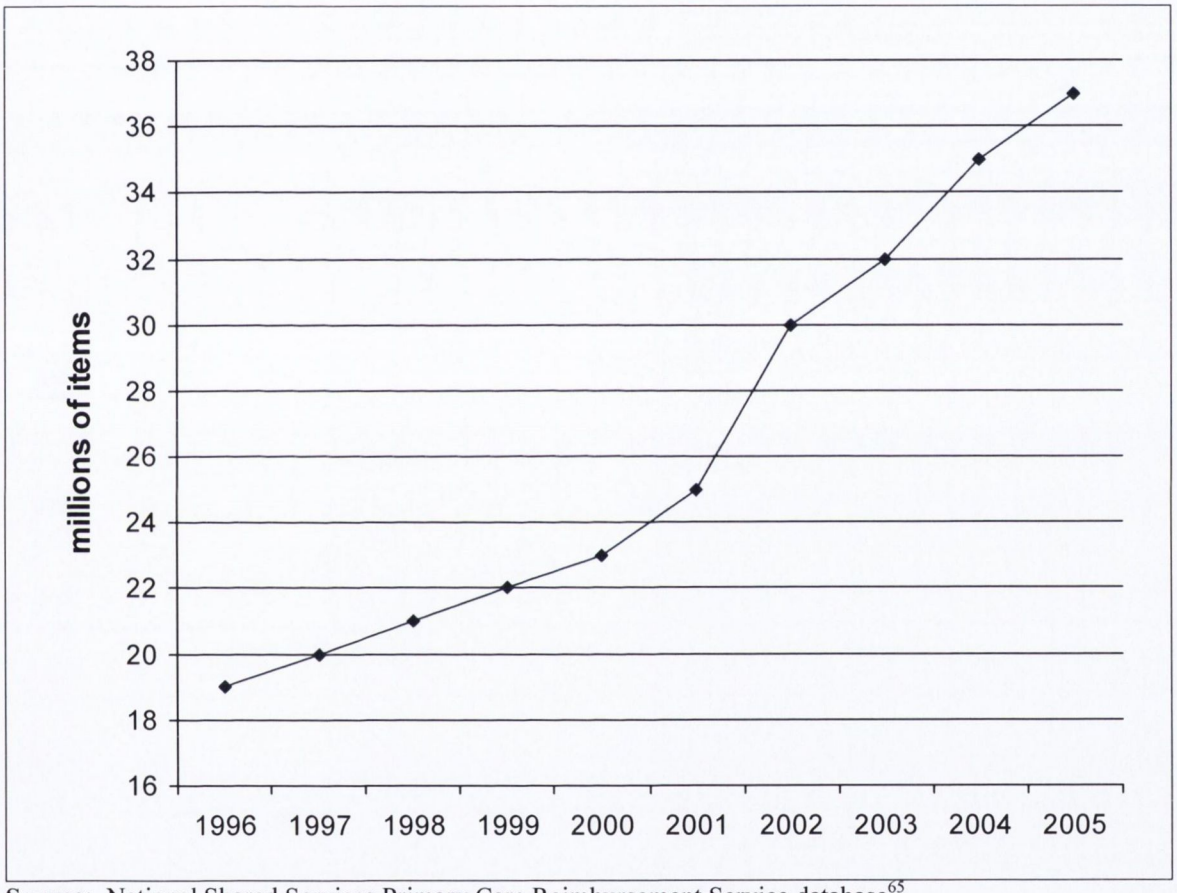
Figure 1.8 Drug expenditure under the Community Drugs schemes from 1996 to 2005



Source: National Shared Services Primary Care Reimbursement Service database[65].

Key drivers of this increased expenditure include the 'volume effect' which relates to the increased rate of prescribing by practitioners, and the 'product mix' which involves the prescribing of newer, more expensive medications. Since 1996, there has been a 96% increase in the number of items dispensed under the GMS scheme alone, to over 37.4 million items in 2005.

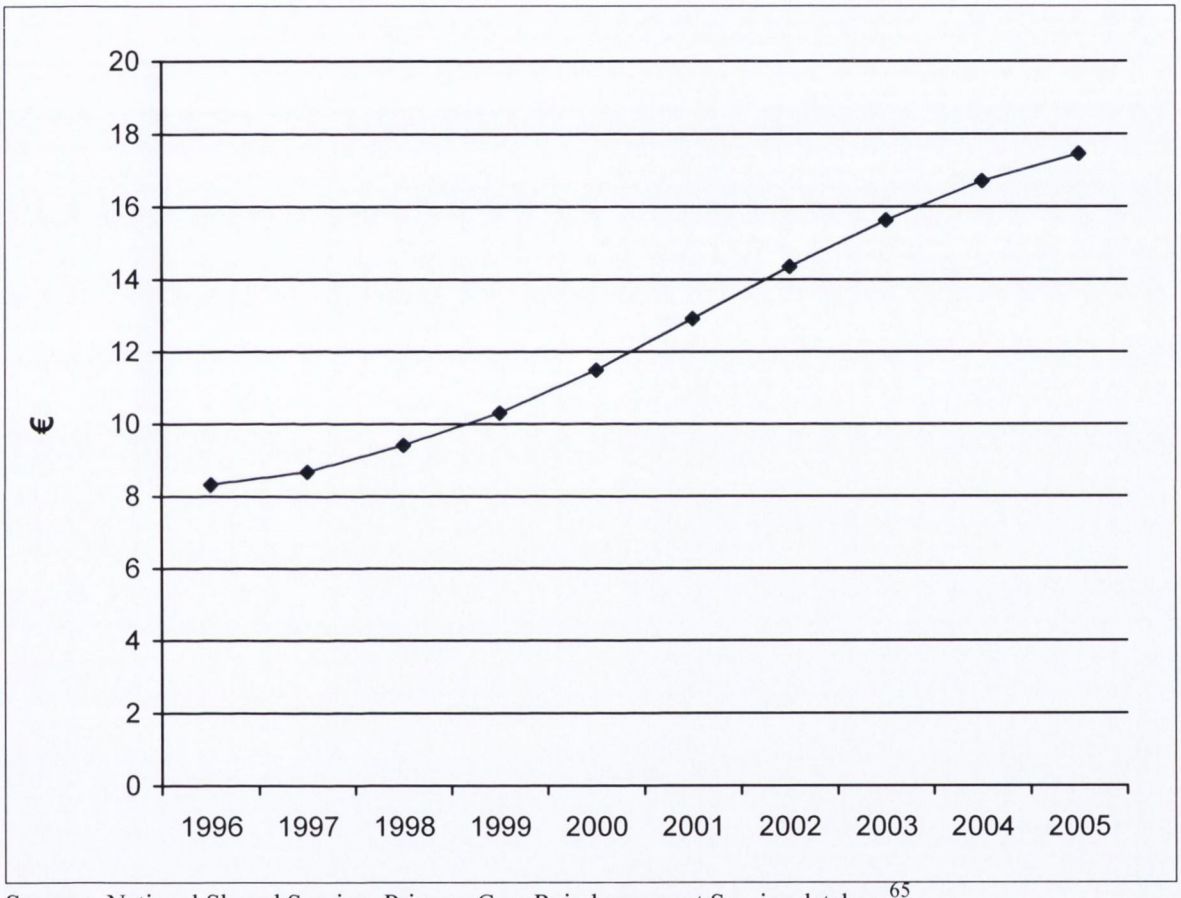
Figure 1.9 Number of items dispensed under the GMS scheme from 1996 to 2005



Source: National Shared Services Primary Care Reimbursement Service database[65].

In Ireland, the price of health related products and services, including pharmaceuticals, increased by 21.3%, versus an 8.4% increase for general goods and services, over the period 2002 to 2005[67]. Between 1996 and 2005, the ingredient cost per item dispensed under the GMS scheme more than doubled, from €8.32 to €17.45, as illustrated in Figure 1.10.

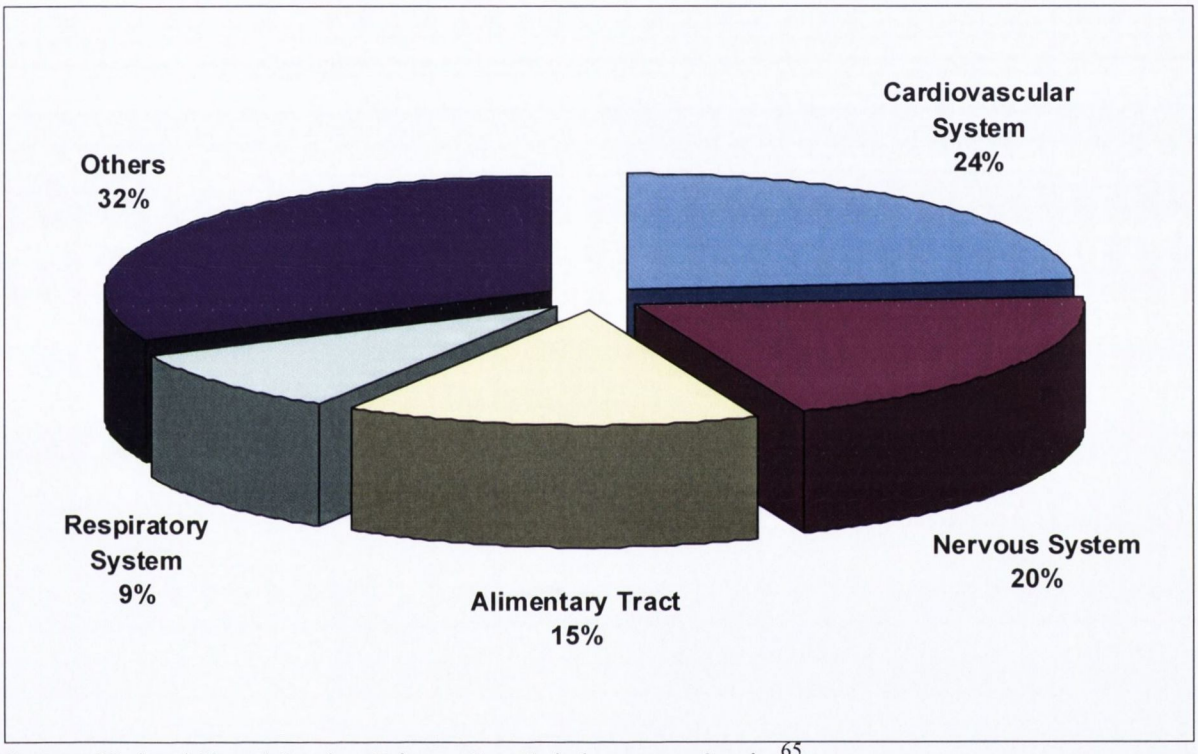
Figure 1.10 Ingredient cost per item under the GMS scheme from 1996 to 2005



Source: National Shared Services Primary Care Reimbursement Service database[65].

In 2005, the cardiovascular system had the highest expenditure of any therapeutic class of drug, medicines and appliances dispensed under the CD schemes. Figure 1.11 illustrates the dominance of the top four therapeutic classes, in terms of cost, dispensed under the CD schemes in 2005.

Figure 1.11 Major therapeutic classification of drug, medicines and appliances under the GMS scheme in 2005



Source: National Shared Services Primary Care Reimbursement Service[65].

1.4 Health economics in the Irish healthcare setting

In recent years, there have been numerous requests for economic analysis of the Irish health services[68, 69, 70, 71, 72, 73]. The lack of an evidence based approach, as well as inefficient practices, has led to the Irish health service's inability to illustrate, and in some cases, achieve value for money (VFM)[70]. This section briefly explores health economics in the Irish healthcare setting, in advance of the application of the economic frameworks developed later in this thesis.

1.4.1 Delivery organisations

The main organisations involved in the delivery of health economic analysis in the Irish healthcare setting are discussed in this section.

1.4.1.1 Comptroller and Auditor General

The Comptroller and Auditor General (C&AG) is responsible for examining whether state bodies administer their resources economically and efficiently, and for ensuring that these bodies have mechanisms in place to evaluate the effectiveness of their operations. The C&AG conducted a number of health service reviews including:[74]

- VFM report 55: Medical consultants contract (April 2007);
- VFM report 52: Provision of disability services by non-profit organisations (March 2006);
- VFM report 51: Development of human resource management system for the health service (Dec 2005);
- VFM report 49: Waste management in hospitals (June 2005);
- VFM report 44: Waiting list initiative (Nov 2003); and,
- VFM report 19: Prescribing practices and the development of general practitioner services (Jan 1998).

1.4.1.2 Department of Finance

The Department of Finance (DoF) leads VFM and policy reviews for the Irish government. Some ninety formal VFM reviews, across various government departments, have been planned for the period 2006-2008. The DoF established a central expenditure evaluation unit to drive the implementation of a VFM review framework, and ensure compliance with VFM requirements, such as audits of major projects.

A high level health service VFM group was established to ensure that VFM is achieved, in a coherent and effective manner. This group consists of the Secretary General of the DoHC, the CEO of the HSE, the CEO of HIQA, and a senior official from the DoF. The role of the group is to oversee and promote initiatives in the area of VFM and cost-effectiveness within the health service. Under this initiative, the health service has committed to undertake three significant reviews examining 13% of the total health budget in 2006/7. These reviews include an examination of:

- the allocation and utilisation of funds for acute hospitals (€664m budget);
- the efficiency and effectiveness of long stay mental health residential care for adults (€485m budget); and,
- the equal opportunities childcare programme (€114m budget).

1.4.1.3 Health Service Executive

Economic analysis plays an important role within the HSE's strategic planning function. The Corporate Performance Assessment Unit uses economic indicators to evaluate the overall performance of the Irish health service. The Corporate Pharmaceutical Unit makes use of economic evaluation to promote best practice in the use of drugs and medical devices. The Finance Directorate has the lead responsibility for achieving VFM within the health service and applies an array of economic evaluation techniques to assist in this process. The NHO undertakes detailed economic analysis of hospital costing and activity assisting the service planning process.

1.4.1.4 National Centre for Pharmacoeconomics

The National Centre for Pharmacoeconomics (NCPE), established in 1998, aims to promote expertise in Ireland for the advancement of the discipline of pharmacoeconomics, through practice, research, and education. Its main activities are the economic evaluation of pharmaceutical products and the promotion of cost-effective prescribing. The NCPE reviews the cost-effectiveness and budget impact of individual drugs in the Irish healthcare setting. Drug utilisation data from the CD schemes are used to undertake such analysis, and are enhanced by the inclusion of Irish cost data.

1.4.1.5 Health Information and Quality Authority

HIQA was established in May 2007 as part of the government's Health Service Reform Programme[54]. HIQA is responsible for driving quality and safety in Ireland's health and social care services through the setting of standards, monitoring quality, and providing relevant and timely health information. HIQA is tasked with making recommendations aimed at achieving best outcomes from the available resources. The organisation is responsible for evaluating the clinical and cost-effectiveness of health technologies, including drugs. It has been tasked with leading the planning, prioritisation and development of Health Technology Assessment (HTA) in Ireland, as well as the development and management of health economic capacity.

1.4.2 Significant policy applications

This section discusses three significant health economic applications which have a strong policy influence within the Irish healthcare setting.

1.4.2.1 Irish Pharmaceutical Healthcare Association agreement

Since 1972, a multi-annual agreement between the DoHC and the Irish Pharmaceutical Healthcare Association (IPHA) has governed the terms, conditions, and prices of medicines supplied to the Irish health service. The agreement covers all medicines prescribed and reimbursed under the CD schemes, in hospitals, and by the HSE, and covers over 1,600 different drugs[75]. The newly renegotiated agreement came into effect on 1st September 2006, and will last for a period of 4 years.

Under this agreement the HSE reserves the right to assess new and existing technologies including pharmaceuticals, diagnostics, and devices that may be high cost or have a significant budget impact. Medicines may be subjected to economic analysis in the form of pharmacoeconomic assessment. Products subjected to an assessment will become reimbursable under the schemes within 40 days of a positive reimbursement decision.

Other key elements of the IPHA agreement include:

- The price to the wholesaler of any new medicine shall not, exceed the currency adjusted average price to the wholesaler in the nominated EU member states which include, the UK, Belgium, Denmark, France, Germany, the Netherlands, Spain, Finland and Austria;

- The price shall be realigned to the currency adjusted average wholesale price in the EU nominated states at 2 and 4 years;
- Price modulation will be permitted on an exceptional basis and on condition that it will be cost neutral for the state;
- For patent expired medicines, the price to the wholesaler will be reduced by 35% (20% initially, and a further 15% after 22 months); and,
- The rebate to the HSE for medicines dispensed under the GMS scheme will be 3.53% except for medications subjected to a price reduction.

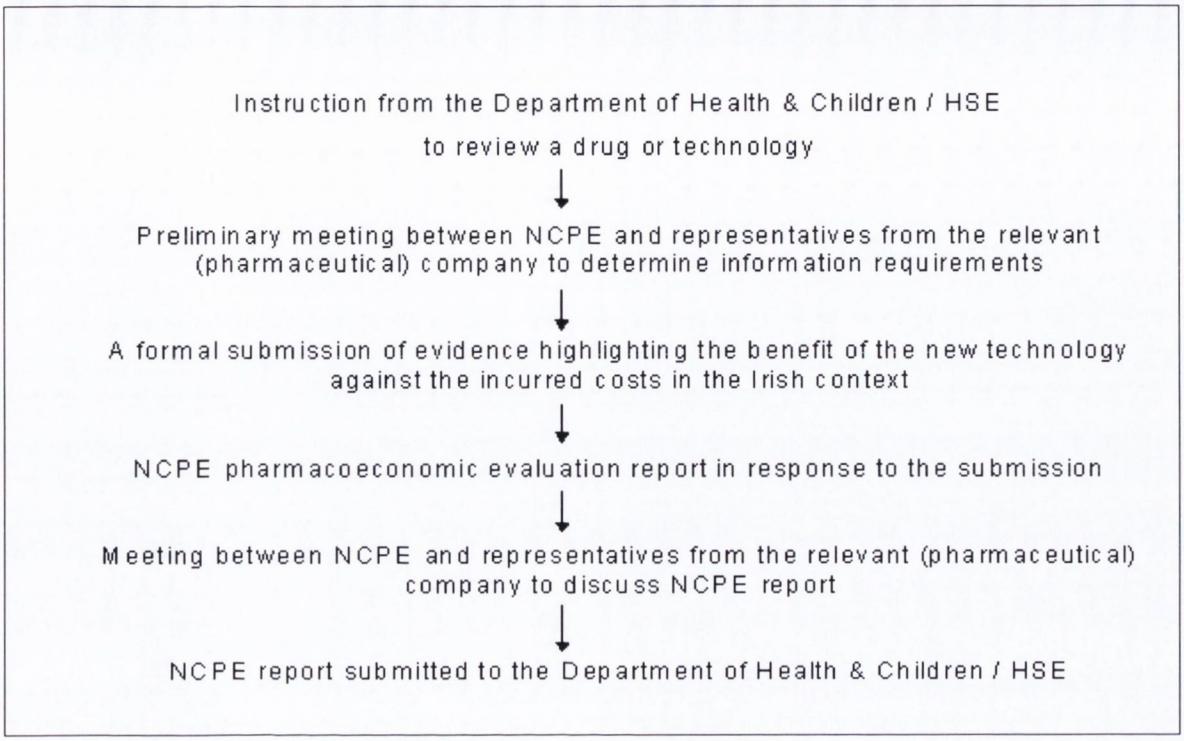
1.4.2.2 Health Technology Assessment guidelines

HTA is a multidisciplinary process that summarises information about the medical, social, economic and ethical issues related to the use of health technology[76]. HTA examines what works, how well it works, and at what cost[77].

HTA uses explicit analytic frameworks to inform the formulation of safe and effective health policies. The importance of economic modelling within HTA has grown significantly in recent years with many countries now requesting manufacturers to provide cost-effectiveness data in support of applications for funding by the health system. Australia[78] and Ontario, Canada[79] were the first areas to adopt such an approach and have since been followed by many other jurisdictions, and several private payers[80]. In 2004, the European Commission and Council of Ministers targeted HTA as a political priority. A sustainable European network on HTA (EUnetHTA) was established coordinating the efforts of 27 European countries. HTA now boasts a thriving international scientific community, including organisations such as Health Technology Assessment International[81] and the International Network of Agencies for Health Technology Assessment[82].

In Ireland, the approach to HTA is summarised in Figure 1.12.

Figure 1.12 Approach to Health Technology Assessment in Ireland



As part of the approach to HTA in Ireland, pharmaceutical companies are requested to produce a formal submission of evidence highlighting the benefits of the new technology against the incurred costs. This submission should follow the Irish HTA guidelines produced by the NCPE and is required in advance of a decision on product reimbursement by the Irish health service. The first section of the submission, the study design should include information on the:

- Study question and the study perspective;
- Selection of alternatives including the rationale for choosing the comparisons;
- Type of study undertaken (i.e. CEA);
- Benefit measurement and evaluation used (i.e. QALYs);
- Method of data capture;
- Costings detailing individual quantities and Irish-specific costs;
- Type of modelling used (i.e. Markov model); and,
- The appropriate time horizon used in the model.

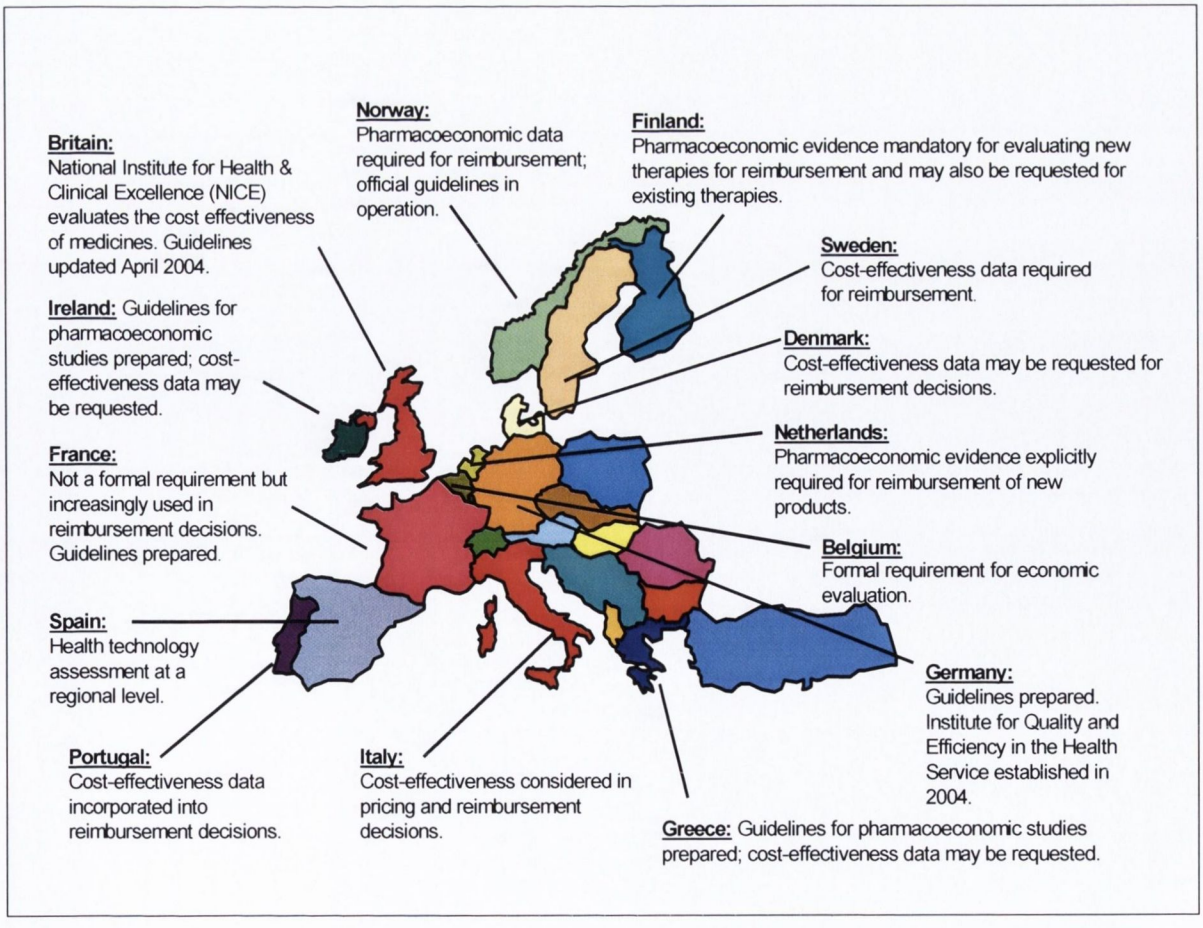
The second section of the submission, should describe the data analysis undertaken. The model should include adjustments for the differential timing of costs and benefits. It should also address the issue of uncertainty via standard statistical tests or the use of sensitivity

analysis, where appropriate. The third section, the results section, should detail the major outcomes using appropriate measures such as QALYs or LYG. Comparisons should be made to other healthcare interventions. This section should also ensure that the original study question has been clearly answered.

1.4.2.3 Pharmacoeconomic evaluations

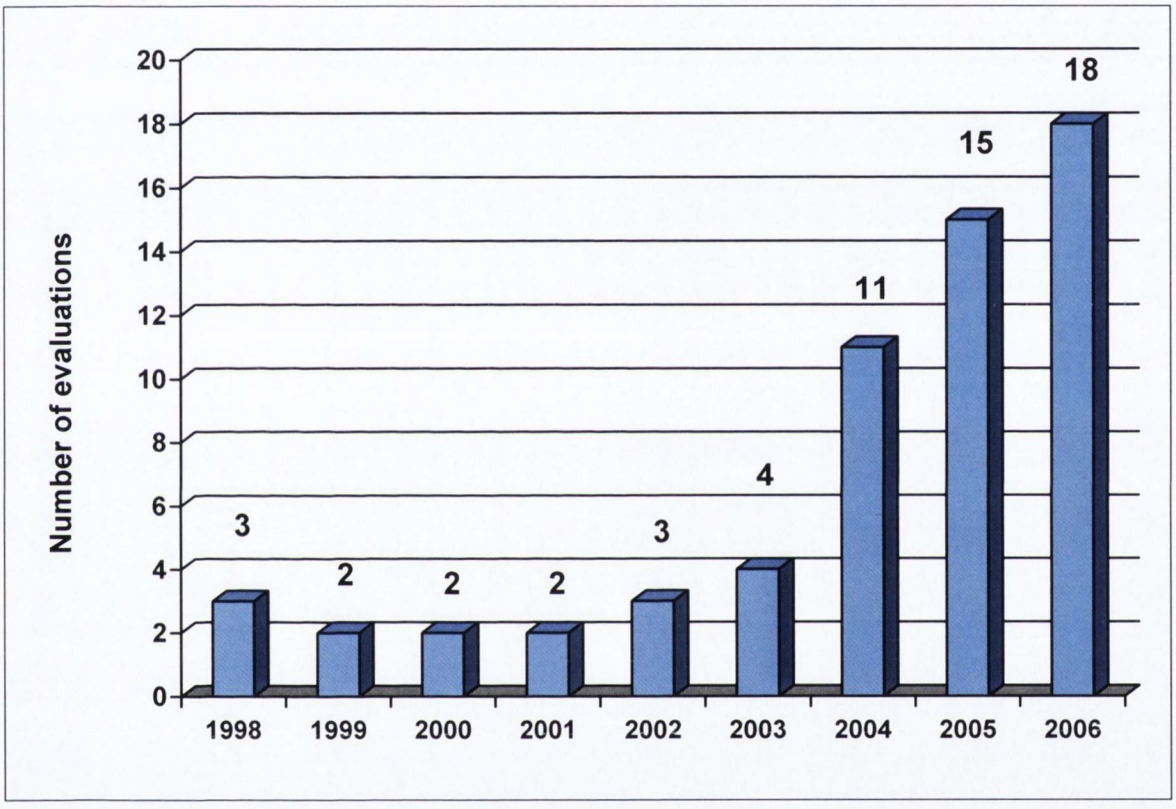
Pharmacoeconomic analysis involves assessing the implications of projected outcomes and costs of pharmaceutical products for the decision whether to continue development of a drug for pricing strategies or for product reimbursement[83]. Some European countries have made pharmacoeconomic evaluation a formal requirement in pharmaceutical reimbursement decisions, while others have issued voluntary guidelines. An overview of the current state of pharmacoeconomic evaluation in selected European countries is provided in Figure 1.13.

Figure 1.13 Overview of pharmacoeconomic evaluation in selected European countries



In Ireland, a key element of the HTA process includes a pharmacoeconomic evaluation by the NPCE. The purpose of the pharmacoeconomic evaluation is to assess the overall cost-effectiveness of the new drug or technology and make a product reimbursement recommendation for the Irish health services. The number of evaluations undertaken by the NCPE has increased significantly in recent years, as displayed in Figure 1.14.

Figure 1.14 Number of NCPE pharmacoeconomic evaluations from 1998 to 2006



During 2005 and 2006, the NCPE undertook a total of 33 evaluations. The majority of these reports were individual product or price modulation reviews to support decisions on product reimbursement under the CD schemes. Of the 28 such reports, 13 products were accepted without modification, 2 were accepted with modifications, and the remaining 13 were rejected.

Pharmacoeconomic evaluations use the ICER to assess the cost-effectiveness of the product under review. The Irish ICER threshold is in the region of €45,000/QALY[33 - 38]. This implies that if a drug has an ICER of less than €45,000/QALY, the drug is cost-effective. The majority of drugs with an ICER less than €45,000, and a strong clinical case are reimbursed under the CD schemes. Above the €45,000/QALY threshold, the drug is

not deemed to be cost-effective. It may be reimbursed, however, due to the lack of alternative treatments or because it is a new innovative technological advance. Table 1.9 highlights some of the more recent pharmacoeconomic evaluations undertaken by the NCPE. The drug, clinical indication, ICER, and whether it was reimbursed under the CD schemes are included.

Table 1.9 Some Irish pharmacoeconomic evaluations

Drug	Clinical indication	ICER €/ QALY	Reimbursed
Spironolactone (Aldactone)	Heart failure	€400	Yes
Atorvastatin (Lipitor)	Secondary prevention CHD	€1,700	Yes
Atorvastatin (Lipitor)	Primary prevention CHD	€17,107	Yes
Rimonabant (Acomplia)	Anti obesity drug	€30,666	Yes
Natalizumab (Tysabri)	Multiple sclerosis	€39,800[1]	Yes[2]
Inhaled Insulin (Exubera)	Diabetes mellitus	€44,526	Yes[3]
Omalizumab (Xolair)	Asthma	€57,196	No
Sunitinib (Sutent)	GIST & mRCC	€57,280	Yes[4]

Source: National Centre for Pharmacoeconomics [33 - 38].
Key: ICER: incremental cost-effectiveness ratio, QALY: Quality-adjusted life-years, CHD: coronary heart disease, GIST: Gastro-intestinal stromal tumours, mRCC: metastatic renal cell carcinoma,.
1: Refers to therapy with interferon beta for the sub optimally treated subgroup, 2: confined to the hospital setting, 3: with a 15% price reduction, 4: new, innovative technological advance,

A review of the cost-effectiveness of spironolactone (Aldactone®) for heart failure produced an ICER of €400/QALY. This treatment was found to be extremely cost-effective and has been prescribed widely for many years.

The cost-utility of statin therapy for the primary prevention of CHD in Ireland also produced a highly cost-effective ICER of €17,107/QALY for atorvastatin (Lipitor®). This study is described in detail in chapter 4.

A pharmacoeconomic evaluation of natalizumab (Tysabri®) for the treatment of relapsing remitting multiple sclerosis was undertaken by the NPCE in April 2007[38]. A CUA, using a twelve-state Markov model with a one-year time cycle was constructed and run over twenty years. The base case analysis, taken from a societal perspective, demonstrated

natalizumab to be dominant as it was more effective and less expensive than the alternatives. A series of sensitivity analysis were conducted. The cost-effectiveness acceptability curve illustrated that the therapy was cost-effective 92% of the time, at the €45,000/QALY threshold. A budget impact analysis indicated that the total cost of treating patients with natalizumab would be in the region of €5.9 million in 2007, rising to over €16 million by 2011. The review found the drug to be borderline cost-effective (€39,800/QALY), and in view of the significant budget impact suggested that the drug be confined, initially, to the hospital setting.

A review of the cost-effectiveness of inhaled insulin (Exubera®) versus standard sub-cutaneous therapy for diabetic mellitus patients, produced an ICER of €44,526/QALY[34]. This was considered to be borderline cost-effective. When a budget impact assessment was undertaken it was shown that Exubera would have a substantial financial impact due to the high cost of the product and the large number of patients eligible for treatment. Following this evaluation, the manufacturers dropped the price of Exubera by 15% in advance of reimbursement under the CD schemes. Exubera has since been withdrawn from the Irish market due to low product uptake.

Finally, a review of omalizumab (Xolair®) indicated an ICER of €57,196/QALY. This was above the Irish ICER threshold and, hence, was not reimbursed under the High Tech Drug scheme.

1.5 Conclusion

In this chapter, the health economic concepts used in the analysis undertaken in this thesis were discussed. Economic evaluation was introduced including cost-of-illness, cost-effectiveness and cost-utility analysis. Decision analytic models such as decision tree and Markov models were explored. The use of the ICER in the decision making process was examined. Sensitivity analysis, used to assess uncertainty in the evaluations, was also discussed.

An overview of the Irish healthcare setting was provided including the main Irish data sources used in the economic analysis undertaken in this thesis. Casemix, the performance-related acute hospital activity programme was described as well as the CD schemes which provide valuable information on prescribing trends in the Irish community setting.

Health economics in the Irish healthcare setting was discussed. Organisations involved in the delivery of Irish health economic analysis were examined. Three significant health economic applications, which have a strong policy influence in the Irish healthcare setting were discussed, namely, the IPHA agreement, HTA guidelines and pharmacoeconomic evaluations.

Chapter 2

A cost-of-illness analysis of cardiovascular disease in Ireland

Chapter 2

2.1 Introduction

Cardiovascular disease (CVD) is the leading cause of death in Ireland[84]. The cost of treating CVD from an Irish health service perspective is estimated at €648m in 2005.

This chapter estimates Irish healthcare CVD treatment costs using a cost-of-illness analysis. CVD was chosen as it is the leading cause of death in Ireland and absorbs the highest proportion of healthcare resources of any of the MDCs. The cost of CVD from the Irish health service perspective is estimated focusing on acute hospital activity and drugs dispensed under the CD schemes. The data sources used include Casemix and the CD prescribing databases. The analysis used in this chapter can be adapted and applied to other care areas within the Irish health services, and may be particularly relevant in the area of cancer which is currently being restructured as a separate directorate within the Irish health services with its own budget and resources.

2.2 Cardiovascular disease

CVD is the principle cause of death in Ireland. CVD has a substantial impact on the patients' quality-of-life as well as the lives of their family and friends. Prevention and treatment of CVD, in line with the Irish Cardiovascular Health Strategy[85], has been very successful in recent years. This success, however, has come with significant healthcare costs. In Ireland, the treatment of CVD consumes more acute hospital bed days than any other disease category. CVD also has the highest drug cost and prescribing frequency of any medication group dispensed under the CD schemes.

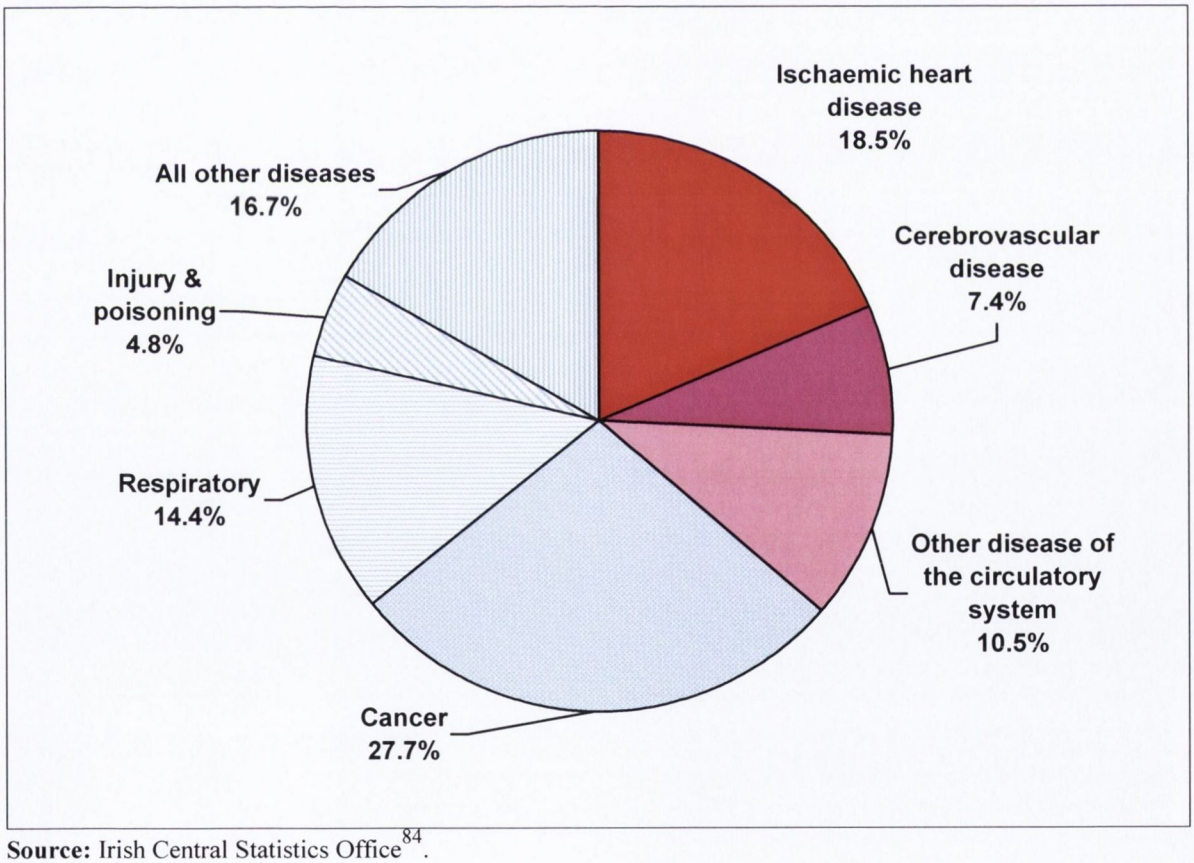
CVD is a disease of the heart, blood vessels, arteries and veins. CVD incorporates CHD, including heart attacks and cerebrovascular disease. A key aim of the WHO is lowering the incidence, morbidity and mortality of CVD. This can be achieved by reducing CVD risk factors and their determinants. It can also be achieved through the development of cost-effective healthcare innovations.

2.2.1 Cardiovascular trends

Over 17 million people, worldwide, die of CVD each year[86]. CVD is the largest cause of mortality in the EU, resulting in over 1.5 million deaths a year. This represents 40% of total mortality before the age of 75 years[87, 88]. CVD is also the largest cause of sickness, morbidity, and reduced quality-of-life for citizens of the EU[89].

CVD in the form of ischaemic heart disease, cerebrovascular disease, and other diseases of the circulatory system represented 36.4% of total mortality in Ireland in 2005, as illustrated in Figure 2.1.

Figure 2.1 Principal cause of death at all ages in Ireland in 2005



Source: Irish Central Statistics Office[84].

CVD mortality has been declining in recent years due to a combination of primary and secondary prevention, as well as medical and surgical treatments[90, 91]. There were 13,380 deaths from CVD in Ireland in 1999, which by 2005 had fallen to 9,984[84]. CHD mortality fell

by 47% in Ireland, between 1985 and 2000 with 3,765 fewer observed CHD deaths, in persons aged 25-82 years, in 2000[91]. Medical and surgical treatments together prevented, or postponed 1,640 deaths. This represented 44% of the observed decrease in mortality, with substantial contributions coming from specific treatments for secondary prevention, heart failure, and angina. Changes in the major CVD risk factors accounted for 48% of the total mortality decrease. A comparatively small reduction (4.6%) in population total cholesterol levels gave rise to the greatest decrease in mortality, consistent with previous research[92, 93].

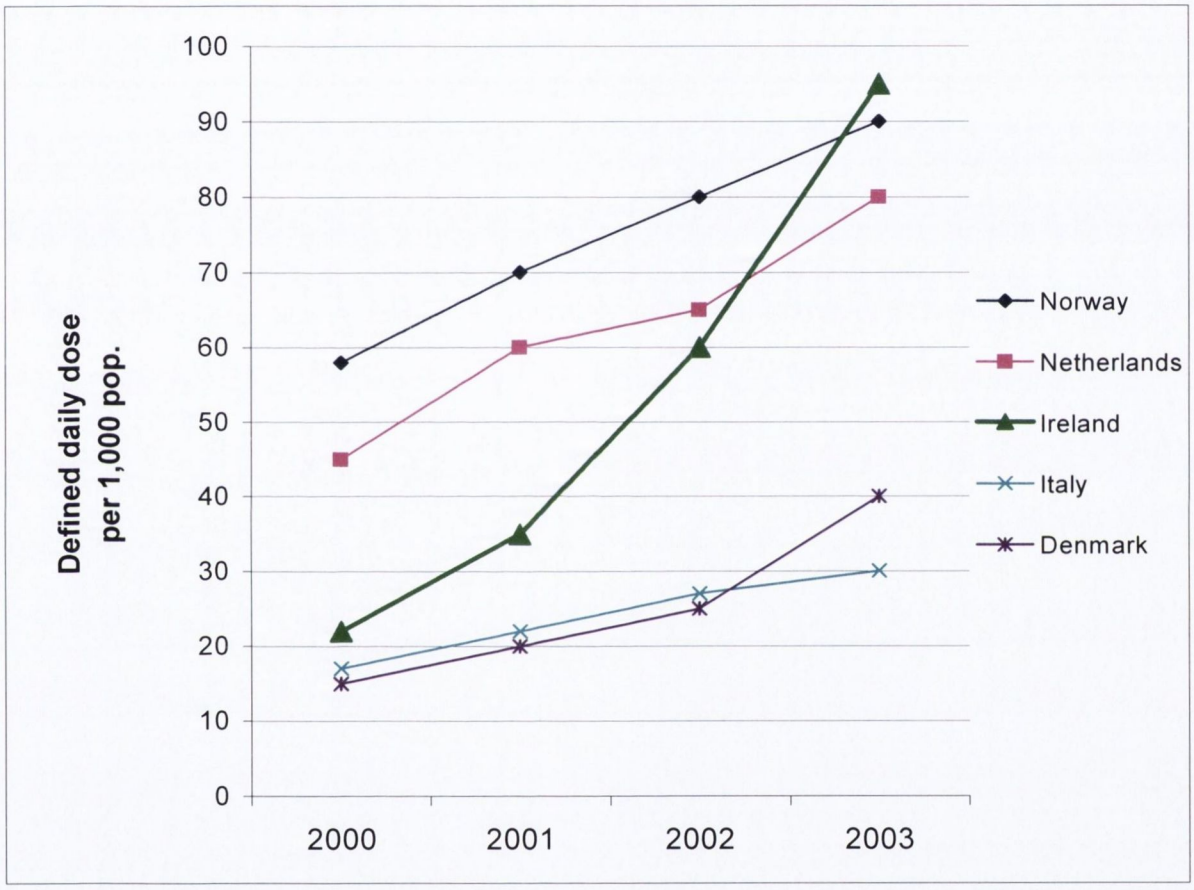
2.2.2 Statin therapy

Serum lipid reducing agents are used to reduce the relative risk of coronary events[94]. Statins are by far the most widely used serum lipid reducing agent with a market share ranging from 75% to 99% across the European countries[95] and global drug sales of nearly €24 billion in 2006[96]. Statin therapy delivers substantial benefits to patients. They are very effective for lowering low density lipoprotein (LDL) cholesterol levels. Statins have consistently proven to reduce the risk of all-cause, CVD, and, CHD mortality. They also reduce the risk of fatal and non-fatal myocardial infarction, non-fatal stroke, revascularisation procedures and unstable angina[97, 98, 99, 100, 101, 102, 103]. The relative risk of various coronary events, including death, has been shown to be reduced by 30% with statin therapy[104].

Statin therapy is used for both the primary and secondary prevention of CHD. Primary prevention statin therapy targets patients who have not experienced a cardiac event but are at increased risk of such events because of factors such as smoking, hypertension and diabetes mellitus. Secondary prevention statin therapy is recommended for all patients who have experienced a CVD event, unless contraindicated[105]. Statin therapy is well tolerated with few side effects and should be used in conjunction with lifestyle measures including diet, smoking cessation, and exercise, as well as other appropriate interventions such as adequate control of chronic conditions. Commonly prescribed statins include atorvastatin (Lipitor®), simvastatin (Zocor®). pravastatin (Lipostat®), fluvastatin (Lescol®) and rosuvastatin (Crestor®).

The use of statin therapy has increased rapidly in recent years. Figure 2.2 illustrates the increase in statin use in selected European countries including Ireland, measured by total defined daily dose (DDD) per 1,000 population covered by each national database.

Figure 2.2 Statin utilisation in selected European countries from 2000 to 2003



Source: Walley *et al.* Trends in prescribing and utilization of statins and other lipid lowering drugs across Europe 1997-2003[95].

Statin utilisation in Ireland increased from 26.54 DDD per 1,000 GMS population in 2000, to 99.29 DDD in 2003. This represented an increase of 274%, or 91% per annum. Over 70% of this increase was due to an increase in the number of patients' treatment days, as a result of more patients being treated. The remaining increase (29%) was attributed to an increase in the prescribed daily dose[95].

Statin therapy has been shown to be cost-effective for the primary and secondary prevention of CHD in Ireland[106, 107]. Other medical treatments such as angiotensin converting enzymes (ACE) inhibitors, beta blockers and spironolactone, have also been shown to be cost-effective in the Irish setting[108, 109] and should be considered, where appropriate.

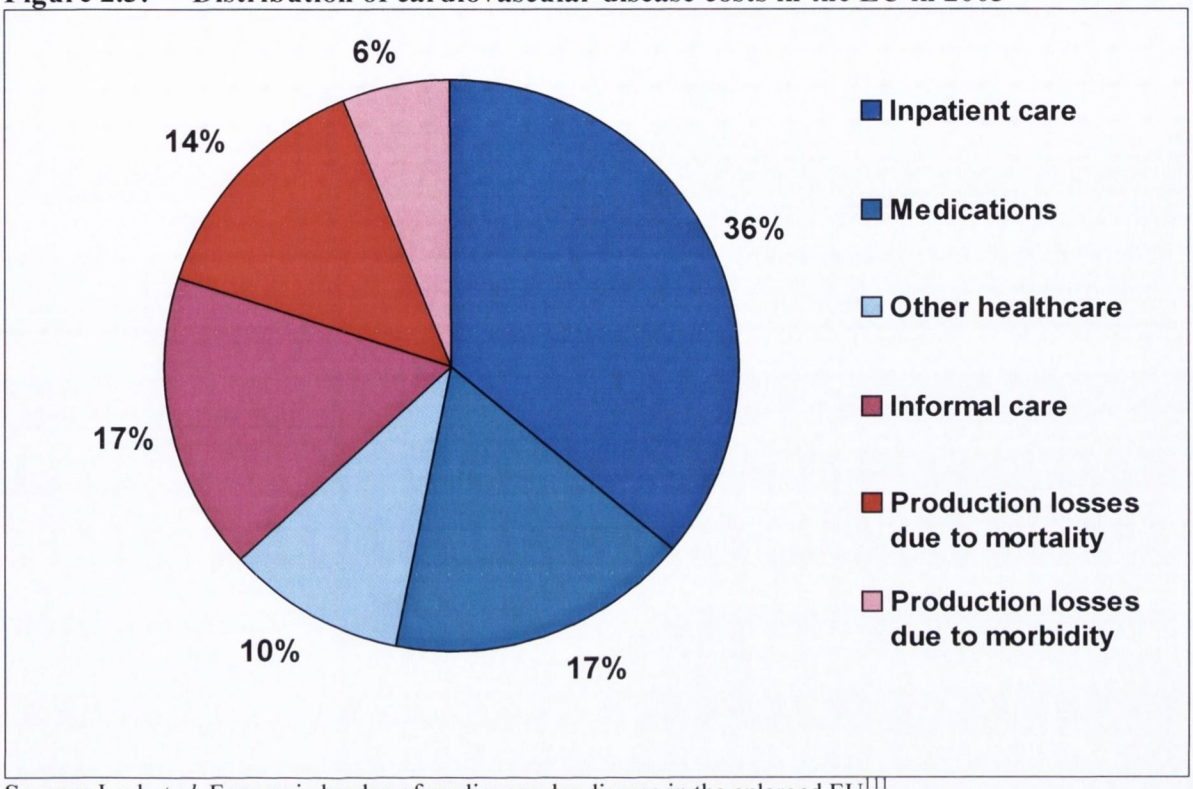
2.3 Cost of cardiovascular disease

2.3.1 International costs

In the US, the cost of CVD is estimated at $431.8 billion (€302bn) for 2007, more than twice the estimated cost of all cancers[110]. Two-thirds of the cost relates to direct healthcare provision, including hospital, nursing home, physician and drug costs. The largest component of the indirect costs is productivity losses due to mortality and is estimated at $112.3 billion (€79bn).

The cost of CVD in the EU was estimated at €169 billion in 2003[111]. Over €100 billion (62%) was spent on direct healthcare provision. The largest direct cost was for inpatient care (€60bn), which included the cost of 126 million hospital bed days. Medication costs were estimated at €28bn. The non-healthcare cost of CVD was estimated at €64 billion, 38% of the total cost. An estimated 268.5 million working days were lost due to CVD in the EU in 2003. Figure 2.3 details the distribution of these costs for the EU.

Figure 2.3: Distribution of cardiovascular disease costs in the EU in 2003



Source: Leal *et al.* Economic burden of cardiovascular disease in the enlarged EU[111].

2.3.2 Irish costs

CVD healthcare expenditure in Ireland is among the lowest in the EU. In 2003, Ireland allocated only 4.4% of its total healthcare budget to CVD care compared to an EU average of 12.0%[111]. Ireland spent €91 per person on CVD care, less than two-fifths of the EU average in the same year. Table 2.1 provides detail on CVD expenditure in selected EU countries in 2003.

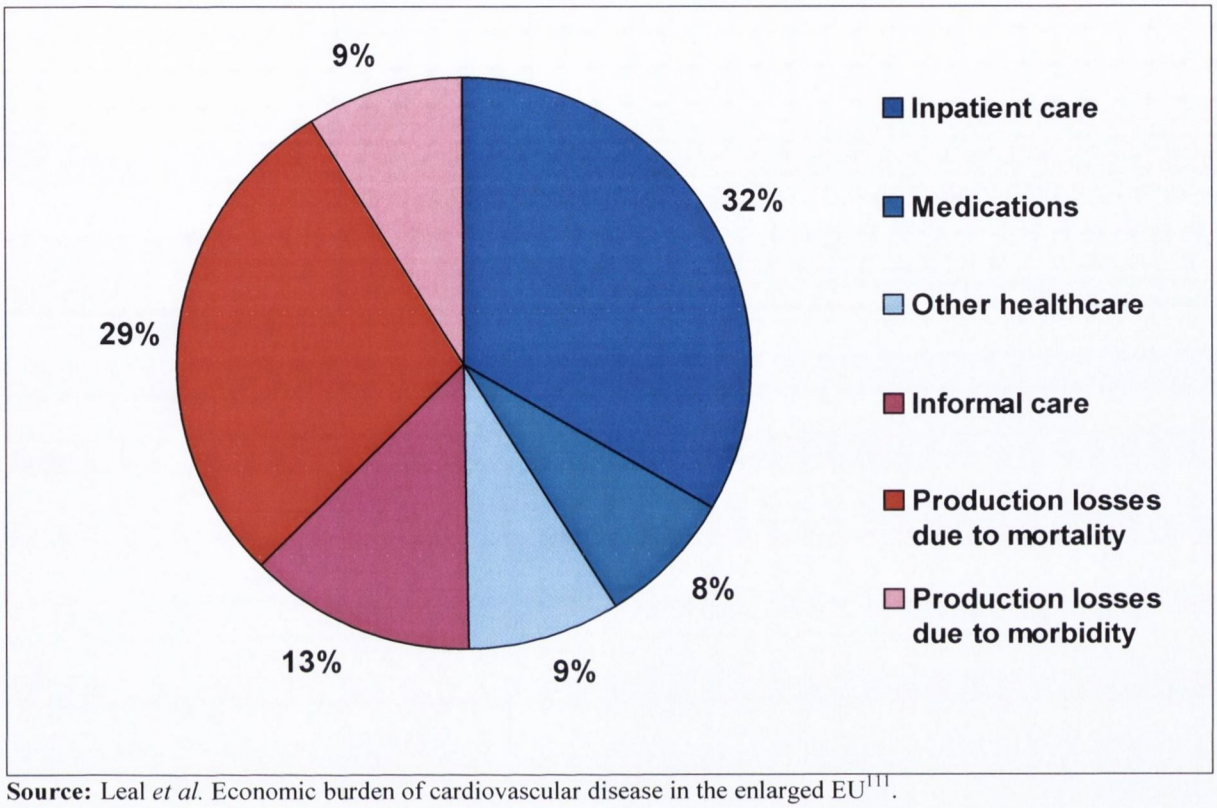
Table 2.1 Cardiovascular expenditure in selected EU countries in 2003

Country	Cardiovascular expenditure	
	% of health expenditure	per capita (€)
Ireland	**4.4**	**91**
Malta	2.0	38
France	8.4	198
UK	17.1	342
Germany	15.0	379
EU average	**12.0**	**230**

Source: Leal *et al.* Economic burden of cardiovascular disease in the enlarged EU[111].

The economic cost of CVD in Ireland, in 2003, was estimated at €866m[111]. This included healthcare costs of €429m and non-healthcare costs of €437m. The most significant component of the healthcare cost was inpatient care, including day cases, which was estimated at €288m, representing 33% of the total cost. Medication costs were the second largest healthcare cost followed by outpatient care, primary care, and A&E attendances. Total CVD non-healthcare costs included production losses due to mortality (€248m), informal care (€112m), and production losses due to morbidity (€77m). Figure 2.4 details the distribution of these Irish CVD costs in 2003.

Figure 2.4 Distribution of cardiovascular costs in Ireland in 2003



Source: Leal *et al.* Economic burden of cardiovascular disease in the enlarged EU[111].

2.4 Irish healthcare costs

In this section, an economic framework is established to estimate disease-specific treatment costs for the health service in Ireland. A cost-of-illness framework is used as a cost description with no comparison of alternative strategies is required. A CVD cost-of-illness study is undertaken from the Irish health service perspective in 2005. Irish acute hospital costs are examined in detail using the Irish Casemix system and other relevant sources. Cost estimates are produced for the four key areas of acute hospital activity, inpatient, day case, outpatient and A&E. The cost of CVD medications dispensed in the community is explored using the CD schemes database.

2.4.1 Hospital costs

In 2005, diseases and disorders of the circulatory system accounted for more than 83,000 cases and 489,000 bed days in Irish public hospitals. Over 65,000 CVD inpatient cases were undertaken at a cost of €323m[62]. Percutaneous coronary intervention without AMI but with a

stent(s), (DRG F15Z) had the highest expenditure of any CVD DRG at nearly €23m. Chest pain interventions, (DRG F74Z) were the most frequently performed CVD inpatient DRG with over 11,700 such cases undertaken in 2005. The ten most expensive CVD inpatient DRGs, including the number of cases, average length of stay, cost per case and total expenditure for Irish hospitals in 2005 can be seen in Table 2.2.

Table 2.2 Top ten cardiovascular inpatient Diagnostic Related Groups by expenditure in 2005

DRG	Description	No. of cases	Alos (days)	Cost per case €	Expenditure €m
F15Z	Percutaneous coronary intervention w/o AMI w stent	2,847	3.7	8,034	22.9
F62B	Heart failure and shock	4,420	9.8	4,241	18.7
F06A	Coronary bypass w/o invasive investigation	635	15.3	21,966	13.9
F74Z	Chest Pain	11,716	3.0	1,170	13.7
F71B	Non-major arrhythmia /conduction disorders	5,002	4.9	2,345	11.7
F60B	Circulatory disorders w AMI w/o invasive cardiac investigation procedures	2,272	8.0	5,065	11.5
F10Z	Percutaneous coronary intervention w AMI	809	7.1	13,686	11.1
F42B	Circulatory disorders w/o AMI w invasive cardiac investigation procedure w/o complex diagnostic procedure	2,552	4.9	3,923	10.0
F72B	Unstable angina	2,972	6.1	3,324	9.9
F73B	Syncope & collapse	4,745	4.5	1,942	9.2
	Total for top ten DRGs	**37,970**			**132.6**

Source: National Casemix programme database[62].
Key: Alos: average length of stay, A: with catastrophic or severe complications, B: without catastrophic or severe complications, Z: no differentiation made, w: with, w/o: without, AMI: acute myocardial infarction.
Note: Costs relate to 2006, activity to 2005.

The greatest proportion of Irish hospital CVD costs relate to pay. CVD nursing was the largest cost centre contributing 21% to the total CVD inpatient costs in 2005. When medical pay and allied health professionals were also included the pay costs rose to 42% of the total CVD costs. Table 2.3 presents the distribution of CVD inpatient costs for one of the largest Irish teaching hospitals in 2005.

Table 2.3 Distribution of cardiovascular inpatient costs for an Irish teaching hospital in 2005

Cost centre	% total cost	Cost centre	% total cost
Allied health professionals	5	Prosthesis	10
Intensive care unit	8	Nursing	21
Coronary care unit	10	Pharmacy	5
Imaging	3	Operating theatre	9
Pathology	4	Non-operating theatre	6
Medical pay	16	Blood	3

Source: National Casemix programme database[62].

The Irish Casemix programme can also be used to estimate the total cost of CVD day cases undertaken in Irish hospitals in 2005. Over 17,000 CVD day case procedures were undertaken in 2005 at a cost of nearly €19m. The most frequently performed day case which also resulted in the greatest expenditure of any CVD Day case Group (DG) in 2005 was circulatory disorders without AMI with invasive cardiac investigation procedure, DG F42. The top ten CVD day case groups by expenditure, undertaken in Irish hospitals in 2005, are shown in Table 2.4.

Table 2.4 Top ten cardiovascular Day case Group by expenditure in 2005

DG	Description	No. of cases	Cost per case €	Expenditure €m
F42	Circulatory disorders w/o AMI w invasive cardiac investigation procedure	6,484	1,250	8.1
F20	Vein ligation and stripping	1,213	1,821	2.2
F15	Percutaneous coronary intervention w/o AMI w stent	558	3,549	2.0
F12	Cardiac pacemaker implantation	245	3,353	0.8
F01	Implantation / replacement AICD	48	16,169	0.8
F71	Non-major arrhythmia & conduction disorders	1,242	424	0.5
F74	Chest Pain	2,039	227	0.5
F64	Skin ulcers circulatory disorders	360	1,093	0.4
F17	Cardiac pacemaker replacement	148	2,487	0.4
F10	Percutaneous coronary intervention w AMI	95	3,763	0.4
	Total for top ten DGs	**12,432**		**16.1**

Source: National Casemix programme database[62].
Key: AMI: acute myocardial infarction, AICD: arrhythmia implantable cardioveter defibrillator, w: with, w/o: without.
Note: Costs relate to 2006, activity to 2005.

The total hospital cost of CVD activity includes CVD outpatient appointments, and CVD A&E visits. Unfortunately, the Irish Casemix programme does not segregate outpatient and A&E activity by MDC. Therefore, estimates from Leal *et al.* were used to approximate the number of CVD outpatient appointments (80) and A&E visits (36) per 1,000 population in Ireland[111]. The average cost of an outpatient appointment and A&E visit from the Casemix system for 2005 was €150 and €227, respectively. Therefore, the cost of this activity was estimated at €50m for CVD outpatient appointments and €34m for CVD A&E visits.

Combining CVD hospital activity and costs provides an estimate of the total Irish hospital costs for CVD in 2005, as displayed in Table 2.5.

Table 2.5 Irish hospital cardiovascular costs in 2005

Patient setting	No. of episodes	Total costs €m
Inpatient	65,000	323
Day case	17,000	19
Outpatient	328,000	50
Accident & Emergency	148,000	34
Total		**€426m**

Note: Costs relate to 2006, activity to 2005.

Table 2.5 produces an estimate of €426m for all CVD activity in Irish hospitals in 2005. The most significant component of these costs was for inpatient care estimated at €323m. The greatest volume of activity took place in the outpatient setting with 328,000 CVD episodes in 2005.

The estimates produced in this chapter related to 2005 costs and are greater than the 2003 costs examined by the international study detailed earlier. The use of national information sources as opposed to international databases[112, 113] also facilitated a more detailed examination and assessment of total Irish CVD costs.

2.4.2 Community Drugs costs

The Irish CD schemes contain information on the cost and frequency of CVD drugs dispensed in the community setting in Ireland in 2005. CVD drugs have the highest cost of any drug group dispensed under these schemes, accounting for nearly one quarter of the schemes' total ingredient costs. They are also the most frequently prescribed medications dispensed under the HSE CD schemes with nearly 12.1m prescriptions recorded in 2005, as illustrated in Table 2.6.

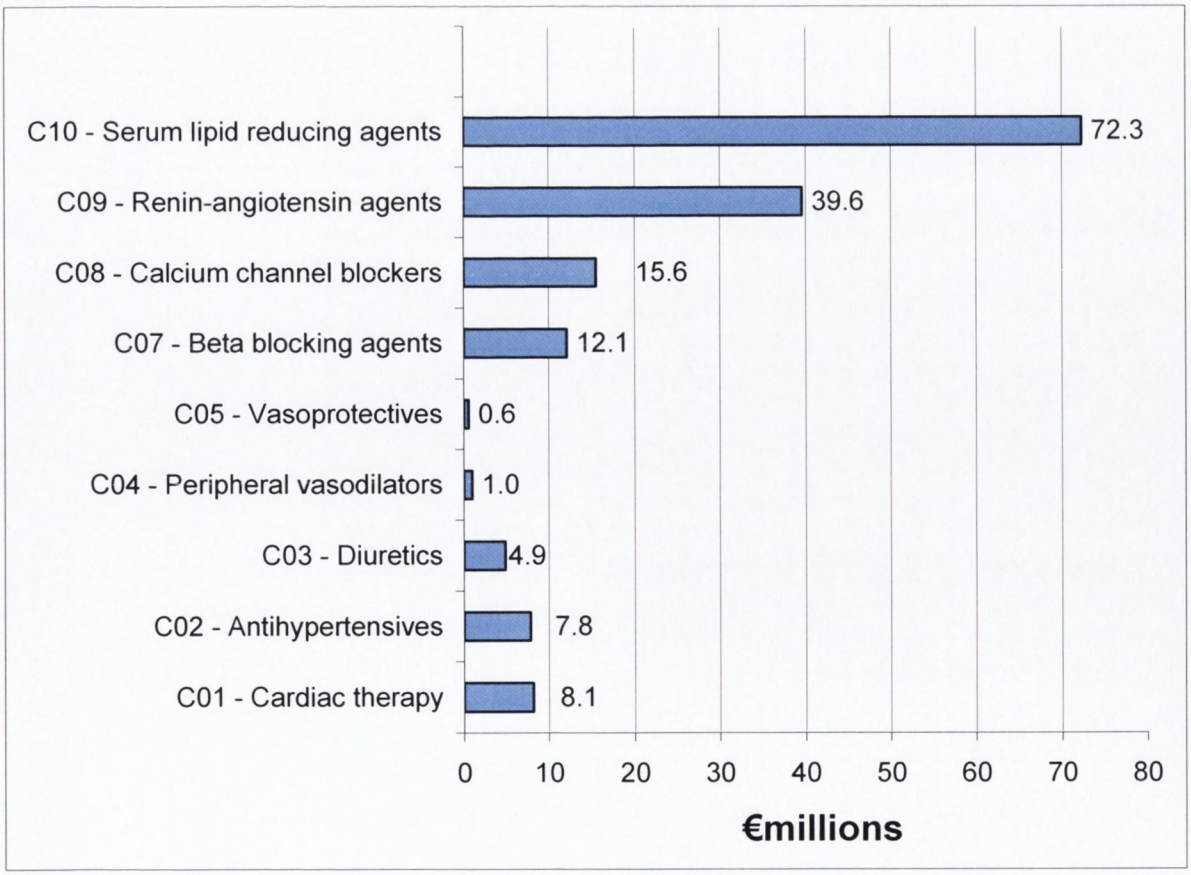
Table 2.6 Distribution of cardiovascular medicines under the Community Drugs schemes in 2005

Scheme	Prescribing frequency	% of total scheme	Ingredient cost €	% of total scheme
GMS	9,377,404	25.0	162,026,128	24.4
DPS	2,683,640	25.4	59,916,357	25.7
Total	**12,061,044**		**221,942,485**	

Source: National Shared Services Primary Care Reimbursement Service[65].

The ingredient cost of CVD drugs dispensed under the CD schemes in 2005 was nearly €222m with the GMS scheme contributing €162m. CVD medications dispensed under the GMS scheme can be examined by drug class, as illustrated in Figure 2.5.

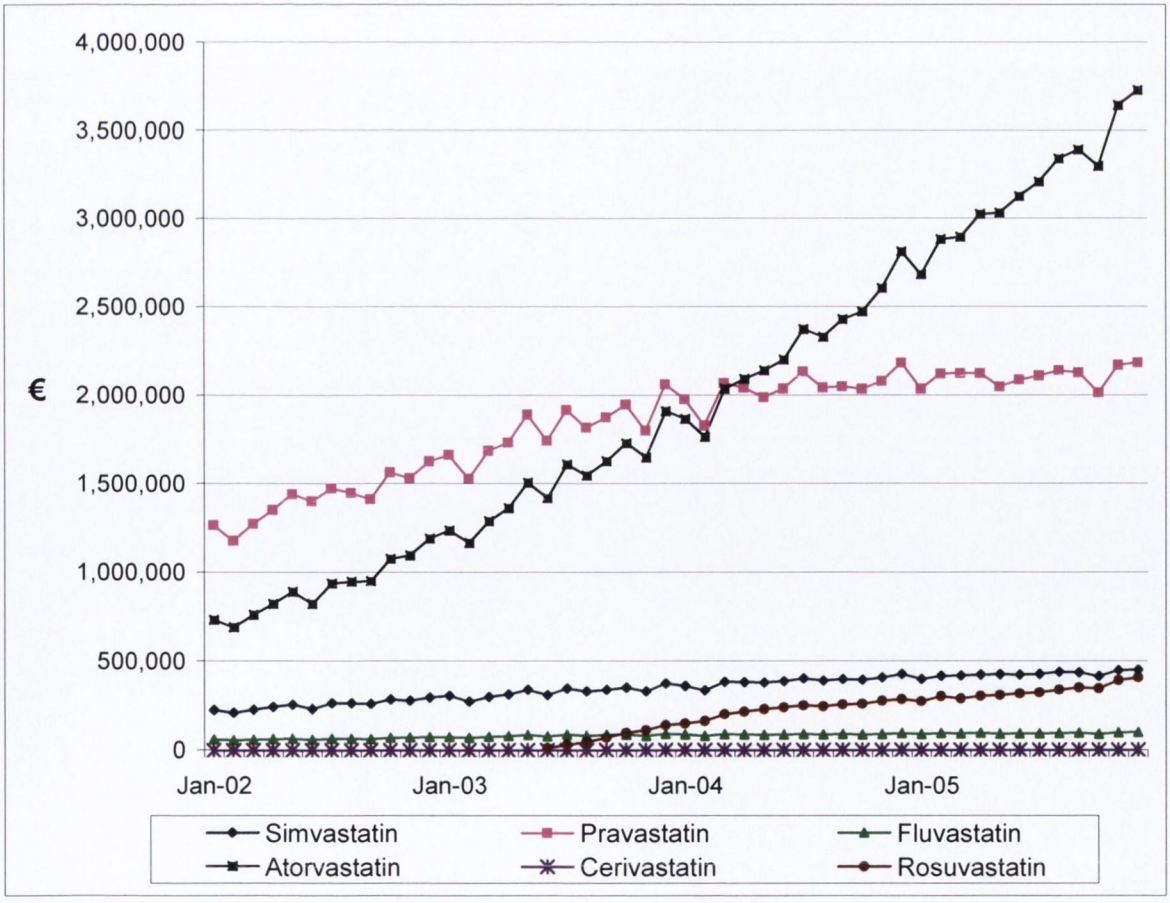
Figure 2.5 Cardiovascular expenditure by drug class under the GMS scheme in 2005



Source: National Shared Services Primary Care Reimbursement Service[65].

Serum lipid reducing agents (C10) contributed most to the cost of CVD drugs with an annual cost of €72.3m. This represented 45% of the total cost of all CVD medications in 2005. Statins are the most commonly prescribed serum lipid reducing agent in Ireland. The ingredient cost of statins, under the GMS scheme, was €69m in 2005, consuming over 10% of the total GMS budget. Atorvastatin had the highest expenditure of any product dispensed under this scheme, with an ingredient cost of €36.5m. Pravastatin was the third most expensive product dispensed under the GMS scheme in the same year, at a cost of €24.2m. Figure 2.6 illustrates the increase in the monthly ingredient cost for all statins under the GMS scheme from 2002 to end 2005.

Figure 2.6 Statin ingredient cost under the GMS scheme from 2002 to 2005



Source: National Shared Services Primary Care Reimbursement Service[65].

In the month of December 2005, expenditure on atorvastatin, alone, was €3.7m having increased from €729,000 in January 2002. The monthly expenditure on pravastatin was €2.2m in December 2005. Expenditure on all other available statins was significantly lower.

Other Irish healthcare costs should also be included in a cost-of-illness study. Community based costs, in addition to the cost of drugs dispensed under the CD schemes should be assessed. Unfortunately, due to the lack of data it is not possible to accurately estimate this activity, nor the associated costs. This resulted in an under-estimation of the total cost of CVD from an Irish health service perspective as related activity such as GP visits, community diagnostic tests and other primary care services were not included.

The total health service cost of CVD in Ireland in 2005 was estimated in this chapter at €648m. The framework derived in this chapter examined both hospital and community drugs CVD costs as shown in Table 2.7.

Table 2.7 Irish health service cardiovascular costs in 2005

Health service area	Data Source	Cost €m
Hospitals	Casemix	426
Community Drugs	Community drugs database	222
TOTAL		**€648m**

2.5 Conclusion

In this chapter a cost-of-illness analysis was developed to estimate disease-specific treatment costs from the perspective of the Irish health service. This was the first time such an analysis has been undertaken on CVD in Ireland. The approach taken in this chapter may also be useful in estimating the cost of care for other diseases within the Irish health services, such as cancer, which is currently being restructured into a separate directorate requiring the identification of all budgets and resources required to deliver the current level of care.

The healthcare cost of treating CVD in Ireland in 2005 was estimated at €648m. Over €420m was attributable to hospital costs with diseases and disorders of the circulatory system

accounting for more that 84,000 cases and 489,000 bed days in 2005. Over 65,000 CVD inpatient cases were undertaken in Irish public hospitals at a cost of €323m. The CVD DRG with the highest total expenditure was percutaneous coronary intervention without AMI but with a stent(s), at a cost of nearly €23m. Over 17,000 CVD day case procedures were also undertaken in 2005, at a cost of nearly €19m. The cost of CVD outpatient and A&E activity was also estimated at €50m and €34m respectively.

The CD schemes contributed a further €222m to the total direct healthcare costs of CVD in Ireland, €162m of which related to the GMS scheme. Serum lipid reducing agents, which include statins, contributed most to the cost of CVD drugs. The ingredient cost of statins, under the GMS scheme, was €69m in 2005, consuming over 10% of the GMS budget.

Chapter 3

A cost-effectiveness analysis of proton pump inhibitor triple therapy regimens for Helicobacter pylori eradication

Chapter 3

3.1 Introduction

Helicobacter pylori (H. pylori) is a human pathogen and a recognised causative agent of gastritis and peptic ulcer disease. Treatments using proton pump inhibitor (PPI) triple therapy are recommended as the standard of care for the eradication of H. pylori[114].

This chapter undertakes an economic evaluation to examine the cost-effectiveness of PPI triple therapy regimens for H. pylori eradication in the community setting in Ireland in 2003. A cost-effectiveness analysis is considered the most appropriate approach, as the aim of the analysis is to establish the least costly method of meeting the same objective, namely, the cost per asymptomatic patient. Decision tree modelling, over a single time period, is used to construct the model as a graphical illustration of all possible alternative regimens is required. Utilisation data from the GMS scheme is used as a proxy for effectiveness in the model. The use of real-world data to populate the model is a significant component of this evaluation and is used to estimate the cost-effectiveness of PPI triple therapy in the Irish community setting.

3.2 Background

The role of H. pylori as a major cause of dyspepsia and gastro duodenal disease is well established[115, 116]. Dyspepsia, often referred to as indigestion, is a common medical symptom which affects up to 40% of the adult population in any one year, with about 10% of the population seeking advice from their GP[117]. Dyspepsia is a major cause of morbidity and economic loss in the community[118], and also has a significant impact on the patients' quality of life[119]. The benefits of eradicating H. pylori include healing of gastritis, enhanced ulcer healing, reduction or elimination of ulcer recurrence, and prevention of peptic ulcer disease[120, 121, 122]. The eradication of H. pylori is a major component of various guidelines for the management of dyspepsia, including the American Gastroenterology Association[123], the Digestive Health Foundation in the US[124], the Maastricht H. pylori consensus meeting in Europe[125], the Canadian H. pylori consensus conference[126], two Asian-Pacific consensus meetings[127, 128], and the British Society of Gastroenterology[129] guidelines.

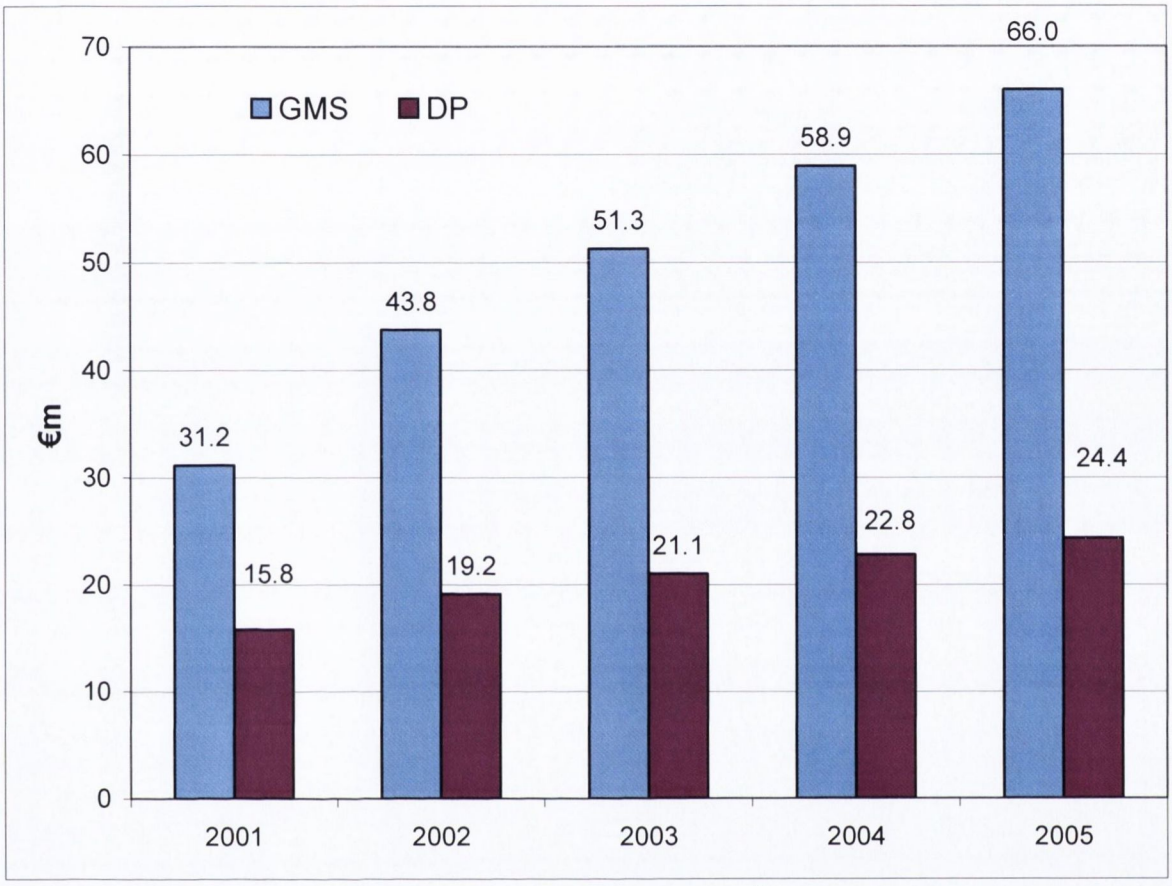
The management of dyspepsia and related diseases consume considerable health resources. In 2005, over 13% of all Irish hospital inpatient discharges, nearly 66,000 cases, and a further

77,000 day cases were attributable to diseases of the digestive system[62]. Over 440,000 acute hospital bed days, 11.5% of the total allocation of bed days, was consumed by diseases of the digestive system. Over €106m, or 16% of the ingredient costs, of the GMS scheme related to the alimentary tract and metabolism in the same year.

Patients with dyspepsia can be treated with PPIs or H_2 receptor antagonists (H_2RAs). Although they have higher acquisition costs, PPIs have been found to be more efficacious than H_2RAs both in terms of the rate, and the time taken to heal[130, 131]. Treatments using PPIs combined with two antibiotics for one week is recommended as the standard of care for the eradication of H. pylori[114].

Recently, concerns have arisen over rising prescription rates and costs of PPIs[132]. In the US, sales of PPIs in 2005 were nearly $13 billion (€9bn)[133]. In Ireland, nearly 10% (€90m) of the CD schemes were for PPIs in 2005, having increased from €8m in 1995. Figure 3.1 illustrates expenditure on PPIs under the two main Irish CD schemes from 2001 to 2005.

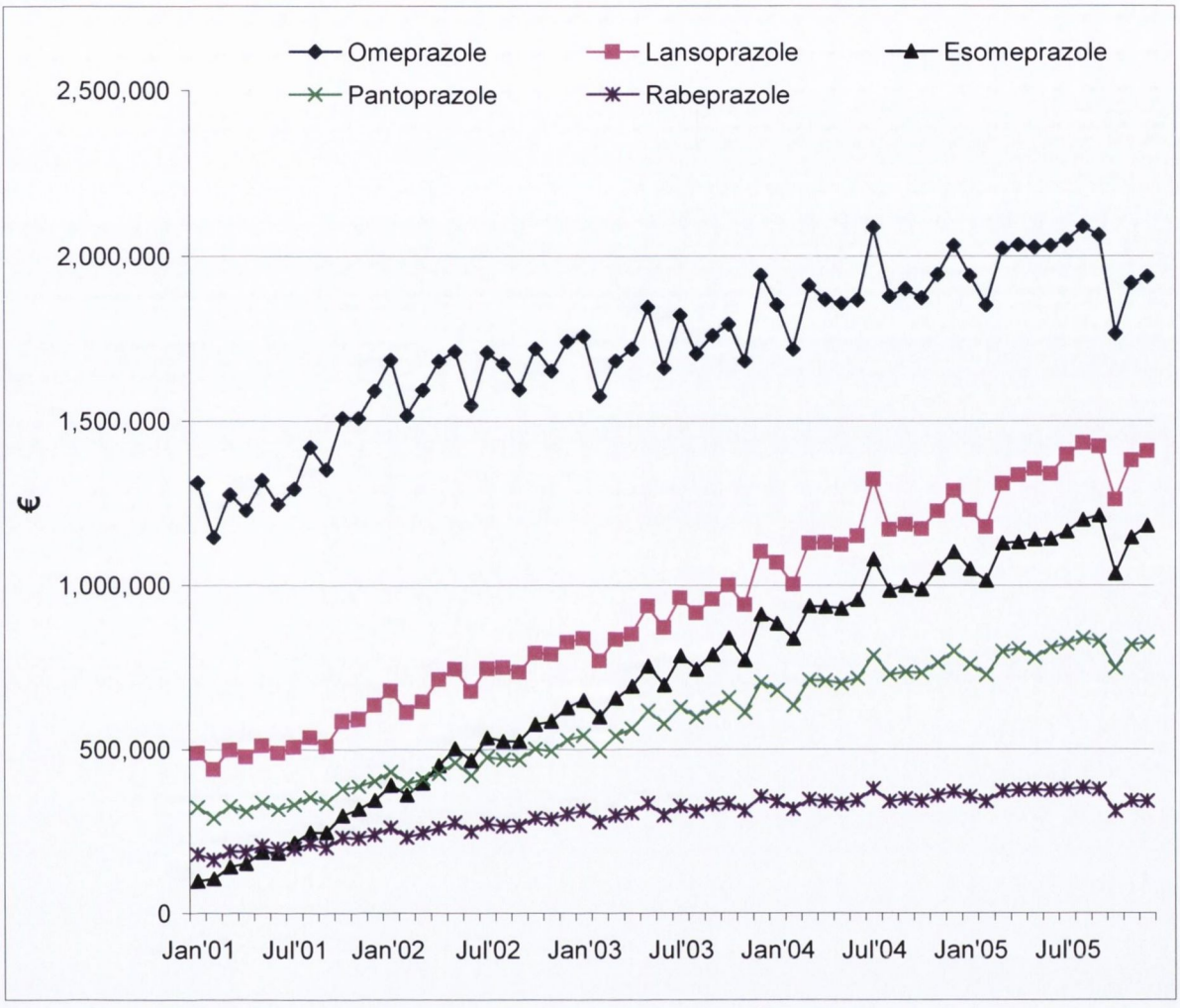
Figure 3.1 PPI expenditure under the GMS and DP schemes from 2001 to 2005



Source: National Shared Services Primary Care Reimbursement Service[65].

With the exception of statins, PPIs are the most expensive drug group reimbursed under the Irish CD schemes. The PPIs currently available in Ireland include omeprazole (Losec mups®), lansoprazole (Zoton®), esomeprazole (Nexium®), pantoprazole (Protium®), and rabeprazole (Pariet®). Omeprazole had the highest ingredient cost of any individual drug dispensed under the GMS scheme from 1995 until 2002, and in 2005 alone had an annual ingredient cost of €23.7 million. The monthly ingredient cost of all individual PPIs, under the GMS scheme, from 2001 to 2005 is provided in Figure 3.2.

Figure 3.2 PPI ingredient costs under the GMS scheme from 2001 to 2005

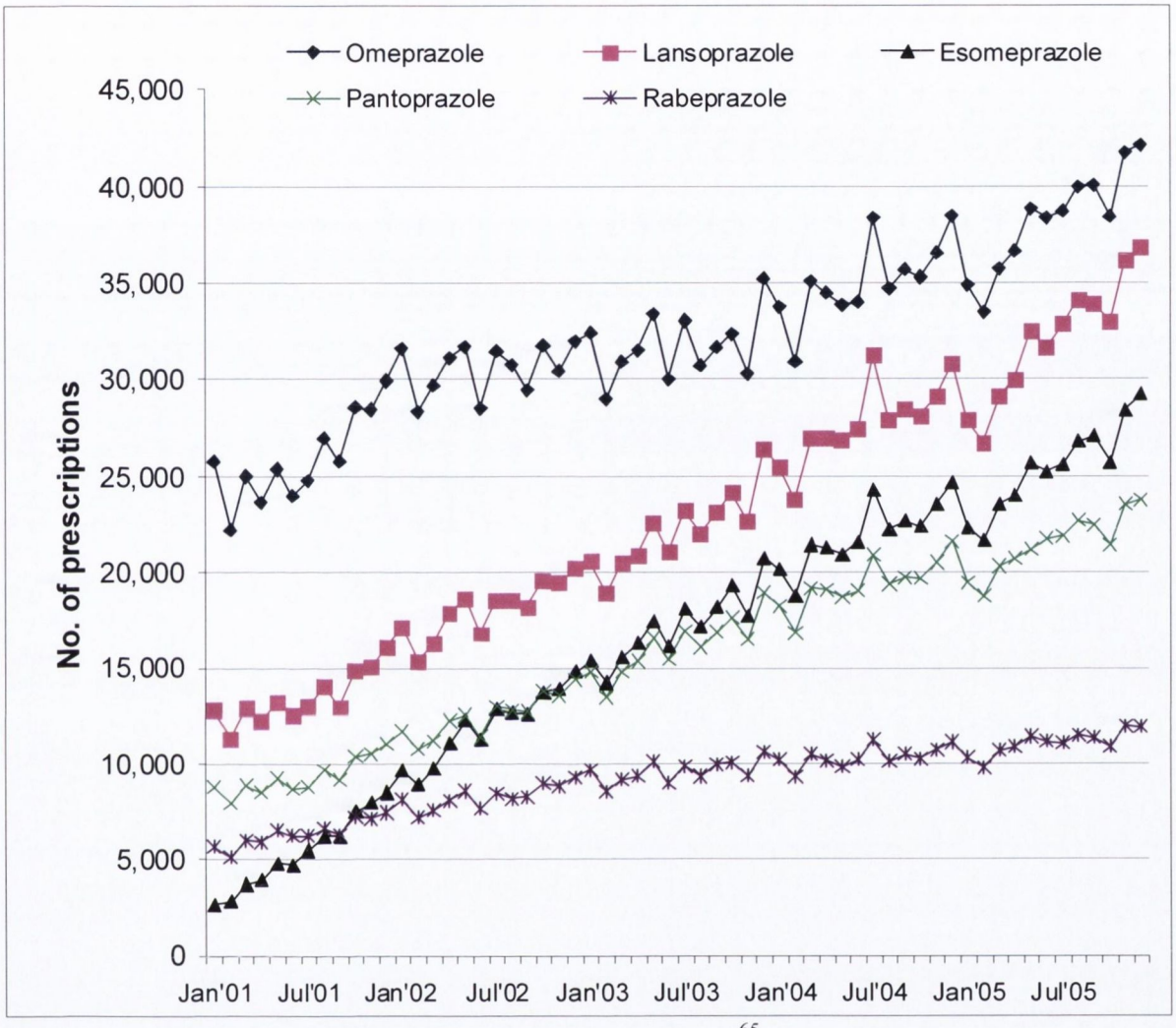


Source: National Shared Services Primary Care Reimbursement Service[65].

The monthly expenditure on omeprazole increased by 48%, from €1.3m in January 2001 to €1.9m in December 2005. Lansoprazole had the second highest monthly expenditure at €1.4m, by the end of 2005. The greatest increase in expenditure over the period studied was for esomeprazole, which increased from under €100,000 to €1.2m.

The number of PPI prescriptions also increased significantly over this period with omeprazole remaining the most commonly prescribed PPI as illustrated in Figure 3.3.

Figure 3.3 PPI prescriptions under the GMS scheme from 2001 to 2005



Source: National Shared Services Primary Care Reimbursement Service[65].

Collectively the number of PPI prescriptions increased from 55,000 in January 2001 to over 143,000 in December 2005. By the end of 2005, the number of PPI prescriptions for omeprazole was 42,081, followed by lansoprazole with 36,836 prescriptions. The greatest increase in prescriptions was for esomeprazole, which finished the period with 29,235 prescriptions in December 2005.

The eradication of H. pylori has proven to be cost-effective in patients with dyspepsia compared to an array of other interventions[134, 135, 136, 137, 138, 139, 140]. NICE issued guidelines for the use of PPI's in the treatment of dyspepsia advocating the use of the least expensive or most

cost-effective PPI[117]. The comparative cost-effectiveness of individual PPIs in the Irish setting has been identified as an area requiring further review[141, 142].

The aim of this chapter is to conduct an economic evaluation to examine the cost-effectiveness of PPI triple therapy regimens for H. pylori eradication in the community setting in Ireland. Decision tree analysis using Treeage® is used to develop the model. All PPI triple therapy prescriptions recorded under the GMS scheme for the ERHA in 2002 are reviewed and tracked for a one-year period. GMS utilisation data is used as a proxy for PPI triple therapy effectiveness. Prescriptions which did not result in subsequent anti-ulcer prescriptions following the initial or second dose of triple therapy are deemed to be effective. Failure of therapy is defined as the subsequent receipt of prescription(s) for an anti-ulcer drug such as maintenance PPI therapy or H_2RA therapy. Costs and effects are collected as patients go through the model with the cost-effectiveness of therapy defined as the weighted average cost of therapy divided by the effectiveness for each PPI examined.

3.3 Methods

3.3.1 Regimens

An economic model in the form of a cost-effectiveness analysis of PPI triple therapy regimens for H. pylori eradication in Ireland in 2003 was constructed. Each regimen involved a seven day treatment with a PPI along with the antibiotics amoxycillin (Amoxil®) and clarithromycin (Klacid LA®) as the first-line treatment. The PPIs included in the model were omeprazole (Losec mups®), lansoprazole (Zoton®), esomeprazole (Nexium®), pantoprazole (Protium®), and rabeprazole (Pariet®). The generic omeprazole preparations Ulcid, Losamel, Lopraz, and Losepine were also included in the model.

Second-line treatment, where required, included 3 options. One further week of PPI triple therapy with the antibiotics amoxycillin (Amoxil®) and metronidazole (Flagyl 400®), maintenance PPI therapy; or, H_2RA (Ranitidine®) maintenance therapy. Doses were taken from the GMS database and represent actual prescribing patterns. All medications were prescribed in accordance with British national formulary[143] guidelines due to the absence of an Irish equivalent.

The GMS prescription database for the largest region, formerly the Eastern Regional Health Authority (ERHA) was examined. This region comprises of Dublin, Kildare and Wicklow and has a population of 1.4m, of which 339,000 (24%) were eligible for the GMS scheme. A total of 2,229 PPI triple therapy prescriptions, on the same prescription note, were identified in the region during 2002 and tracked for a one-year period.

3.3.2 Patient states

Four patient states were identified for each PPI regimen:

1. The patient is deemed asymptomatic if they do not require further related medication therapy;
2. The patient is symptomatic, and is prescribed a second course of weekly PPI triple therapy;
3. The patient is symptomatic, and is prescribed maintenance PPI therapy; and,
4. The patient is symptomatic, and is prescribed maintenance H_2RA therapy.

Patient states 1, and 4, do not have any further sub-states. Patients in state 2, may reside in one of three sub-states:

- One, they may become asymptomatic after the second course of triple therapy and require no further therapy;
- Two, they may remain symptomatic and be prescribed maintenance PPI therapy. This may be prescribed in low, medium or high dose for the original PPI, or they may switch PPIs for the maintenance phase of treatment; or,
- Three, they may remain symptomatic and be prescribed maintenance H_2RA therapy.

Patients in state 3, remain symptomatic and are prescribed maintenance PPI therapy as per state 2 but without a second course of PPI triple therapy.

The number of prescriptions per patient state, the maintenance dose and the number of patients who switched PPIs was recorded for each PPI triple therapy regimen. The average duration of the PPI maintenance phase and the H_2RA maintenance phase was calculated from the GMS database by summing the duration of the relevant maintenance phase for each prescription and

dividing by the number of maintenance phase prescriptions for that PPI regimen. The average duration is recorded in days and can be no longer than one year as this is the duration for which all initial PPI triple therapy prescriptions were tracked. Outcomes for branded and generic omeprazole preparations were assumed similar as the small number of generic preparations did not facilitate further scrutiny.

3.3.3 Costs

Only direct costs relating to the community setting were included in the model as the perspective of the study was the health service primary care payer. All medication costs refer to ingredient costs only and were determined from the Monthly Index of Medical Specialities 2005[144]. These costs are shown in Table 3.1.

Table 3.1 PPI medication costs in 2005

PPI regimen	Triple therapy (€ weekly cost)		Maintenance phase (€ daily cost)		
	Initial (Cost_AC)	Second (Cost_CM)	Low Dose (CostPPI_l)	Medium Dose (CostPPI_m)	High Dose (CostPPI_h)
Losamel	54.12	59.04	1.38	1.38	2.76
Ulcid	60.70	54.62	1.07	1.07	2.14
Lopraz	60.75	54.67	1.03	1.03	2.06
Esomeprazole	61.49	53.29	1.12	n/a	1.73
Rabeprazole	62.98	53.78	0.74	n/a	1.16
Losepine	64.76	58.68	0.68	1.36	2.72
Pantoprazole	65.42	57.22	0.76	n/a	1.40
Lansoprazole	69.04	60.84	0.85	n/a	1.53
Omeprazole branded	70.58	64.60	0.94	1.77	3.54

Source: Medical Publications Ireland. Monthly Index of Medical Specialities[143].
Key: _: refers to the appropriate PPI, A: Amoxycillin, C: Clarithromycin, M: Metronidazole, l: low dose, m: medium dose, h: high dose, n/a: not available.

Table 3.1 includes abbreviations used in the economic model. The cost of the initial triple therapy was denoted by Cost_AC where _ was substituted by the first letter of the relevant PPI. For example, the cost of an initial one week course of PPI therapy with rabeprazole was

represented by CostRAC. The daily cost of maintenance PPI therapy varied depending on the dose prescribed. All PPIs had low and high dose preparations, however, omeprazole also had medium dose preparations. The daily cost of low and high dose rabeprazole maintenance phase therapy was represented by CostPPIRl and CostPPIRh, respectively.

From Table 3.1 it can be seen that the weekly ingredient cost of initial PPI triple therapy with rabeprazole was €62.98 (CostRAC). If a second course of rabeprazole triple therapy was prescribed the weekly cost was €53.78 (CostRAM). The daily maintenance cost for low dose rabeprazole was €0.74 (costPPIRl) and €1.16 (costPPIRh) for the higher dose. The branded omeprazole preparation examined refers to Losec mups.

The H_2RA maintenance therapy was administered at a daily cost of €0.43 ($costH_2RA$). An alternative average daily maintenance PPI cost of €1.44 (costAltPPI) was used for patients who switched PPIs during the maintenance phase of treatment. The cost of a GP consultation was set at €40 (costGP) and it was assumed that patients attended their GP prior to the initiation of medication and in advance of any changes to their medication. A H. pylori test was administered if patients remained symptomatic post the initial triple therapy. The cost of the H. pylori test was set at €60 (costHPtest).

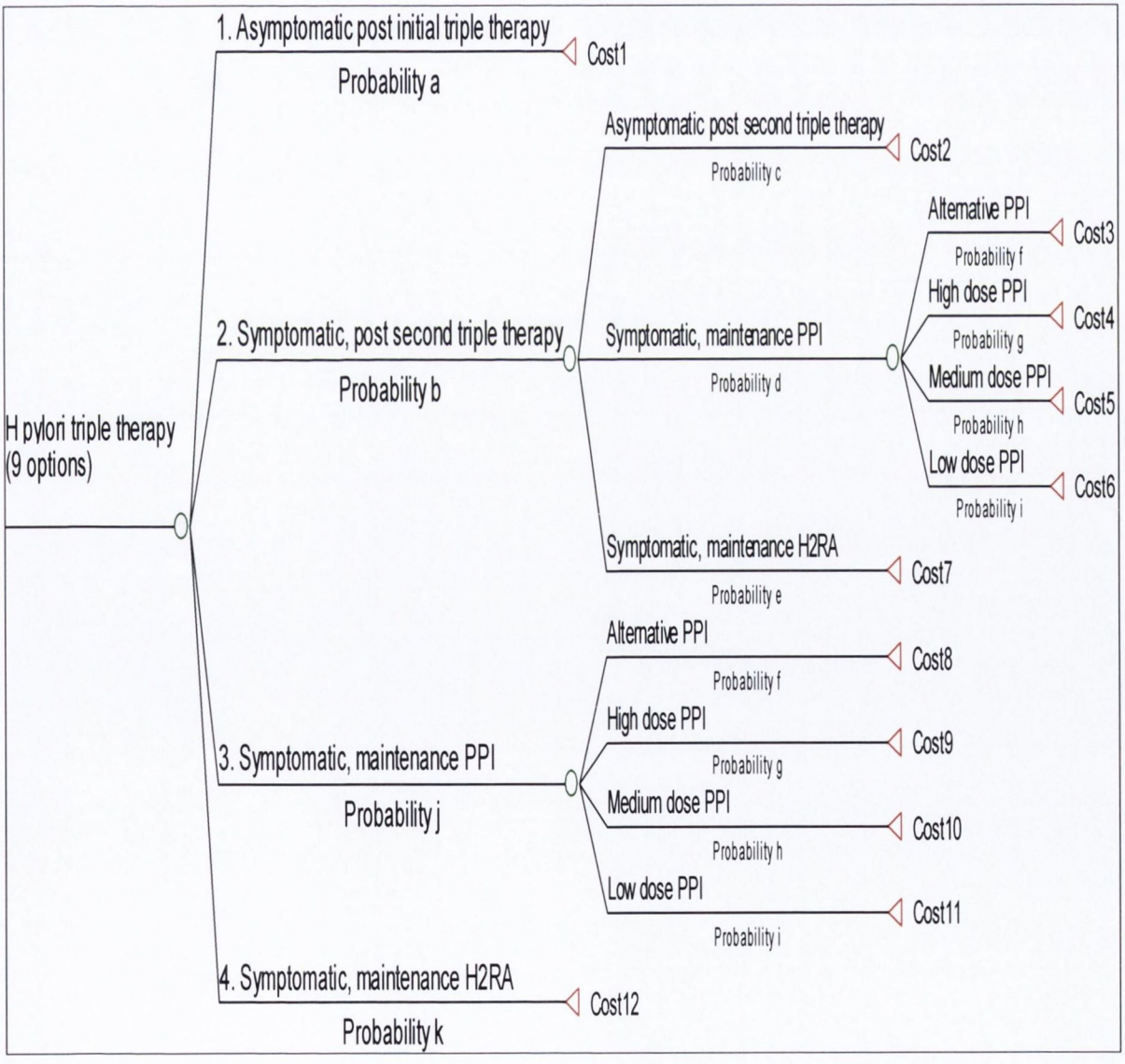
3.3.4 Effectiveness

The effectiveness of each PPI triple therapy regimen was inferred from drug utilisation data taken from the GMS database as patient outcomes are not recorded in this database. Effectiveness was defined as the lack of subsequent anti-ulcer prescriptions following PPI triple therapy. Therapy was deemed effective if no further anti-ulcer related prescriptions were required after either the initial or second course of triple therapy. Failure of therapy was defined as the subsequent receipt of prescription(s) for an anti-ulcer drug, such as maintenance PPI or H_2RA. The number of PPI prescriptions for each patient state, and sub-state were used to generate patient probabilities and effectiveness.

3.3.5 Building the model

All patients who received PPI triple therapy, in the ERHA in 2002, were included in the model and tracked for a one-year period. The basic structure of the decision tree model used to examine the cost-effectiveness of PPI triple therapy regimens for H. pylori eradication is presented in Figure 3.4.

Figure 3.4 Decision tree model for the cost-effectiveness of PPI triple therapy regimens for Helicobacter pylori eradication



The four patient states were identified by the four arms of the model. Patients in state 1, were deemed asymptomatic and did not require any further related medication after the initial treatment. This is illustrated in the top arm of the model. The associated costs include a GP visit and seven days of initial PPI triple therapy and is represented by Cost1. The probability of this event is represented by probability a.

Patients in state 2, were not relieved of symptoms following the initial course of triple therapy and were prescribed a second course of triple therapy. This is illustrated by the second arm of the model. One of three sub-states is open to these patients:

- One, the patient may become asymptomatic. The associated costs for these patients include an initial and second course of PPI triple therapy, 2 GP visits and a H. pylori test. This is represented by Cost2. The associated probability is calculated by probability b * probability c, where probability b is the probability of a patient being symptomatic and being prescribed a second dose of weekly PPI triple therapy. Probability c is the probability that the patient is cleared of all symptoms following the second dose of triple therapy;
- Two, the patient may remain symptomatic and be prescribed maintenance PPI therapy. Costs include the initial and second course of triple therapy, 3 GP visits and a H. pylori test as well as the cost of the maintenance PPI phase which depends on the PPI used, the dose and the duration of the maintenance phase. These costs are represented by Cost3 through to Cost6. The probability is calculated as probability b * probability d * the relevant probability f – i.; and,
- Three, the patient may remain symptomatic and be prescribed maintenance H_2RA therapy. This cost is represented by cost7, which includes the initial and second weekly course of triple therapy, 3 GP visits, a H. pylori test and H_2RA maintenance therapy. The probability of this event is calculated as probability b * probability e.

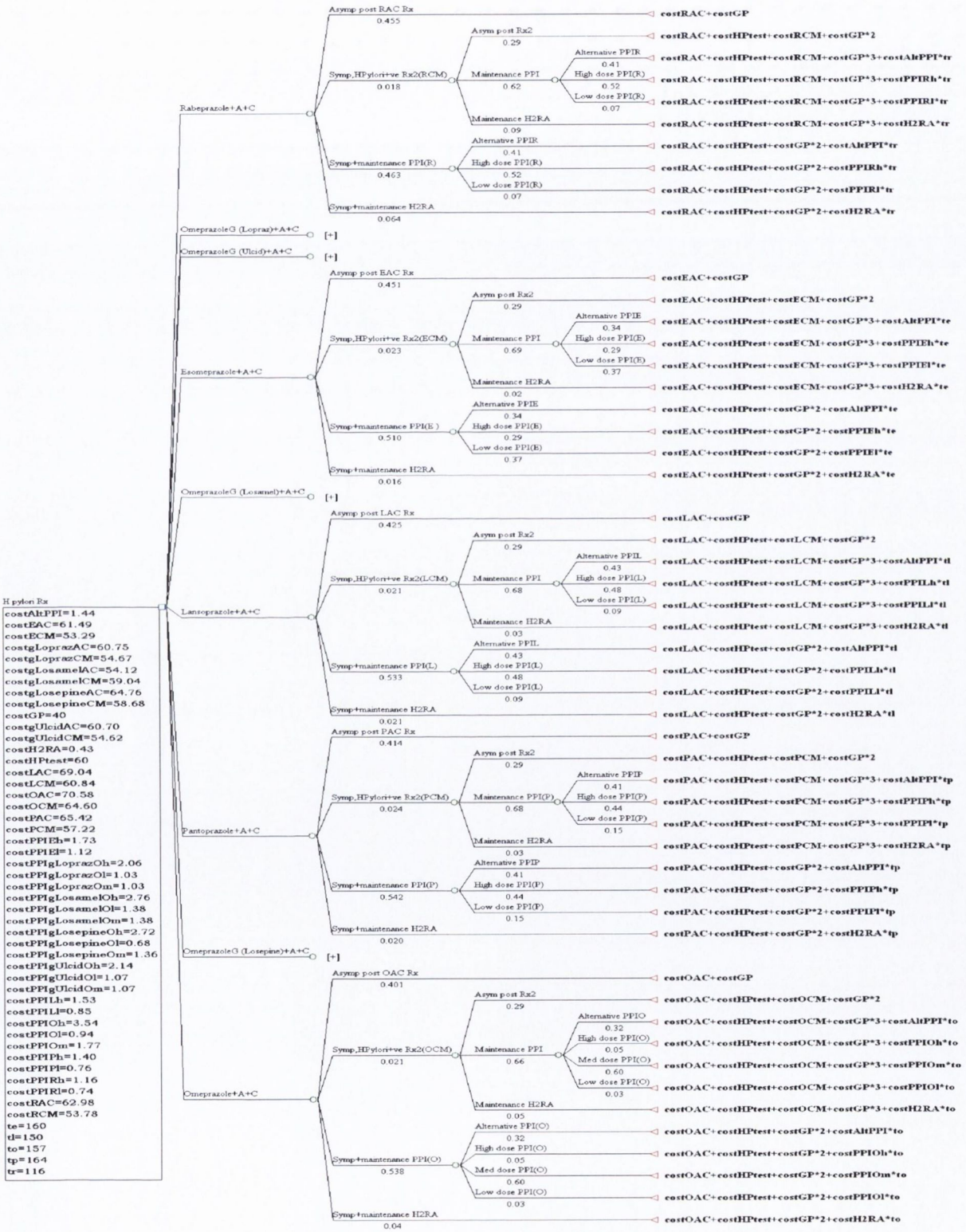
Patients in state 3, as illustrated by the third arm of the model, remain symptomatic after the initial PPI triple therapy and were prescribed maintenance PPI therapy. The costs were similar to the costs for patients prescribed maintenance PPI therapy in the second arm of the model

but exclude the second course of triple therapy. The probabilities are calculated as probability j * the relevant probability f – i.

Finally, patients in state 4 remain symptomatic after the initial PPI triple therapy and were prescribed maintenance H_2RA therapy, as illustrated by the fourth arm of the model. The cost is represented by cost12 and includes the initial triple therapy, 2 GP visits, a H. pylori test and the H_2RA maintenance therapy. The associated probability is probability k.

The detailed model is presented in Figure 3.5. All five branded PPI preparations including their costs and probabilities are shown. The sub-trees for the four generic omeprazole preparations are collapsed for display purposes only. The model was run by sending the appropriate number of patients down each arm of the model. The model's results include up to twelve costs and twelve probabilities for each PPI regimen depending on the patient's symptoms and the subsequent course of action prescribed. The model can be 'rolled back' to display the weighted average cost for each PPI regimen.

Figure 3.5 Decision tree model for the cost-effectiveness of PPI triple therapy regimens for Helicobacter pylori eradication in Ireland in 2003



3.3.6 Calculating cost-effectiveness

To calculate the cost effectiveness of each PPI triple therapy regimen the weighted average cost of therapy is divided by the effectiveness. This can be represented as follows:

$$\text{Cost-effectiveness } PPI_x = \frac{\text{Weighted average cost of } PPI_x}{\text{Effectiveness of } PPI_x}$$

3.3.7 Sensitivity analysis

Sensitivity analysis was performed to identify the robustness of the model and the most important variables affecting the cost-effectiveness results. One-way sensitivity analysis was undertaken on the initial cost of PPI triple therapy. Costs were reduced by 35% reflecting the impact of the new IPHA agreement. One-way sensitivity analysis was also undertaken on the effectiveness of the regimens, using the upper and lower estimates of the 95% confidence intervals (CIs), and the duration of the PPI maintenance phase. Two-way sensitivity analysis was conducted on the initial cost of PPI triple therapy and the duration of the maintenance phase.

3.3.8 Potential for savings

Prescribing only the most cost-effective PPI triple therapy regimen could result in substantial savings. Substituting the most cost-effective regimen for all other regimens produces an average saving per prescription. Applying this saving to the total number of prescriptions for each PPI regimen in 2005, estimates the potential annual savings under the GMS scheme in the same year.

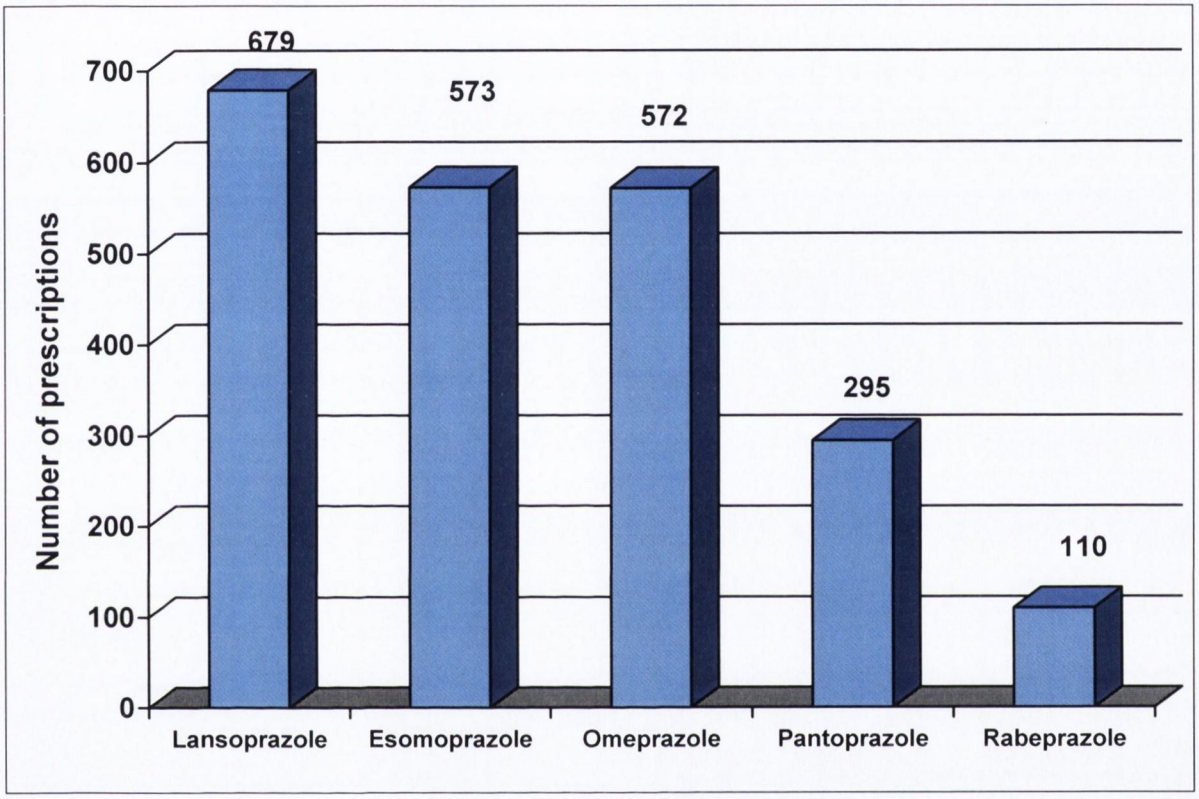
3.4. Results

3.4.1 Strategies

The most frequently prescribed PPI triple therapy strategy, in this study, included lansoprazole. Of the 2,229 prescriptions analysed 679, or 30.5% of all prescriptions included lansoprazole as part of the triple therapy regimen. Esomeprazole and omeprazole were prescribed with similar levels of frequency at 573 and 572 prescriptions, respectively. Pantoprazole and rabeprazole were less frequently prescribed at 13.2% and 4.9% of the total

prescriptions, respectively. Figure 3.6 shows the number of prescriptions examined in this analysis for each PPI triple therapy regimen in the ERHA in 2003.

Figure 3.6 PPI triple therapy regimen prescriptions in the ERHA in 2003



Even though omeprazole was the most frequently prescribed PPI regimen under the GMS scheme at the time of the study, a greater number of lansoprazole prescriptions were examined in this analysis. This is as a result of the greater increase in lansoprazole prescriptions and the concentration on new PPI triple therapy prescriptions only.

3.4.2 Outcomes

The patient state probabilities for each PPI regimen are presented in Table 3.2.

Table 3.2 Patient state probabilities by PPI triple therapy regimen

	Rabeprazole	Esomeprazole	Lansoprazole	Pantoprazole	Omeprazole
1. Asymptomatic post initial therapy	0.455	0.451	0.425	0.414	0.401
2. Symptomatic, 2nd triple therapy	0.018	0.023	0.021	0.024	0.021
3. Symptomatic, maintenance PPI	0.463	0.510	0.533	0.542	0.538
4. Symptomatic, maintenance H_2RA	0.064	0.016	0.021	0.020	0.040
TOTALS	**1.000**	**1.000**	**1.000**	**1.000**	**1.000**

Table 3.2 displays the probability of the four patient states for each PPI regimen. The probability of a patient being asymptomatic post initial omeprazole triple therapy was 0.401. This was the lowest asymptomatic rate of all PPI regimens examined. The triple therapy including rabeprazole displayed the most favourable asymptomatic rate, at 0.455. The majority of patients were symptomatic post the initial triple therapy and were prescribed maintenance PPI therapy.

Table 3.3 provides the probabilities for patients prescribed a second course of triple therapy. Only 0.29, or 29% of prescriptions for a second course of triple therapy did not result in further related prescriptions compared to over 40% after the initial triple therapy. Again, the majority of patients were prescribed maintenance PPI therapy.

Table 3.3 Patient sub-state probabilities following second PPI triple therapy

	Rabeprazole	Esomeprazole	Lansoprazole	Pantoprazole	Omeprazole
Asymptomatic	0.29	0.29	0.29	0.29	0.29
Symptomatic, maintenance PPI	0.62	0.69	0.68	0.68	0.66
Symptomatic, maintenance H_2RA	0.09	0.02	0.03	0.03	0.05
TOTALS	**1.00**	**1.00**	**1.00**	**1.00**	**1.00**

Table 3.4 provides the probabilities for patients prescribed maintenance PPI therapy. The probability of switching PPIs for the maintenance phase of treatment ranged from 0.32 to 0.43, depending on the initial PPI prescribed. The dose level prescribed also varied significantly by PPI. Only 0.03 or 3% of the omeprazole prescriptions were for a low dose of the preparation versus 0.37, or 37% for esomeprazole. Omeprazole was the only PPI to have a medium dose for the maintenance phase of treatment.

Table 3.4 Patient sub-state probabilities following maintenance PPI triple therapy

	Rabeprazole	Esomeprazole	Lansoprazole	Pantoprazole	Omeprazole
Alternative	0.41	0.34	0.43	0.41	0.32
High dose	0.52	0.29	0.48	0.44	0.05
Medium dose	-	-	-	-	0.60
Low dose	0.07	0.37	0.09	0.15	0.03
TOTALS	**1.00**	**1.00**	**1.00**	**1.00**	**1.00**

3.4.3 Patient pathways

The number of prescriptions per patient pathway is shown in Figure 3.7.

Figure 3.7 Number of prescriptions per patient pathway

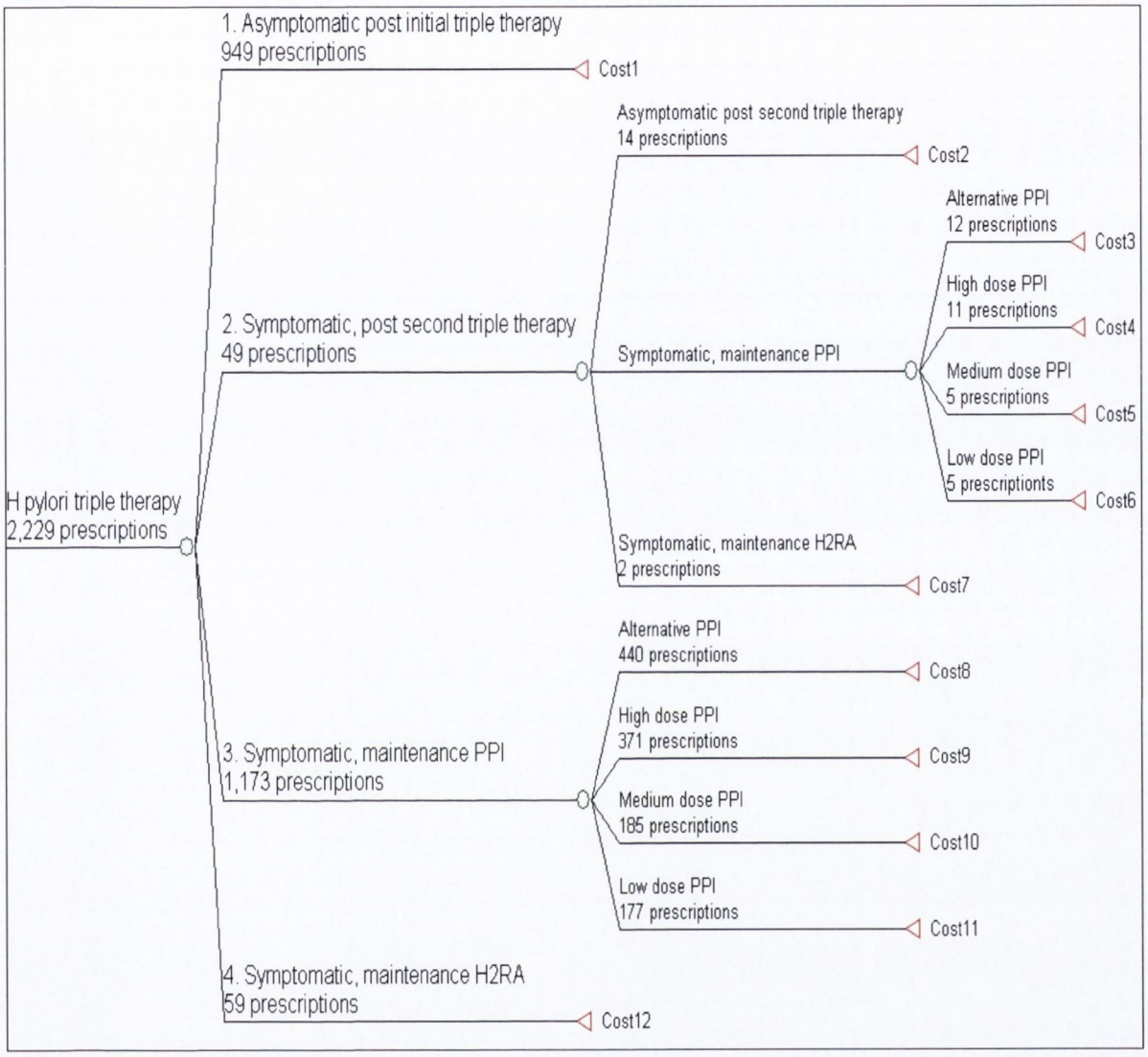
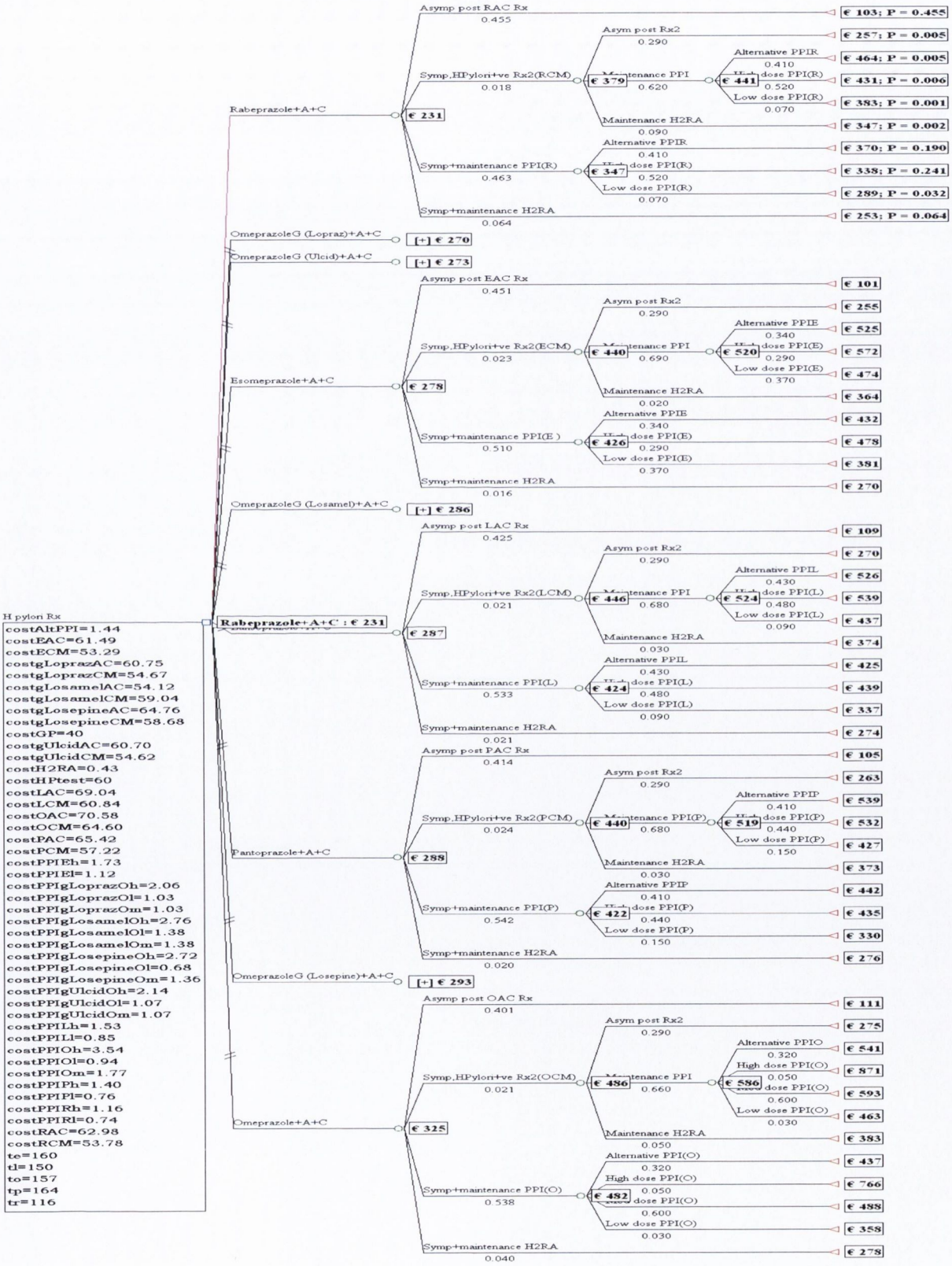


Figure 3.7 shows that of the 2,229 prescriptions for PPI triple therapy only 949 (42.6%) prescriptions did not generate further anti-ulcer prescriptions following the initial triple therapy regimen. Of the 49 prescriptions for a second course of triple therapy, only 14 of these were deemed asymptomatic post treatment. The majority of prescriptions, 1,173, were for maintenance PPI therapy. Only 59 (2.6%) of the 2,229 prescriptions examined were for maintenance H_2RA therapy.

3.4.4 Costs

The cost of treating patients with PPI triple therapy varied greatly depending on the PPI regimen prescribed, the dose, the patients' symptoms and the strategy adopted. Figure 3.8 displays the costs of each patient state and sub-state for each PPI triple therapy regimen. The cost for the generic omeprazole preparations are collapsed for display purposes only.

Figure 3.8 PPI triple therapy regimen costs in 2005



Patients prescribed rabeprazole triple therapy incurred one of ten costs depending on the patients' symptoms, the dose and the strategies adopted. These costs varied from €103 to €464. Patients prescribed omeprazole incurred one of twelve costs including a medium dose of maintenance therapy. The weighted average patient costs, as well as the lowest and highest costs for each PPI regimen is presented in Table 3.5.

Table 3.5 PPI triple therapy regimen patient costs in 2005

PPI regimen	€ Average cost	€ Low cost	€ High cost
Rabeprazole	231	103	464
Lopraz	270	101	619
Ulcid	273	101	631
Esomeprazole	278	101	572
Losamel	286	94	726
Lansoprazole	287	109	539
Pantoprazole	288	105	539
Losepine	293	105	730
Omeprazole branded	325	111	871

The most favourable average patient cost was for rabeprazole at €231. The next most favourable average costs were for the generic omeprazole preparations Lopraz (€270), and Ulcid (€273). The highest average cost was for branded omeprazole (Losec mups) at €325. Losamel had the most favourable low patient cost at €94. The PPI strategy including rabeprazole had the most favourable high patient cost at €464. Branded omeprazole had the highest cost across all three categories.

3.4.5 Effectiveness

The effectiveness of PPI triple therapy for H. pylori eradication was defined as asymptomatic post the initial, or second course of triple therapy. Due to the absence of patient outcome data, GMS utilisation data was used as a proxy for the effectiveness of therapy. The effectiveness of each PPI triple therapy regimen, including the associated 95% CI, is provided in Table 3.6.

Table 3.6 PPI triple therapy regimen effectiveness in 2003

PPI regimen	Effectiveness	Confidence Interval
Rabeprazole	0.460	0.37 – 0.55
Esomeprazole	0.458	0.42 – 0.50
Lansoprazole	0.431	0.39 – 0.47
Pantoprazole	0.421	0.37 – 0.48
Omeprazole	0.407	0.37 – 0.45

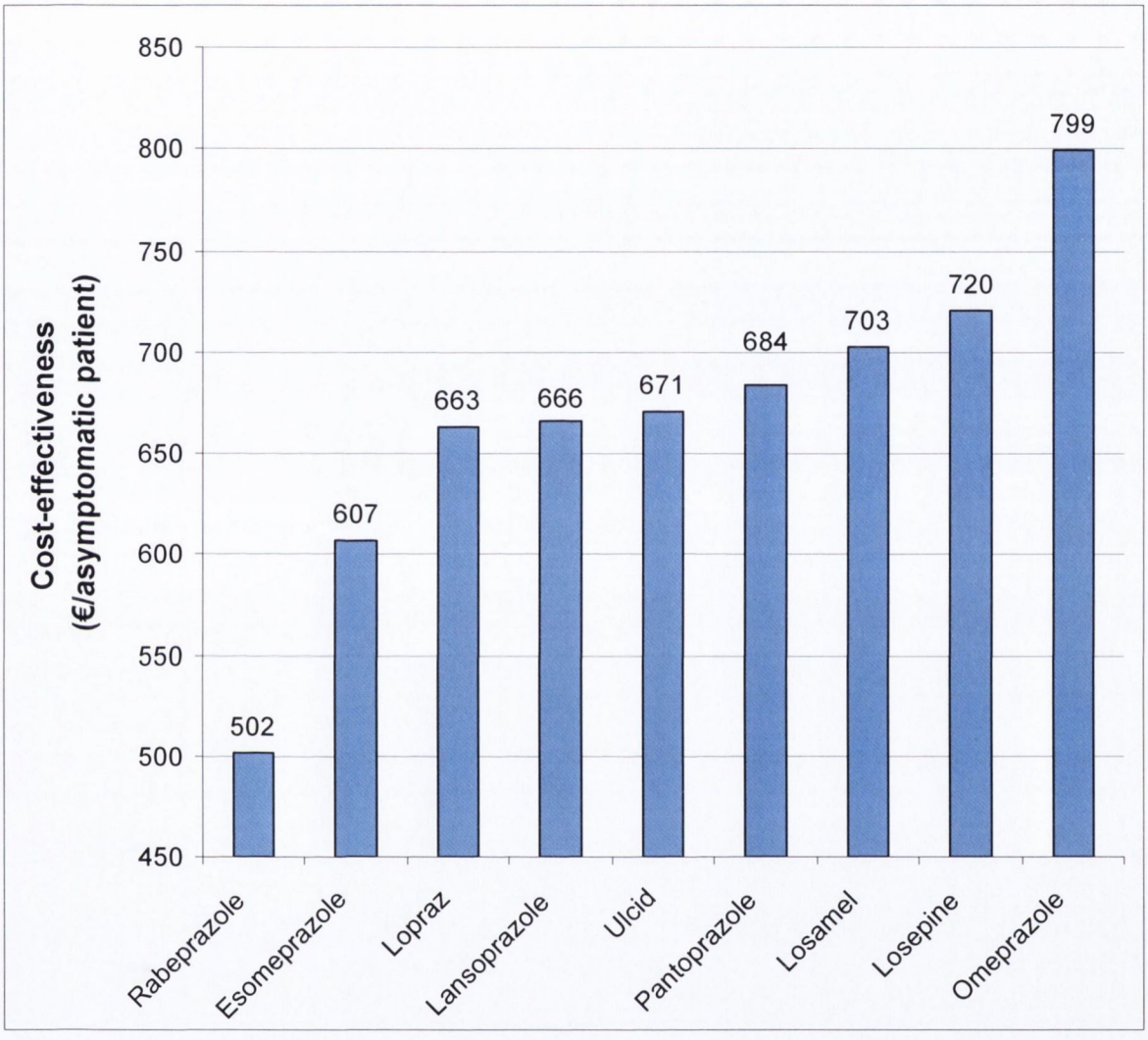
The most effective PPI, under the GMS scheme in 2003 was rabeprazole with an effectiveness rate of 0.460. This means that 46% of prescriptions did not result in any further H. pylori related medication prescriptions in the year post rabeprazole triple therapy. Alternatively, 54% of patients who were prescribed rabeprazole triple therapy required further related medication in the following year. The second most effective PPI triple therapy included esomeprazole at 0.458. The least effective therapy included omeprazole at 0.407 implying that 59.3% of patients prescribed omeprazole triple therapy required further related treatment.

The 95% CIs for the effectiveness of each PPI regimen are also provided in Table 3.6. Rabeprazole had the widest confidence interval as a result of the small number of patients prescribed this strategy. The differences in effectiveness were not statistically significant as the CIs overlap, however, establishing statistically significant efficacy differences was not the aim of this analysis.

3.4.6 Cost-effectiveness

The cost-effectiveness of each PPI triple therapy regimen was calculated by dividing the average patient cost from Table 3.5 by the PPI regimen effectiveness in Table 3.6. The cost-effectiveness of each PPI triple therapy regimen for H. pylori eradication in Ireland in 2003 is presented in Figure 3.9.

Figure 3.9 Cost-effectiveness of PPI triple therapy regimens for Helicobacter pylori eradication in Ireland in 2003

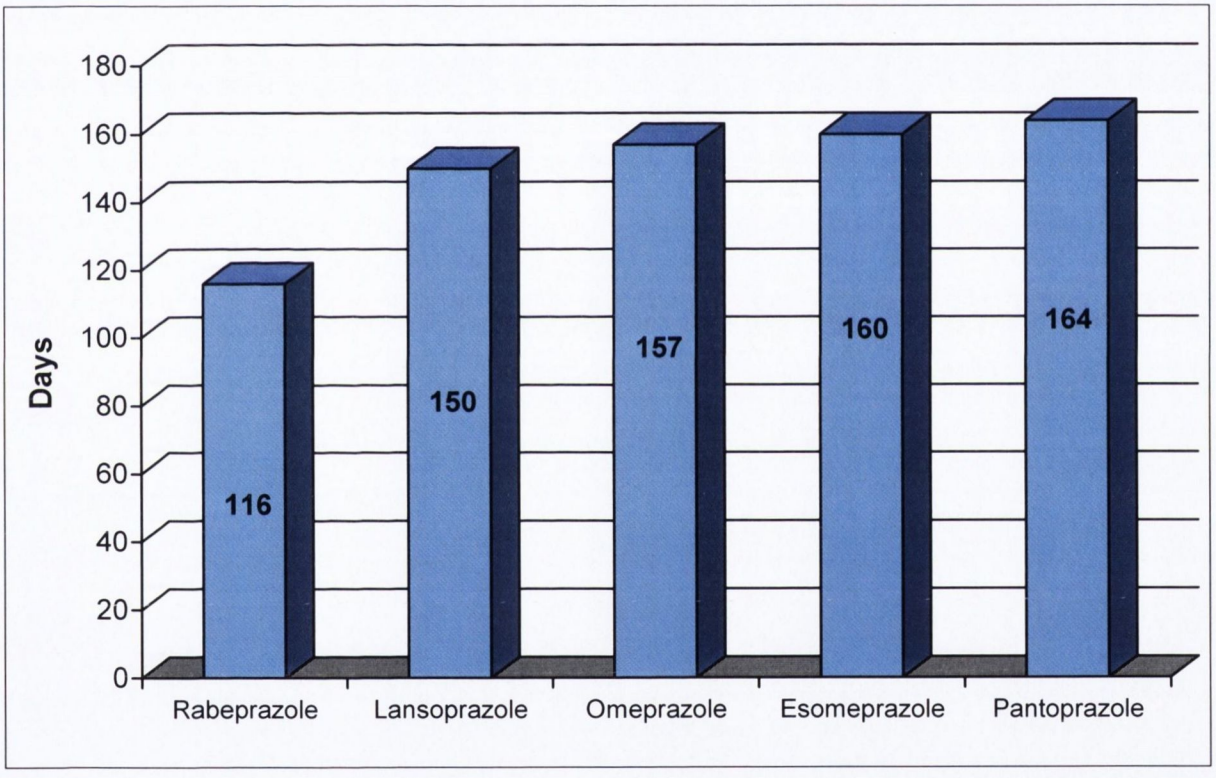


The most cost-effective strategy, in the terms defined, included rabeprazole, at €502 per asymptomatic patient. This means that the average annual cost, of relieving a patient of H. pylori related symptoms, with rabeprazole triple therapy was €502. The least cost-effective regimen was branded omeprazole at €799 per asymptomatic patient. Lansoprazole, (€666 per asymptomatic patient) the most frequently prescribed PPI triple therapy in this study, was 33% less cost-effective than rabeprazole. The generic omeprazole preparations ranked third, fifth, seventh and, eight, in terms of cost-effectiveness, illustrating that generic preparations do not always display superior cost-effectiveness in the Irish healthcare setting.

3.4.7 Duration of maintenance phase

This study found that the average duration of the PPI maintenance phase varied significantly depending on the PPI strategy adopted. The duration of the rabeprazole maintenance phase was at least 30% shorter than the maintenance phase for the other regimens, as illustrated in Figure 3.10.

Figure 3.10 Average duration of PPI triple therapy regimen maintenance phase



3.4.8 Sensitivity analysis

Key results from reducing medication costs by 35% in line with the recent IPHA agreement are presented in Table 3.7:

Table 3.7 Results of sensitivity analysis reducing medication costs by 35%

PPI regimen	Base case € per asymptomatic patient	Sensitivity analysis € per asymptomatic patient
Rabeprazole	€502	€209
Esomeprazole	€607	€256
Lansoprazole	€666	€263
Pantoprazole	€684	€266
Omeprazole branded	€799	€300

PPI triple therapy with rabeprazole remained the most cost-effective strategy when all medication costs were reduced by 35%. Currently under the IPHA agreement, only lansoprazole and omeprazole are subjected to the 35% patent expired price decrease which would make lansoprazole the most cost-effective preparation at €263 per asymptomatic patient.

A summary of the other key sensitivity analysis results is presented in Table 3.8.

Table 3.8 Other key sensitivity analysis results

Variable(s)	Sensitivity analysis	Most cost-effective regimen
Effectiveness of rabeprazole	Base case = 0.46%	Rabeprazole
	More than 0.31%	Rabeprazole
	Less than 0.31%	Lopraz
Duration of rabeprazole maintenance phase	Base case = 116 days	Rabeprazole
	Less than 180 days	Rabeprazole
	More than 180 days	Lopraz
Cost of initial rabeprazole triple therapy and duration of rabeprazole maintenance phase	Base case cost = €62.98, duration = 116 days	Rabeprazole
	30% increase in both variables	Rabeprazole
	30+% increase in both variables	Lopraz

The effectiveness of rabeprazole would have to drop from 46%, to below 31% before an alternative strategy became more cost-effective. In fact, even when the effectiveness of rabeprazole was reduced to the lower bounds of its 95% CI (i.e. 0.37 effectiveness) and the next most cost-effective strategy, Lopraz, increased to the upper bounds of its CI (i.e. 0.45), rabeprazole remained the most cost-effective regimen.

The duration of the PPI maintenance phase was also a key driver of cost-effectiveness. For all rabeprazole maintenance phase durations of less than 180 days, rabeprazole was the most cost-effective regimen, after which, lopraz became more cost-effective. This variable was examined in greater detail in Figure 3.11.

Figure 3.11 Sensitivity analysis on the duration of the rabeprazole triple therapy maintenance phase

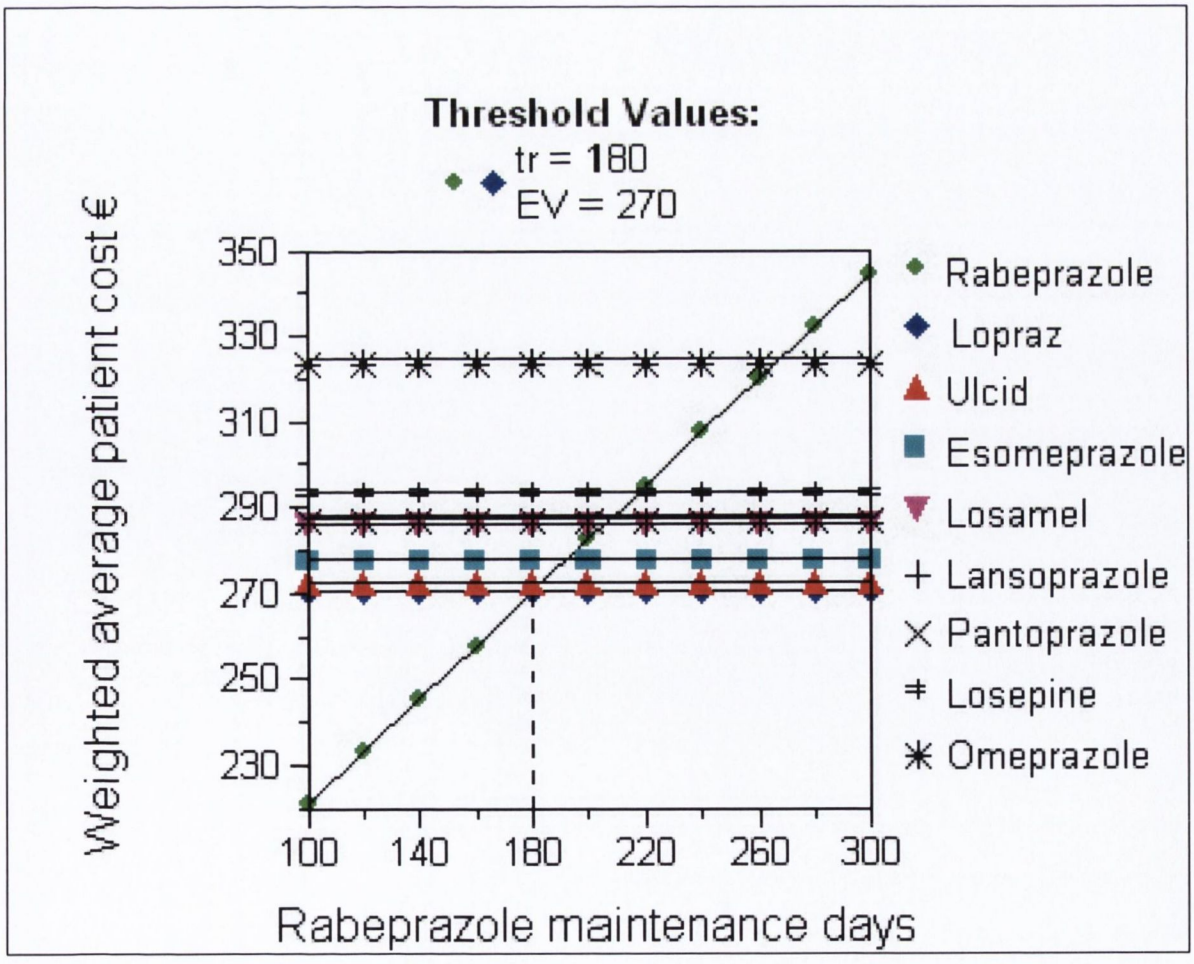


Figure 3.11 demonstrates that the duration of the rabeprazole maintenance phase would have to increase by 55% to more than 180 days before Lopraz, the next most cost-effective regimen, produced the lowest weighted average patient cost. The rabeprazole maintenance phase would have to increase to over 269 days (a 132% increase) during the course of the year before branded omeprazole would produce a lower average patient cost.

Two-way simple sensitivity analysis on the cost of the initial rabeprazole triple therapy and the duration of the rabeprazole maintenance phase was also undertaken. Both of these variables would have to increase simultaneously by more than 30% before changing the key finding that rabeprazole was the most cost-effective PPI regimen.

Figure 3.12 Sensitivity analysis on the initial cost of rabeprazole triple therapy and the duration of the rabeprazole maintenance phase

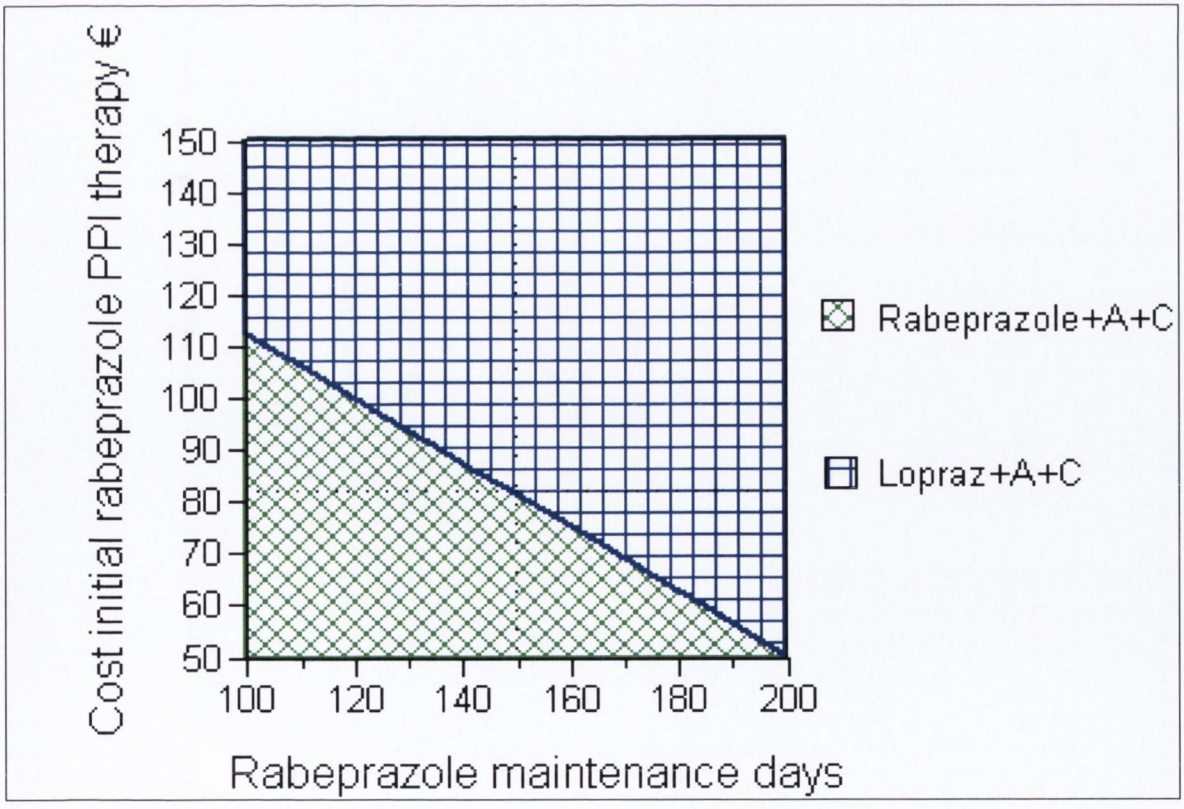


Figure 3.12 shows that rabeprazole was the most cost-effective regimen for all values of the initial cost of rabeprazole triple therapy and the duration of the rabeprazole maintenance phase, which produce the lower green triangle. In the base case, the cost of rabeprazole triple therapy was €62.98 and the duration of the maintenance phase was 116 days. Rabeprazole remained the most cost-effective strategy even when a 30% increase was applied to both variables, as illustrated by the dotted line in Figure 3.12. With simultaneous increases in excess of 30%, Lopraz became the most cost-effective regimen.

3.4.9 Potential for savings

Savings generated by substituting all PPI triple therapy regimens with the most cost-effective PPI regimen, rabeprazole, under the GMS scheme in 2005, are shown in Table 3.9.

Table 3.9 Potential savings by substituting all PPI triple therapy regimens with rabeprazole under the GMS scheme in 2005

Original PPI regimen	Saving per prescription €	No. of GMS prescriptions	Total GMS savings €
Omeprazole branded	94	42,081	3,955,614
Lansoprazole	56	36,836	2,062,816
Esomeprazole	47	29,235	1,374,045
Pantoprazole	57	23,740	1,353,180
TOTAL			**8,745,655**

Over €8.7 million of savings could be generated via the adoption of a policy to only prescribe rabeprazole, the most cost-effective PPI triple therapy regimen. Savings could increase further if this policy was applied to all CD schemes.

3.5. Discussion

3.5.1 Study setting

Success rates of over 90% for first-line management, and recurrence rates as low as 1% per annum have been found for the eradication of H. pylori with PPI triple therapy[145, 146, 147]. The model developed in this analysis found that only 40.7% to 46.0% of prescriptions did not

result in any further related medication in the year following the initial prescription. Previous analysis[148] including work undertaken in the Irish community setting also found PPI triple therapy eradication rates of less than 50%[149].

Clinical trials reporting higher eradication rates are often conducted within strictly controlled environments, and with clearly selected patient cohorts. In practice, however, controls are looser and patients are not so clearly defined. Patients presenting in general practice can have profiles, or an array of conditions, which would exclude them from the clinical trials. Most patients presenting with upper gastrointestinal symptoms in primary care are un-investigated, and the cause of the symptoms is often unknown[119]. Diagnosis is not always confirmed endoscopically and hence, the status of H. pylori infection is unclear. Family practitioners can often prescribe over 2 courses of empirical drug treatment for patients with such symptoms before undertaking clinical investigations[150]. Therefore, even if the eradication therapy cures the infection, symptoms may remain due to other conditions including reflux disease. Increasing resistance levels, as is frequently the case in the community setting are also likely to have contributed to the lower effectiveness rates used in this analysis. As GMS utilisation data was used as a proxy for effectiveness, the effectiveness captured in this analysis may be lower than the true success of therapy if patients who were relieved of symptoms continued collecting related prescriptions.

3.5.2 Effectiveness of PPI regimens

Since 1995, many new PPIs including, lansoprazole, pantoprazole, rabeprazole, and esomeprazole have become available. The effectiveness of these PPI regimens compared to omeprazole is still under review, however, many studies have found the effectiveness of the newer PPIs to be equal to, or slightly better than that of omeprazole[151, 152, 153]. A recent meta analysis including fourteen PPI studies found omeprazole to have marginally lower effectiveness rates compared to lansoprazole, esomeprazole and, rabeprazole[154].

This analysis also found omeprazole to have marginally poorer effectiveness compared to the other PPIs examined, however, this did not prove to be statistically significant. The effectiveness of rabeprazole was marginally better than omeprazole and the other PPIs, though

again, this did not prove statistically significant. Due to the smaller number of patients prescribed rabeprazole, the possibility that there is a real difference in effectiveness can not be ruled out. It is recommended that a further study, appropriately powered to examine the effectiveness of individual PPIs in the community setting in Ireland, should be conducted to further investigate this finding.

3.5.3 Cost-effectiveness of PPI regimens

Cost-effectiveness should play an important role in choosing any health strategy including H. pylori eradication strategies. Choosing strategies on the basis of cost, or effectiveness alone does not always identify the most cost-effective strategy[140]. Determinations of cost are frequently based on the initial cost of medication, but this approach can be erroneous as the overall cost of a treatment strategy is dependent on its success. Patients' continued interaction with healthcare providers and their need for further therapy increases the costs associated with ineffective regimens.

The relative cost-effectiveness of individual PPI triple therapy regimens for the eradication of H. pylori has been identified as an area requiring further review[136, 137]. This study assessed the cost-effectiveness of nine PPI triple therapy H. pylori eradication regimens in the community setting in Ireland. It found the regimen including rabeprazole, which did not have the cheapest initial treatment costs, to be the most cost-effective option, even when subjected to extensive sensitivity analysis.

3.5.4 Generic prescribing

The cost of generic PPI preparations in Ireland can vary by up to 22%[155]. In this study, the cost of an initial course of PPI triple therapy with the generic preparation Losamel was €54.12 compared to €64.76 with Losepine. The cost of generic PPI preparations can also be greater than that of branded products with Losepine costing nearly 3% more than branded rabeprazole. The prescribing of generic medications has often been advocated to reduce costs and increase the cost-effectiveness of therapies, including PPIs [136-139, 156, 157], however, of the nine strategies examined in this analysis the generic omeprazole preparations ranked third, fifth, seventh, and eight in terms of cost-effectiveness.

3.5.5 Cost-effective prescribing

The rapid rise in healthcare costs in recent years, particularly in the area of pharmaceuticals, has meant that increased VFM should not be ignored. The potential for cost savings in the prescribing of PPI triple therapy for the eradication of H. pylori is substantial. Annual savings under the GMS scheme of €3.1m to €6.8m have been found following the substitution of omeprazole (Losec mups) with alternative PPIs during the maintenance phase of therapy[154]. The analysis undertaken in this thesis shows that savings in excess of €8.7m could arise if only the most cost-effective PPI regimen, rabeprazole, was prescribed under the GMS scheme in 2005.

Increasing the step down from healing to maintenance PPI doses in line with current guidelines would facilitate further savings. In this study, with the exception of omeprazole and esomeprazole, the majority of patients on maintenance PPI therapy receive the higher dose of maintenance therapy. However, a regular low dose of maintenance therapy would prevent gastro oesophageal reflux disease symptoms in 70-80% of patients, and should be used in preference to the higher healing dose[158].

Further savings could be realised by aligning the most cost-effective PPI in the community with the most cost-effective PPI in the hospital setting. Hospital initiated prescriptions are responsible for a significant proportion of GP prescribing, estimated at 66-77% for PPI prescriptions[159], and have been demonstrated to be more expensive than those initiated in the Irish community setting[160].

The new IPHA agreement sees the price of older, post-patent medicines reduce by up to 35%. This should produce substantial savings under the Community Drugs schemes. The price of omeprazole and lansoprazole preparations, which are already off patent, may be subjected to this reduction and could result in combined annual savings under the Community Drugs schemes in excess of €18m. Savings could increase even further when the pharmacy fee and the 50% mark-up on medications applied via the DP scheme, are taken into account.

3.6 Conclusion

Nearly half the adult population suffer from dyspepsia in any year. The eradication of H. pylori has been shown to greatly improve symptoms and has proven to be cost-effective. However, the cost-effectiveness of PPI triple therapy regimens for the eradication of H. pylori in Ireland has been identified as requiring further analysis.

In this chapter, a cost-effectiveness analysis was undertaken. It found the regimen including rabeprazole (Pariet®) to be the most cost-effective PPI triple therapy for the eradication of H. pylori infection in the community setting in Ireland in 2003. Decision tree analysis was used to construct the model using real-world utilisation data from the GMS scheme.

The overall effectiveness of PPI triple therapy, in terms of no further maintenance anti-secretary therapy during the one-year follow-up period, was 40%-46% depending on the PPI prescribed. Only 963 of the 2,229 prescriptions examined did not result in further related therapy. The majority of prescriptions resulted in the prescribing of PPI maintenance therapy.

The annual cost of treating patients with PPI triple therapy varied from under €100 to nearly €900, depending on the PPI prescribed, the patients' symptoms and the strategy adopted. The regimen including rabeprazole was the most cost-effective regimen at €502 per asymptomatic patient. This result did not change even when subjected to extensive sensitivity analysis. The greatest number of prescriptions reviewed in the study was for lansoprazole (Zoton®) at a cost-effectiveness of €666 per asymptomatic patient. Generic prescribing did not decrease costs. Prescribing only the most cost-effective PPI regimen, however, has the potential to result in annual savings under the GMS scheme in excess of €8.7m.

Chapter 4

A cost-effectiveness and cost-utility analysis of statin therapy for the primary prevention of coronary heart disease

Chapter 4

4.1 Introduction

Coronary heart disease (CHD) mortality rates are decreasing internationally and in Ireland [84, 86, 88]. Statin therapy is the main therapy used for the primary prevention of CHD [97-99].

This chapter undertakes an economic evaluation to examine the cost-effectiveness of statin therapy for the primary prevention of CHD in Ireland in 2005. A cost-effectiveness and cost-utility analysis is undertaken as outcomes are measured in both natural units, LYG and health years, QALY. Markov modelling is used as it facilitates the representation of the natural history of the disease in terms of a succession of states, each of which are associated with certain costs and outcomes. Irish epidemiological data and statin therapy clinical trial data are used to populate the model.

4.2 Background

Recent epidemiological data has shown a decrease in CHD mortality in Ireland[84]. Nearly half of this decrease is attributable to changes in the major CHD risk factors, such as cholesterol levels[91]. Statin therapy is a significant contributor to lowering cholesterol[97-103]. The rate of increase in statin use and expenditure has far outstripped increases in other medications giving rise to frequent cost-effectiveness evaluations of these agents in many healthcare settings[161, 162, 163, 164, 165, 166, 167].

Statin therapy is justified in the secondary prevention of CHD with the Standing Medical Advisory Committee[168] recommending a policy of treating patients above an annual CHD risk threshold of 3%. Primary prevention with statins is more contentious,[169] with some advocating no treatment outside secondary prevention[170], and others advocating treatment for all patient groups that have been shown to benefit[171]. It is generally acknowledged that the 3% annual CHD risk that marked the threshold between the cost-effective and cost-ineffective use of statins is now dated[172, 173, 174]. Revised guidelines recommend primary prevention statin therapy in people with high blood pressure and a 1.5% annual CHD risk[175].

4.3 Methods

4.3.1 Model structure

A Markov model was constructed in Treeage®, comparing the cost-effectiveness and cost-utility of primary prevention statin therapy, versus no primary prevention therapy in 55 year old Irish males with an annual CHD risk of 1.5%. The model consists of four basic health states:

1. The patient may remain well and experience no cardiovascular event;
2. The patient may suffer a single cardiovascular event;
3. The patient may suffer further cardiovascular events; and,
4. The patient may die.

All patients begin in the first state, the cardiovascular event free state. Patients who remain alive can pass through any number of cardiovascular event states. These states track the occurrence of specific cardiovascular events, including acute myocardial infarction (AMI), angina, coronary artery bypass graft (CABG), percutaneous transluminal coronary angioplasty (PTCA), and stroke. The probability of a patient moving between health states depends on the current health state. For example, a patient might remain healthy for a given period, experience an AMI and survive in a cardiovascular event state. The patient may then suffer a secondary event, such as a PTCA, and move from the single event state through to the secondary cardiovascular event state or death. Following each event, the patient moves to the appropriate health state, but can not return to the initial, or single cardiovascular event states once exiting these states.

The increased likelihood of cardiovascular events and death for the Irish male population of interest was estimated using event rates from the general population and the statin therapy clinical trials. Age-specific Irish cardiovascular event rates were used to incorporate the impact of aging. Costs and effects were collected as patients go through the model. The ICER was calculated for all statins available under the GMS and DP schemes in 2005. The model concludes when all patients are absorbed into the death state or the model is brought to a close after 15 years as the administration of statin therapy to the elderly population is under debate since the findings of the PROSPER trial[176]. Cost-effectiveness results are presented in terms of

LYG facilitating comparison with other primary prevention statin therapy studies. Cost-utility results are also given, presented by QALYs, however, as the utility measures are not Irish specific these results are presented as a secondary analysis.

4.3.2 Event rates

Event rates for the general Irish male population aged 55 years were used to adjust the event rates from the statin therapy clinical trials. These in turn were used to estimate the effectiveness of statin therapy for Irish males with an annual CHD risk of 1.5%.

4.3.2.1 General population

Cardiovascular event rates for the general male population were taken from the Irish Public Health Information System (PHIS). This activity relates to 2003[177]. Event rates for AMI, angina, CABG, and PTCA were recorded by the database. Event rates for stroke were not recorded in PHIS and, therefore, cerebrovascular disease data taken from HIPE were downwardly adjusted for the proportionate number of strokes. CVD event rates were captured in 10-year age categories. Individual age-specific event rates were estimated by calculating the midpoint of the 10-year rates and using linear interpolation to estimate age-specific event rates. Event rates for 55 year old Irish males, including the all cause mortality rate, are presented in Table 4.1.

Table 4.1 Cardiovascular event and death rates for Irish males aged 55 years

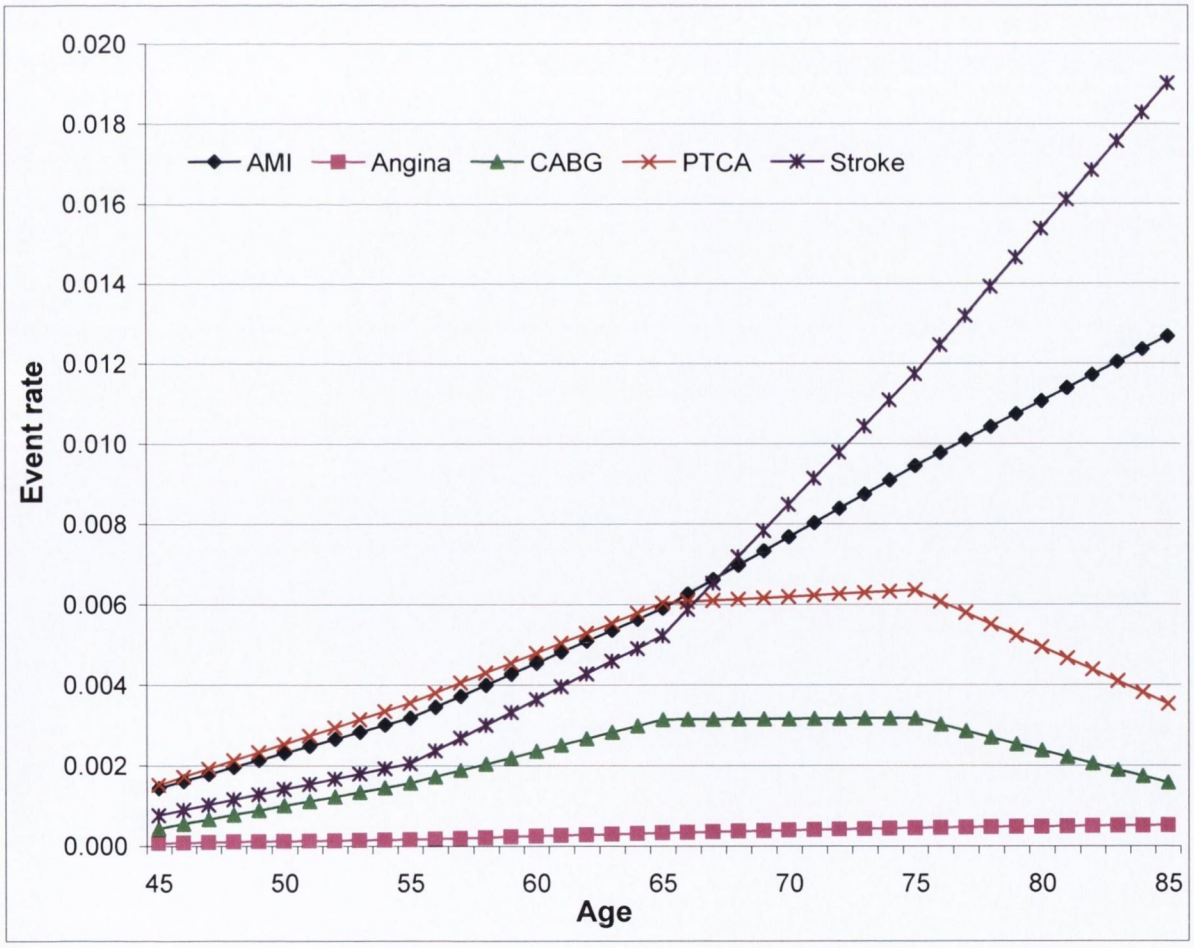
Event	Abbreviation	Rate
AMI	pAMI[1stage]	0.00318
Angina	pAng[1stage]	0.00018
CABG	pCABG[1stage]	0.00157
PTCA	pPTCA[1stage]	0.00357
Stroke	pStr[1stage]	0.00210
Death	pDie[1stage]	0.00637

Source: Hospital Inpatient Enquiry programme database[63]. Irish Central Statistic Office, Deaths from principal causes[84]. Department of Health and Children, Health Statistics[177].

The annual death rate for 55 year old Irish males was 0.00637 or 0.637%. The annual event rate for the specified cardiovascular occurrences varied from 0.00018 for angina to 0.00357 for PTCAs. The abbreviations in Table 4.1 were used in the Markov model to denote the probability of the specific events for various patient ages. For example, pAMI[1stage] denotes the probability of an AMI at stage 1 which refers to the base case of 55 year old Irish males.

Event rates for all ages between 45 and 85 years were used to assess the impact of ageing on the model. They were also used when undertaking the sensitivity analysis in chapter 5. These event rates are shown in Figure 4.1.

Figure 4.1 Cardiovascular event rates for Irish males aged 45 to 85 years

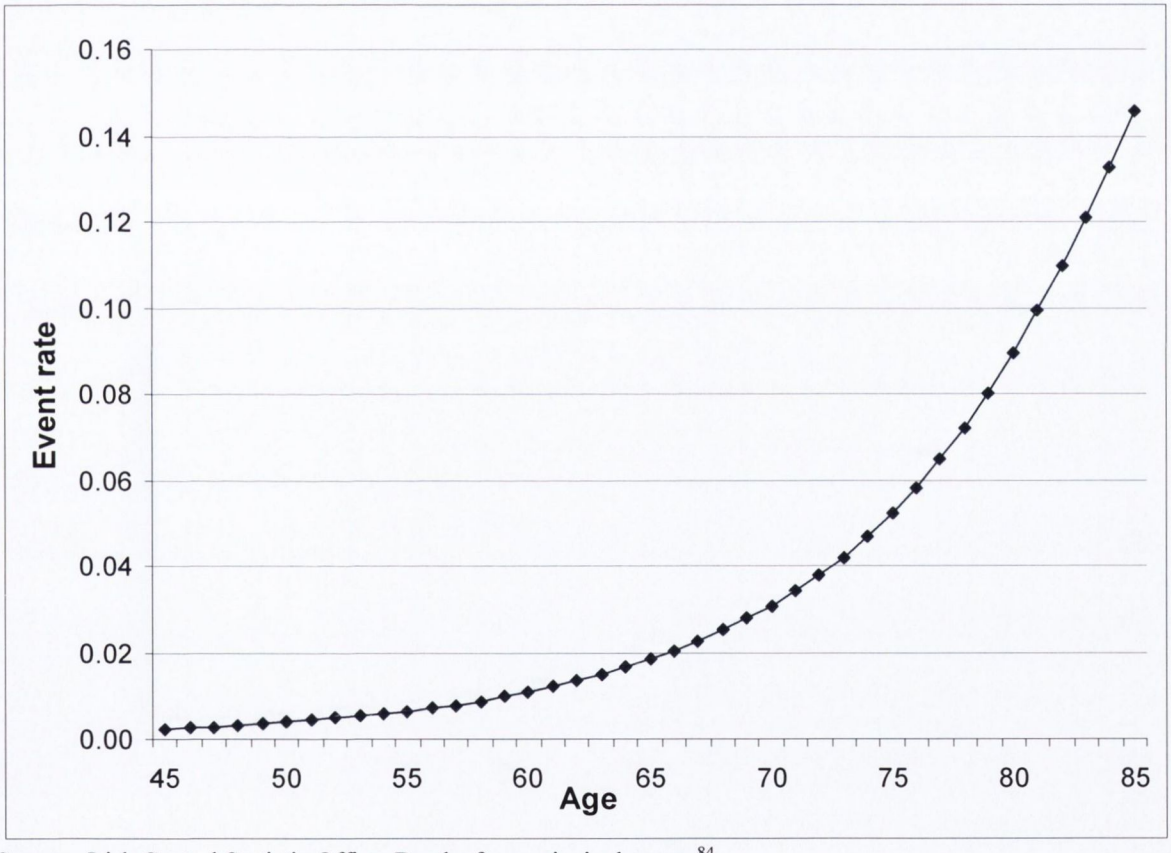


Source: Hospital Inpatient Enquiry programme database[63]. Department of Health and Children, Health Statistics[177].

From Figure 4.1 it can be seen that event rates for AMI and stroke increase rapidly after 65 years. Event rates for PTCA and CABG decline from 75 years on and event rates for angina are relatively age-independent.

All cause mortality rates for the Irish male population aged 45 to 85 years are displayed in Figure 4.2.

Figure 4.2 All cause mortality rates for Irish males aged 45 to 85 years



Source: Irish Central Statistic Office, Deaths from principal causes[84].

The average annual death rate increases dramatically from 65 years onwards increasing to over 0.145, or 14.5%, for an 85 year Irish old male.

4.3.2.2 Trial population

Cardiovascular event rates for the rate of transition, from health to CVD, were based on data from the West of Scotland Coronary Prevention (WOSCOPs) trial[97]. This double-blinded trial

examined the effect of primary prevention statin therapy on male subjects with a CHD risk of 1.5% per annum. It randomly assigned 6,595 men, 45 to 64 years of age, with a mean cholesterol concentration of 7.0 mmol/l, and no evidence of previous myocardial infarction, to receive either pravastatin (40 mg each evening) or placebo, in addition to dietary advice. The average follow-up period of the study was 4.9 years with medical records, electrocardiograph recordings, and the national death registry used to determine clinical end points. The WOSCOPs trial found that treatment with pravastatin reduced the risk of non-fatal myocardial infarction or death from coronary disease by 31% (95% CI 17% to 43%) with similar reductions in the risk of death from all cardiovascular causes. A 22% (95% CI 0% to 40%) reduction in the risk of death from any cause was also reported.

Event rates from the WOSCOPs trial were converted to annual rates using the formula "$tr_1 = 1-(1-tr_t)^{1/t}$", where tr_1 is the yearly transition rate to be estimated, and tr_t is the overall rate over the time period, t, studied in the clinical trial. The combined WOSCOPs event rate for revascularisation procedures was segregated into CABGs and PTCAs using PHIS data as the WOSCOPs trial did not report these procedures separately. A weighted average of the Collaborative Atorvastatin Diabetes Study (CARDS)[98] and the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/ TexCAPS)[99] findings were used to generate the event rate for angina as this was not recorded in WOSCOPs.

Table 4.2 shows the annual event rates from the clinical trials with, and without, primary prevention statin therapy as used in the Markov model developed in this analysis.

Table 4.2 Event rates from primary prevention statin therapy trials

	Event rate with stain	Event rate without statin
P (AMI)	0.0115	0.0167
P (Angina)	0.0032	0.0050
P (Revascularisation)	0.0035	0.0052
P (CABG)	*0.0011*	*0.0016*
P (PTCA)	*0.0024*	*0.0036*
P (Stroke)	0.0029	0.0032
P (Death)	0.0066	0.0085

Source: Shepherd *et al.*, Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia (WOSCOPs)[97]. Colhourn *et al.*, Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): Multicentre randomised placebo-controlled trial[97]. Downs *et al.*, Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: Results of Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS)[99].

Event rates with primary prevention statin therapy were consistently lower than rates without statin therapy illustrating the effectiveness of therapy. Table 4.2 shows that the annual death rate for males prescribed primary prevention statin therapy was 0.0066 or 0.66%. A male with similar risk who does not receive primary prevention statin therapy was more likely to die, with an event rate of 0.0085 or 0.85% per annum.

Event rates for secondary prevention statin therapy were calculated using weighted averages from four significant secondary prevention trials, examining nearly 40,000 patients. These trials included the Scandinavian Simvastatin Survival Study (4S)[100], the Cholesterol and Recurrent Events trial (CARE)[101] the Long Term Intervention with Pravastatin in Ischaemic Disease (LIPID)[102] trial, and the MRC/BHF Heart Protection Study (HPS)[103]. Similar to the primary prevention trials, the secondary trials did not report separate revascularisation rates for PTCA and CABGs. Again PHIS was used to segregate this rate.

As all patients were administered secondary statin therapy after a cardiovascular event, only event rates with statin therapy were required. These event rates are displayed in Figure 4.3, including the patient weighted average event rates used in the model.

Table 4.3 Event rates from secondary prevention statin therapy trials

	4S	CARE	LIPID	HPS	Average event rate
Number patients	4,444	4,159	9,014	20,536	
P (AMI)	0.0427	0.0198	0.0125	0.0171	0.0193
P (Angina)	n/a	0.0312	0.0405	n/a	0.0376
P (Revascularisation)	n/a	0.0288	0.0226	0.0179	0.0205
P (CABG)	-	-	-	-	*0.0063*
P (PTCA)	-	-	-	-	*0.0142*
P (Stroke)	n/a	0.0051	0.0062	0.0068	0.0064
P (Death)	0.0154	0.0205	0.0189	0.0258	0.0224

Source: 4S Group. Randomised trial of cholesterol lowering in 4,444 patients with coronary heart disease[100]. Sacks *et al.*, The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol (CARE)[101]. LIPID Study Group. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels[102]. HPS Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: A randomised placebo-controlled trial[103].

Table 4.3 shows that the annual probability of dying for a 55 year old Irish male on secondary prevention statin therapy was 0.0224 or 2.24%. All secondary statin therapy event rates were greater than primary prevention rates signifying the increased risk of all cardiovascular events and death for patients requiring secondary prevention statin therapy.

4.3.3 Relative risk adjustment factor

The increased likelihood of cardiovascular events for males with an annual CHD risk of 1.5% relative to the general Irish male population was represented by the relative risk adjustment factor. This was calculated by dividing the appropriate annual event rates from the trials by the event rates for the general Irish male population. The relative risk adjustment factors for patients who receive primary, no primary and secondary prevention statin therapy, are presented in Table 4.4.

Table 4.4 Relative risk adjustment factors

	Primary Prevention		Secondary Prevention
Event (Abbreviation)	**With statin (EventRRPriS)**	**Without statin (EventRRPriNoS)**	**With statin (EventRRSecS)**
AMI	3.62	5.25	6.07
Angina	17.78	27.78	208.89
CABG	0.70	1.02	4.01
PTCA	0.67	1.01	3.98
Stroke	1.38	1.52	3.05
Death	1.04	1.33	3.52

Of the primary prevention population, those treated with a statin were less likely to suffer an event than those who did not receive primary prevention therapy. For example, Irish males with an annual CHD risk of 1.5% treated with primary prevention statin therapy were 1.04 (DieRRPriS) times more likely to die each year compared to the standard Irish male population of the same age. Those not treated with primary prevention statin therapy had a 1.33 (DieRRPriNoS) times greater risk of death than the standard population. The relative risk adjustment factors were highest for patients requiring secondary prevention therapy (represented by EventRRSecS) as these patients had increased likelihood of experiencing another cardiovascular event or death. Those requiring secondary prevention therapy were 3.52 (DieRRSecS) times more likely to die than the general Irish male population.

It was assumed that the relative risk adjustment factors remained constant throughout the model. An adjustment was made to take account of aging by multiplying the appropriate relative risk adjustment factor by the age related probability for that event. The model also assumed that all patients in receipt of secondary prevention statin therapy had the same relative risk adjustment factor regardless of the administration of primary prevention therapy, or lack thereof.

4.3.4 Resource utilisation and costs

Only direct healthcare costs were included in the model as the perspective of the study was the Irish health service provider. The main costs included in the study are statin therapy, cardiovascular interventions and patient monitoring costs. All costs were in 2005 Irish prices.

The cost of statin therapy was determined from the Monthly Index of Medical Specialities[144]. The NCEP ATP III guidelines recommend that patients at moderate to high risk who are treated with a statin should be treated with a dose sufficiently high to achieve a 30 – 40% reduction in LDL cholesterol[105]. The lowest, licensed dose of each statin medication capable of reducing LDL cholesterol by approximately 35% was used to determine drug acquisition costs. The statins examined included atorvastatin (Lipitor®), rousuvastatin (Crestor®), fluvastatin (Lescol®), simvastatin (Zocor®) and pravastatin (Lipostat®). The highest and lowest cost generic preparations for simvastatin and pravastatin were also assessed. Annual costs of drugs under the GMS and DP schemes were examined, including the dispensing fee and mark-up, where appropriate. These costs are shown in Table 4.5.

Table 4.5 Cost of statin therapy under the GMS and DP schemes in 2005

			€				
Statin	**Dose mg**	**Pack size**	**Drug price per pack**	**Dispensing fee GMS**	**Dispensing/ mark-up DP**	**Annual GMS cost**	**Annual DP cost**
Atorvastatin	10	28	25.17	2.98	15.18	367	526
Rosuvastatin	10	28	26.37	2.98	15.78	383	549
Fluvastatin	80	28	26.73	2.98	15.96	387	556
Simvastatin -branded	20	28	42.41	2.98	23.80	592	863
Generic - low cost	*20*	*28*	*29.37*	*2.98*	*17.29*	*422*	*608*
Generic – high cost	*20*	*28*	*49.41*	*2.98*	*27.31*	*683*	*1,000*
Pravastatin –branded	40	28	54.29	2.98	29.74	747	1,095
Generic – low cost	*40*	*28*	*41.26*	*2.98*	*23.23*	*538*	*841*
Generic – high cost	*40*	*30*	*46.96*	*2.98*	*26.08*	*612*	*952*

Source: Medical Publications Ireland. Monthly Index of Medical Specialities[144].

The cost of therapy was greater under the DP scheme than the GMS scheme due to the 50% mark-up applied to the DP scheme. For example, the annual cost of prescribing atorvastatin under the GMS scheme was €367 compared to €526 under the DP scheme. Table 4.5 also shows that the cost of generic statin preparations can be higher than branded preparations. For example, the annual cost of low cost generic pravastatin under the GMS scheme was €538 compared to €367 for atorvastatin.

Cardiovascular intervention costs were taken from the 2006 Irish Casemix database, which uses 2005 costs. The patient weighted average cost of the relevant DRGs used to estimate the cardiovascular intervention costs are shown in Table 4.6.

Table 4.6 Irish cardiovascular intervention costs in 2005

Cardiovascular intervention	DRGs	Cost €
AMI	F10Z, F41A/B, F60A/B/C	6,876
Angina	F72A/B	3,132
CABG	F05A/B, F06A/B	19,119
PTCA	F15Z, F16Z	7,213
Stroke	B70A/B/C/D	11,013

Source: National Casemix programme database[62].

Monitoring patients' prescribed statin therapy involved bi-annual visits to the GP including lipid profile, liver function and creatine kinase tests. The annual cost of this monitoring was estimated, from expert opinion, at €220 per patient. It was assumed that an equal proportion of patients in each cohort received medications such as aspirin, anti-hypertensives, or alternative serum lipid reducing treatments. Dietary and lifestyle advice was given in both the treatment, and non-treatment arms of the study. The net cost of this activity was assumed to be zero, and therefore, not included in the model.

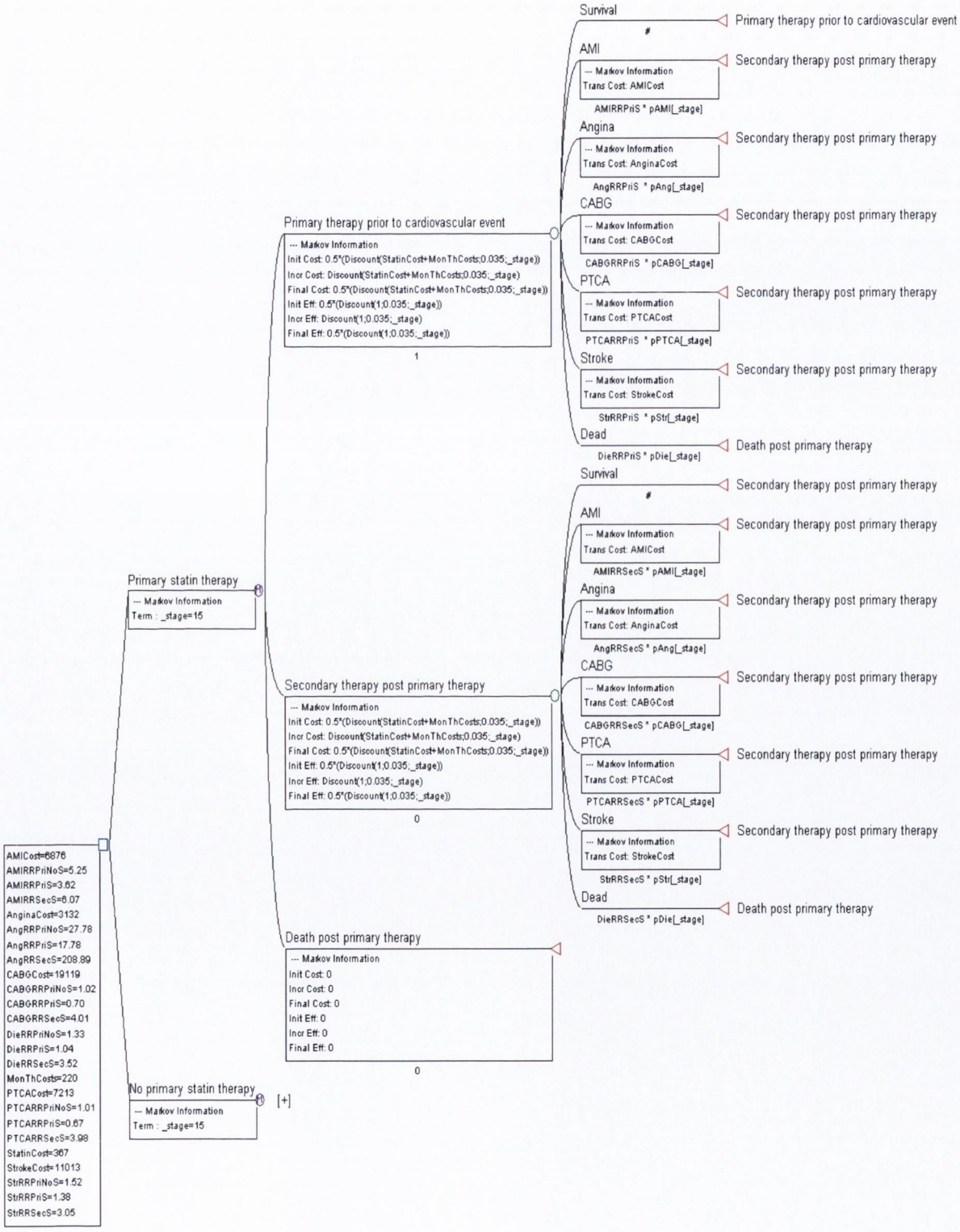
The study did not take account of costs relating to preadmission management, for example, ambulances, costs borne by patients, or indirect costs. To do so may increase costs with a

greater relative increase most likely occurring in the non-treatment arm, due to the increased incidence of cardiovascular events and death.

4.3.5 Building the cost-effectiveness model

The Markov model used to evaluate the cost-effectiveness of statin therapy for the primary prevention of CHD in Irish males with a 1.5% annual CHD risk is presented in Figure 4.3. The base case refers to the administration of atorvastatin under the GMS scheme in 2005. The no primary prevention therapy arm of the model has been collapsed for display purposes.

Figure 4.3 Markov model for the cost-effectiveness of primary prevention stain therapy



As illustrated in Figure 4.3 patients who received primary prevention therapy began in the primary therapy prior to cardiovascular event state. The probability of experiencing an event during the cycle was determined by the appropriate relative risk adjustment factor and the age related event probability. Patients who did not experience a cardiovascular event in any of the previous cycles begin the next cycle in the 'primary therapy prior to cardiovascular event' state. Patients who experienced an event move to the appropriate cardiovascular event arm and begin the next cycle in the 'secondary statin therapy post primary therapy' state. Patients alive at the end of each yearly cycle collect one additional life-year. Patients who die during the cycle move to the dead state and do not collect further effects.

The no primary prevention therapy arm of the model was similar to the primary prevention arm. However, until patients experienced a cardiovascular event no statin therapy costs or monitoring costs occur. The probability of an initial cardiovascular event was dependent on the no primary therapy relative risk adjustment factors and the same age-related probabilities as the treatment arm. The probability of a second or subsequent event was dependent on the secondary therapy relative risk adjustment factors and the age-related probabilities, which was the same for both the treatment and non-treatment arms of the model.

Costs including statin therapy, cardiovascular interventions and patient monitoring costs were collected as patients go through the model. The total statin therapy costs were calculated as the annual cost of statin therapy per patient multiplied by the number of treatment years. Cardiovascular intervention costs were calculated by multiplying the intervention cost by the number of events. Monitoring costs were included in the primary therapy arm of the model and for all patients requiring secondary prevention statin therapy. The total cost for the no primary prevention therapy arm was subtracted from the total cost for the primary prevention therapy arm to calculate the incremental cost of treatment.

The effectiveness of primary prevention therapy versus no primary prevention therapy was measured by estimating the number of life-years gained by statin therapy during each cycle. The life-years gained by treatment was the difference between the total life-years lived by those on primary prevention stain therapy, and those who did not receive primary prevention

statin therapy. The cost-effectiveness of primary prevention statin therapy was calculated as the incremental cost divided by the incremental effectiveness and was measured in life-years gained. The ICER was represented by the following equation:

$$\text{ICER} = \frac{(\text{Cost primary prevention} - \text{Cost no primary prevention})}{(\text{Effectiveness primary prevention} - \text{Effectiveness no primary prevention})}$$

Both cost and effects were discounted at 3.5% per annum in accordance with the most recent NICE guidelines[178]. Half-cycle correction was also performed. The cost-effectiveness of all available statins under both the GMS and DP schemes were examined. Additional findings were also presented for the most cost-effective statin.

4.3.6 Building the cost-utility model

The cost-utility model was similar to the cost-effectiveness model except for the inclusion of utility measures. Utilities in terms of QALYs were used to convert the cost-effectiveness model into a cost-utility model. The utility measurements used in this evaluation followed closely the approach by Ward *et al* when undertaking a systematic review and economic evaluation of statins for the prevention of coronary events[179]. This review examined 1,625 studies from various electronic databases, hand searching, citation searching and reference list checking with 58 hard copies of papers retrieved for closer inspection. The studies were evaluated based on the population setting and the type of instrument used to obtain the utilities.

The utility for AMI and angina was taken from a randomised controlled trial comparing care in a chest pain clinic observation unit with routine care in an emergency department in Sheffield, UK[180]. Nearly 700 patients were administered EQ-5D questionnaires at 6 months. The utility for CABG and PTCA were taken from Hlatky *et al.* examining 934 patients who were randomised in the Bypass Angioplasty Revascularisation Investigation (BARI) and followed up for 10 to 12 years[181]. The utility for stroke was taken from a meta-analysis undertaken by Tengs *et al.* examining 20 articles reporting 53 quality of life estimates[182]. Utilities for mild stroke, moderate stroke and severe stroke were provided. Similar to Ward *et*

al.[179] this evaluation used an overall non-fatal stroke health state that does not distinguish between severities. Therefore a study by Youman *et al.* was used to estimate the proportion of patients experiencing strokes of differing severity from the data set of a UK trial investigating stroke outcomes in 290,000 newly diagnosed patients[183].

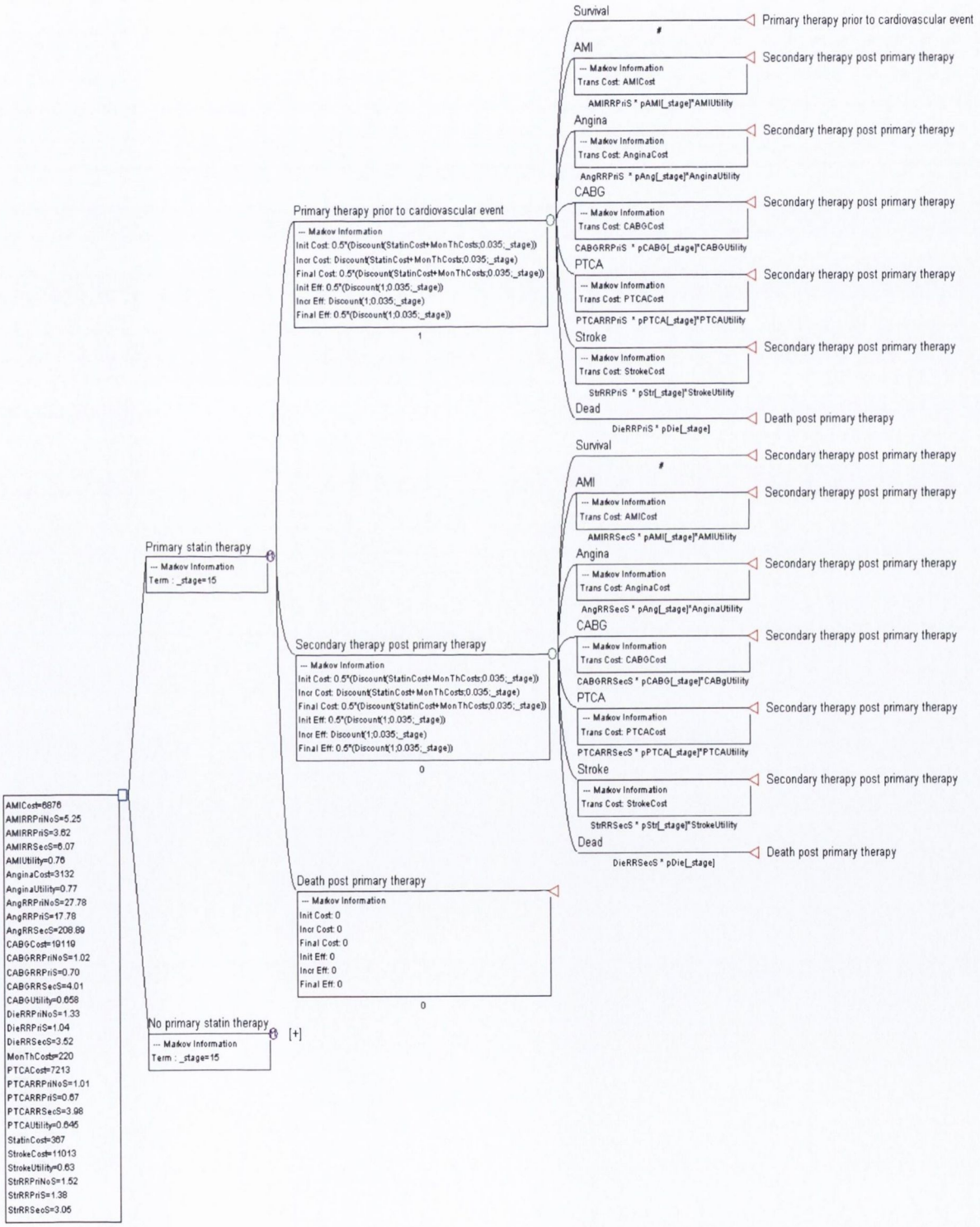
The utilites used in this evaluation are presented in Table 4.7.

Table 4.7 Cardiovascular event utilities

Event	Utility	Source
AMI	0.760	Goodacre *et al.* [180]
Angina	0.770	Goodacre *et al.* [180]
CABG	0.658	Hlatky *et al.* [181]
PTCA	0.645	Hlatky *et al.* [181]
Stroke	0.630	Tengs *et al.* [182] and Youman *et al.* [183]

The appropriate relative risk adjustment factor adjusted for ageing was multiplied by the appropriate utility measure to calculate effectiveness. No disutility associated with taking statin therapy for 15 years was modelled as statin therapy does not appear to have an adverse affect on the patients' health-related quality-of-life[184]. The cost-utility model, using QALYs, examined primary prevention statin therapy in Irish males with a 1.5% annual CHD risk and is presented in Figure 4.4. Again the no primary therapy arm is collapsed for display purposes only.

Figure 4.4 **Markov model for the cost-utility of primary prevention statin therapy**

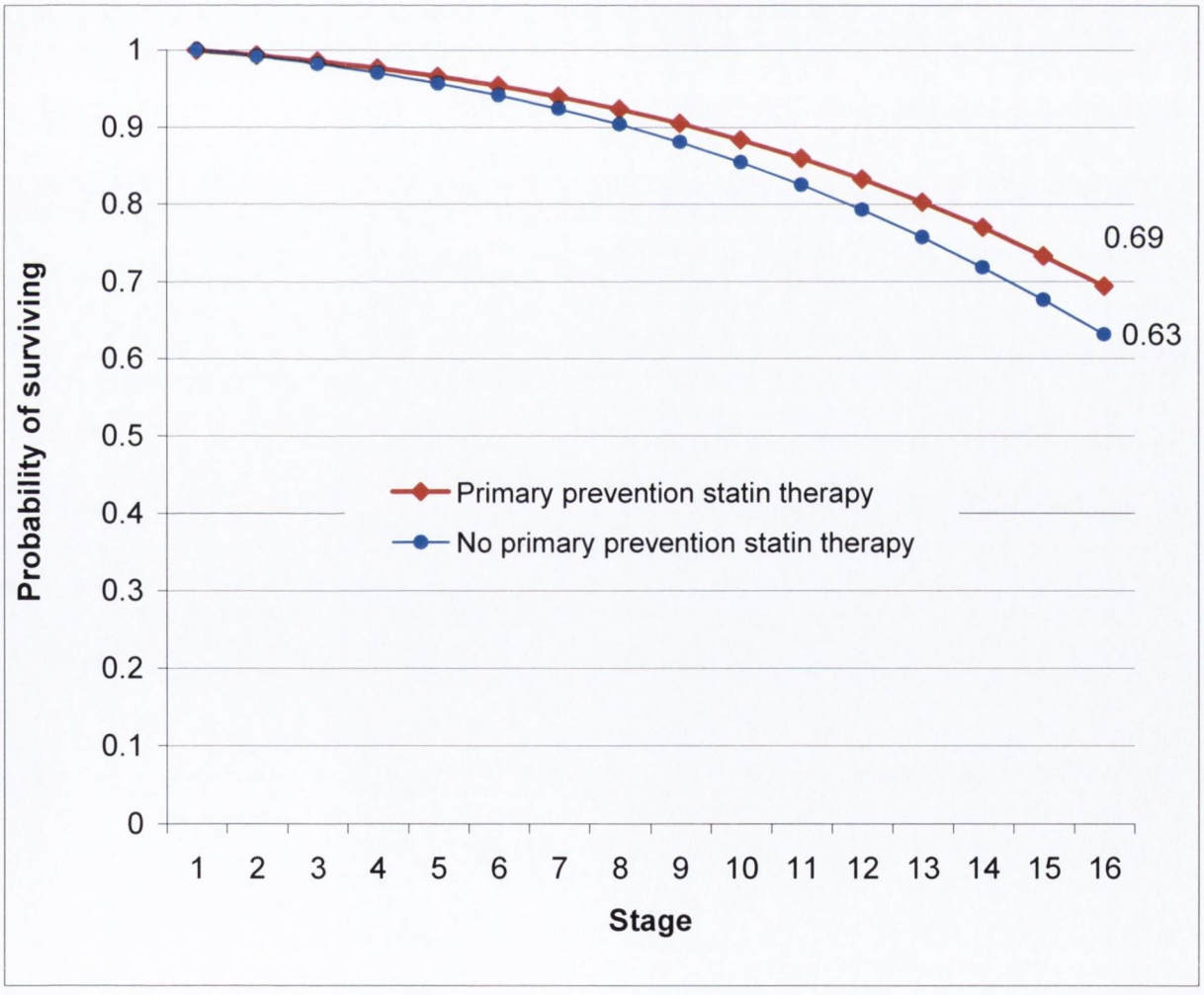


4.4. Results

4.4.1 Survival curves

Figure 4.5 displays the survival curve for both the primary prevention and no primary prevention arms of the study. By the end of the model, 69% of patients in the treatment arm were alive, compared to only 63% in the non-treatment arm. Both curves display a decreasing trend in survival, with the primary prevention arm illustrating more favourable results at each stage of the model.

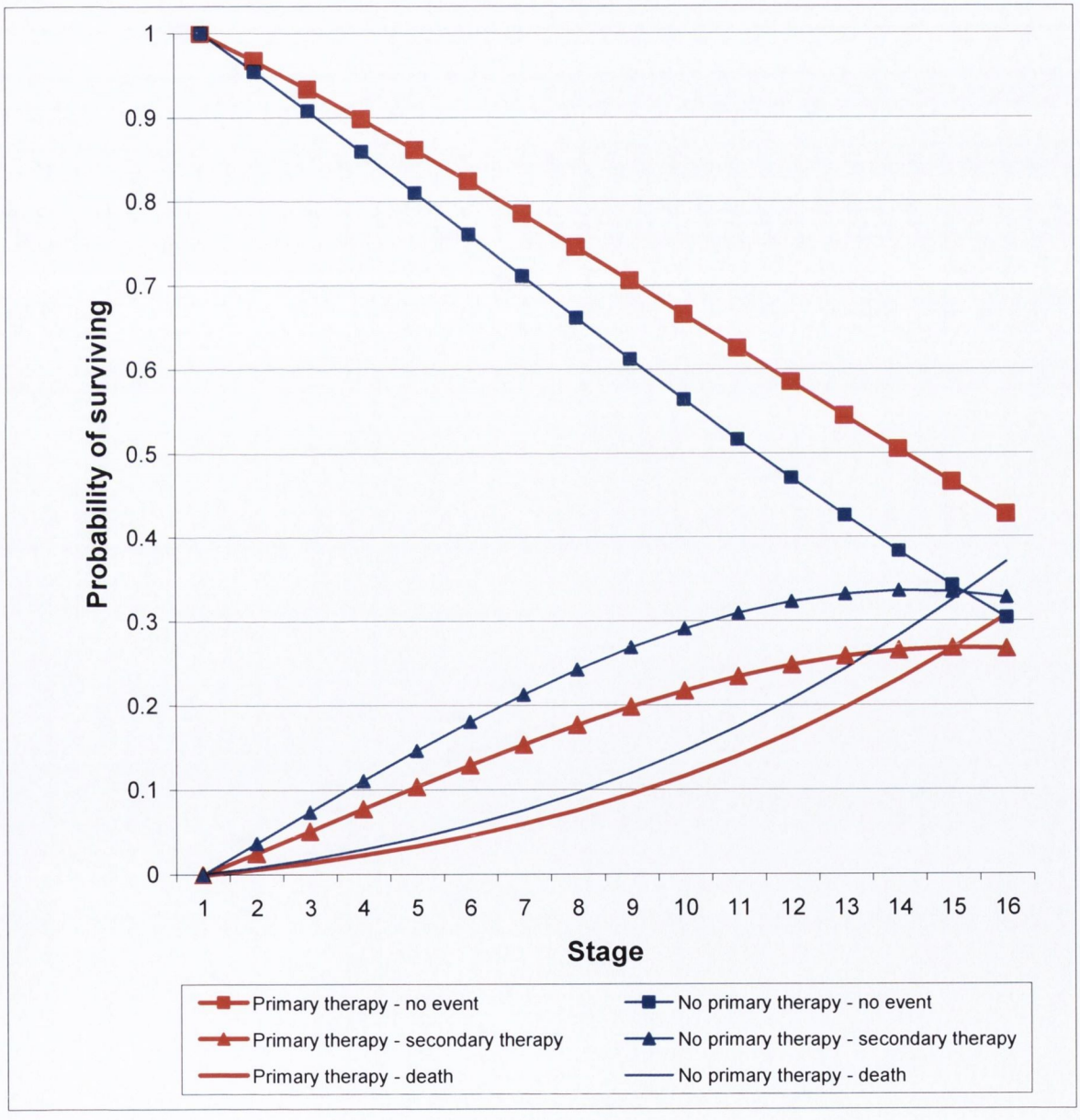
Figure 4.5 Survival curves for primary prevention and no primary prevention statin therapy



4.4.2 State probability curves

The state probability curves display the probabilities of, surviving without any cardiovascular event, survival post event, and death for each arm of the model.

Figure 4.6 State probability curves for primary prevention and no primary prevention statin therapy



Again, the primary prevention arm of the study displayed more favourable results than the no primary prevention arm. By the end of model, 0.307 or 30.7% in the primary prevention arm

have died versus 0.370 or 37.0% in the no primary prevention arm. Primary prevention statin therapy reduced the risk of death by 6.3%. This means that 63 out of 1,000 men with an annual CHD risk of 1.5% would avoid death if administered primary prevention statin therapy. Alternatively, for every 16 men treated with primary prevention statin therapy one death was avoided. More patients survived without experiencing any cardiovascular event in the primary prevention arm than in the no primary prevention arm of the study (42.7% versus 30.3%). Only 8 people have to be treated to avoid one cardiovascular event. The probability of experiencing a cardiovascular event and being put on secondary prevention statin therapy was greater in the no primary prevention arm (32.8% versus 26.7%).

4.4.3 Markov cohort results

Key results can also be assessed via a Markov cohort analysis using 1,000 simulations. This is presented in Table 4.8.

Table 4.8 Markov cohort analysis for primary prevention and no primary prevention statin therapy

	Primary prevention	No primary prevention
Total alive	694	631
Alive, event free	427	303
Alive, post event	267	328
Dead	306	369
Total cohort	1,000	1,000

By the end of the model, 694 people, out of 1,000, in the primary prevention arm of the study were still alive, versus only 631 in the no primary prevention arm. Alternatively, 306 people from the primary prevention arm died during the course of the model, while 369 people from the no primary prevention therapy arm died. Of the patients still alive, 427 patients in the therapy arm did not experience a cardiovascular event, versus only 303 in the no primary prevention arm. This implies that treatment prevented 124 patients from suffering any cardiovascular event.

4.4.4 Cost-effectiveness results

The prescribing of statin therapy was cost-effective for the primary prevention of CHD in Irish males with an average annual CHD risk of 1.5% in 2005 compared to the non prescribing of primary prevention therpy. The results for all statins under both the GMS and DP scheme are presented in Table 4.9.

Table 4.9 Cost-effectiveness results for primary prevention therapy with all available statins under the GMS and DP schemes in 2005

Statin	**GMS (€/LYG)**	**DP (€/LYG)**
Atorvastatin	14,165	19,004
Rosuvastatin	14,652	19,704
Fluvastatin	14,774	19,917
Simvastatin –branded	21,012	29,260
Generic - low cost	*15,839*	*21,499*
Generic – high cost	*23,782*	*33,430*
Pravastatin –branded	25,730	36,321
Generic – low cost	*19,369*	*28,591*
Generic – high cost	*21,621*	*31,969*

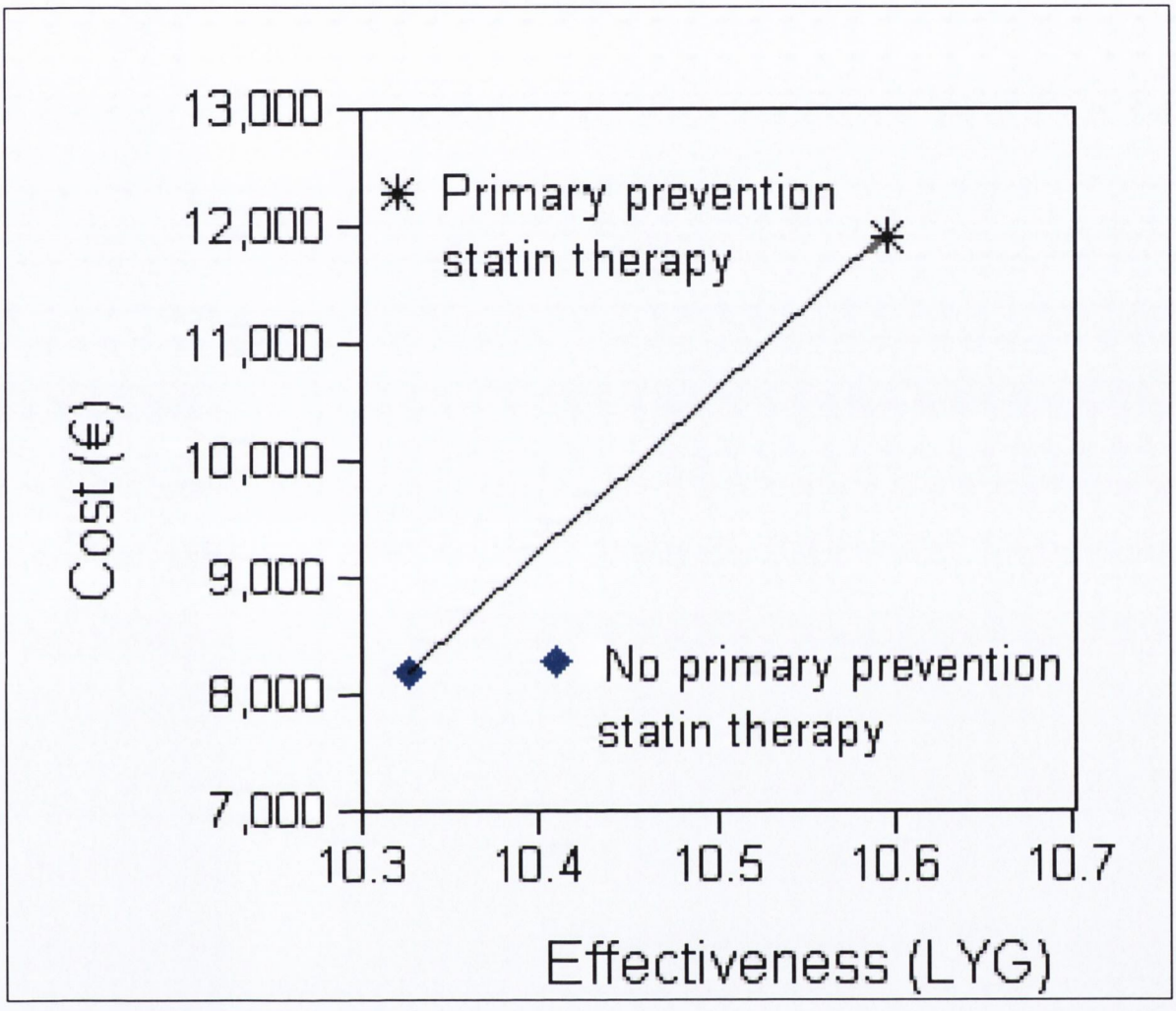
The most cost-effective statin was atorvastatin (Lipitor®), at €14,165/LYG under the GMS scheme, and €19,004/LYG under the DP scheme. This compares favourably with recent economic evaluations of other public health interventions in Ireland i.e. hepatitis B vaccine[185] and pneumococcal conjugate vaccine[186]. The least cost-effective statin was branded pravastatin (Lipostat®), which still compares favourably with the same recent economic evalutaions. Additional cost-effectiveness findings for atorvastatin are presented in Table 4.10.

Table 4.10 Cost-effectiveness results for primary prevention therapy with atorvastatin under the GMS scheme in 2005

Strategy	Cost (€)	LYG
Primary prevention statin therapy	11,964	10.59
No primary prevention statin therapy	8,170	10.33
Difference	*3,794*	*0.26*
ICER	**€14,165/LYG**	

The average cost per patient in the treatment arm of this study, using atorvastatin, was €11,964 over the 15-years. This included the cost of statin therapy, the cost of cardiovascular interventions and the associated monitoring costs. Costs in the no primary prevention arm averaged €8,170 per patient over the same period. Patients in receipt of primary prevention statin therapy were expected to live for 10.59 years, whereas, patients in the no primary prevention group have an average LYG of only 10.33 years. Therefore, over the 15-year period the primary prevention group survived, on average, 3 months (0.26 LYG) longer than the no primary prevention group. The cost-effectiveness curve graphically displays these findings.

Figure 4.7 Cost-effectiveness curve for primary prevention therapy with atorvastatin under the GMS scheme in 2005



4.4.5 Cost-utility results

The cost-utility results for all available statins under the GMS and DP schemes are presented in Table 4.11.

Table 4.11 Cost-utility results for primary prevention therapy with all available statins under the GMS and DP schemes in 2005

Statin	GMS (€/QALY)	DP (€/QALY)
Atorvastatin	17,107	22,457
Rosuvastatin	17,646	23,231
Fluvastatin	17,780	23,466
Simvastatin –branded	24,677	33,795
Generic - low cost	*18,958*	*25,216*
Generic – high cost	*27,739*	*38,404*
Pravastatin –branded	29,892	41,600
Generic – low cost	*22,860*	*33,055*
Generic – high cost	*25,350*	*36,780*

The cost-utility analysis demonstrated that all statins dispensed under both CD schemes were cost-effective and the ICERS fell below the guideline Irish threshold of €45,000/QALY. Similar to the cost-effectiveness model, atorvastatin produced the most favourable results and pravastatin branded the least favourable.

More detailed cost-utility results are presented for atorvastatin under the GMS scheme in Table 4.12.

Table 4.12 Cost-utility results for primary prevention therapy with atorvastatin under the GMS scheme in 2005

Strategy	Cost (€)	QALY
Primary prevention therapy	10,041	10.66
No primary prevention therapy	5,585	10.40
Difference	*4,455*	*0.26*
ICER	**€17,107/QALY**	

As expected, the ICER was higher in the QALY model (€17,107/QALY) than the LYG model (€14,165/LYG) illustrating a decrease in cost-effectiveness due to the inclusion of utility measures.

4.5. Discussion

4.5.1 Model critique

This economic model improves on previous research in a number of ways. It addresses the transition from health to cardiovascular disease reflecting real life experience. If we were to prescribe statin therapy only to patients who have already experienced a cardiovascular event, secondary prevention therapy, we would be forcing a healthy person to experience, and survive a cardiovascular event in order to become eligible for treatment.

This study uses Irish epidemiological data linked to clinical trial data to populate the model. Unit costs, resource utilisation and effectiveness measures are detailed separately facilitating comparison with other studies and increasing the study's adaptability. A number of assumptions were made when constructing this model, including the appropriateness of generalising the effectiveness results obtained from the clinical trials to the community setting in Ireland. The WOSCOPs trial was the predominant source of primary prevention statin therapy effectiveness data used in the model. This trial was chosen due to similarities with the Irish male population of interest including, age profile, cholesterol levels, socio-economic status, and risk factors.

Projections were required to complete the survival curves, and extrapolate beyond the timeframe of the trial data. However, the premise of shortened life expectancy following non-fatal cardiovascular disease is generally acceptable. No costs were attributed to the process of identifying the appropriate patients for treatment as it was assumed that patients would be identified in the course of routine clinical practice. This does not under-estimate the importance of screening, or identification processes but merely reflects current clinical practice. It was also assumed that all patients who experience a cardiovascular event receive secondary prevention statin therapy in accordance with best practice even though this may not always be the case.

Finally, a class effect was also assumed for the efficacy of statins, as it is not possible to differentiate between the different statins on the basis of the evidence from the placebo-controlled trials. Only three head-to-head comparisons of one statin with another have reported clinical outcomes, and only one of these, the PROVE-IT trial, reported statistically significant results[187, 188, 189].

4.5.2 Comparison of results

Comparing cost-effectiveness results across studies is often difficult due to differing study objectives, approach, populations, risk factors and, costing. Our study estimated the ICER for primary prevention statin therapy with atorvastatin under the GMS scheme, to be €14,165/LYG. A range of ICERs (€14,165/LYG to €36,321/LYG) were also produced depending on the statin administered and the CD scheme used. These findings are similar to the findings of other statin therapy cost-effectiveness studies examining patients with a 1.5% annual CHD risk. Pickin *et al.* examined the cost-effectiveness of primary prevention statin therapy in the UK, in persons with a similar level of risk, and produced an ICER of £11,800/LYG (€17,600/LYG)[190]. Ebrahim *et al.* produced statin cost-effectiveness results in the range of £5,400/LYG - £13,300/LYG (€8,100/LYG - €19,900/LYG) for similar levels of CHD risk[191]. Caro *et al.* estimated primary prevention statin therapy cost-effectiveness at £23,747/LYG (€36,000/LYG) [173].

The cost-effectiveness of individual statins also varies greatly[192, 193]. The choice of statin used is paramount to ensure cost-effective prescribing. This study found atorvastatin to be the most cost-effective statin for the primary prevention of CHD in Ireland. Atorvastatin was nearly twice as cost-effective as branded pravastatin, under both CD schemes.

Atorvastatin was also found to be the most cost-effective statin in achieving the UK national service framework target cholesterol levels in patients with diagnosed CHD[194]. The superior efficacy of atorvastatin in terms of percentage reduction in low density lipoprotein-cholesterol resulted in a greater number of patients being treated to target for a given budget. Atorvastatin also proved to be the most cost-effective statin for the secondary prevention of AMI in the UK[195]. Previous analysis in the Irish setting found atorvastatin to be the most cost-effective statin for the secondary prevention of CHD[106].

4.5.3 Reimbursement mechanisms

The cost-effectiveness of statin therapy in Ireland is significantly influenced by the reimbursement mechanism. The GMS scheme produces more favourable results than the DP scheme. The 50% mark up on the acquisition cost of medications reduces the cost-effectiveness of statin therapy under the DP scheme, however, the relative cost effectiveness of statins does not change. The ICERs for the DP scheme range from €19,004/LYG to €36,321/LYG versus €14,165/LYG to €25,730/LYG under the GMS scheme.

It is generally accepted that generic prescribing optimises cost-effectiveness. This is not always the case in the Irish healthcare setting. The cost of statin therapy with generic high cost simvastatin was €683 under the GMS scheme compared to only €367 with branded atorvastatin. As a result, this study found the cost-effectiveness of atorvastatin to be nearly twice that of generic high cost simvastatin.

4.6 Conclusion

Statin therapy lowers cholesterol and is a major contributor to the recent decrease in CHD mortality in Ireland. Increasing statin use and cost has resulted in numerous cost-effectiveness evaluations of statin therapy for the primary prevention of CHD.

This chapter undertook a cost-effectiveness and cost-utility analysis of statin therapy for the primary prevention of CHD in Irish males with an average CHD risk of 1.5% per annum in 2005. Primary prevention statin therapy increased survival rates by 6% with only 31% in the primary prevention arm versus 37% in the no primary prevention arm dying over the 15-year timeframe of the model. This means that only 16 men needed to be treated in order to prevent one death.

All statins prescribed under the GMS and DP schemes were cost-effective when compared to recent economic evaluations of other public health interventions in Ireland. However, the cost-effectiveness of individual statins varied greatly. Atorvastatin (Lipitor®) was found to have the most favourable cost-effectiveness results producing an ICER of €14,165/LYG under the GMS scheme and an ICER of €17,107/QALY under the same scheme in the cost-utility model. The prescribing of generic statin preparations did not promote the most cost-effective prescribing in the Irish healthcare setting.

Chapter 5

Sensitivity analysis applied to the primary prevention statin therapy model

Chapter 5

5.1. Introduction

Over the last decade or so, there have been many developments in the methods to handle uncertainty in cost-effectiveness studies, with particular focus on the use of sensitivity analysis[45].

This chapter addresses the uncertainty in the primary prevention statin therapy model developed in chapter 4, using simple, scenario and probabilistic sensitivity analysis. The robustness of the model's findings to changes in the key model parameters are examined.

5.2. Methods

5.2.1 Simple sensitivity analysis

Simple sensitivity analysis was undertaken to examine the effect, on the cost-effectiveness results, of changing one or more variable at the same time. Both one-way and multi-way simple sensitivity analysis was undertaken in this study. Variables, including their values, assessed under simple one-way sensitivity analysis are presented in Table 5.1.

Table 5.1 Variables examined under simple one-way sensitivity analysis

Model variable	Base case	Sensitivity analysis
Model duration	15 years	5, 10 and 25 years
Statin cost	€367	-35% (€239)
Discount rate	3.5%	0% and 6%
Half-cycle correction	Yes	No

One-way sensitivity analysis included running the model for 5, 10 and, 25 years. The annual cost of statin therapy was decreased by 35% in line with the price decrease negotiated for patent expired medicines in the recent IPHA agreement. The model was run with no discount rate and a discount rate of 6%, as well as with, and without half-cycle correction.

Multi-way simple sensitivity analysis was also undertaken varying a number of parameters at the one time. All costs including statin therapy, procedural, and monitoring costs were reduced

by 35%. Procedural costs were also examined separately. Varying the patient start age to 45 and 65 years was assessed to illustrate the impact of age on the ICER. This involved recalculating the event rates for the general population and adjusting the relative risk adjustment factors accordingly.

Effectiveness data was also subjected to multi-way sensitivity analysis, with a 10% and 20% decrease in effectiveness applied. For example, from the WOSCOPs trial a 10% decrease in effectiveness reduced the relative risk of death from 31%, to 28%. The clinical trial event rates were adjusted and again the relative risk adjustment factors recalculated. Finally, all costs were reduced by 35% while simultaneously decreasing statin effectiveness by 10% and 20%, respectively.

5.2.2 Scenario sensitivity analysis

Scenario sensitivity analysis was also undertaken. The best case analysis assumed a 35% reduction in all costs and a 25-year follow-up allowing additional time for more benefits to occur. The worst case scenario, examined the impact of a 20% reduction in statin effectiveness, which may occur outside of a clinical trial setting, and running the model for a period of only 5 years.

5.2.3 Probabilistic sensitivity analysis

Probabilistic sensitivity analysis was used to examine uncertainty related to the sampling distribution of the parameters and was calculated using 1,000 individual patient simulations. The individual simulation method does not give the same results on any two occasions because of the random nature of the simulation. Estimates of the likely variance associated with the costs and effects of each arm of the model, in terms of the standard deviation are provided. Costs were allocated a normal distribution with a lower bound of zero, a mean of the baseline parameter value and a standard deviation of 10% around the mean. The relative risk adjustment factors were also allocated a normal distribution, again bounded by zero, and a standard deviation of 10% around the mean. In the QALY model, utilities were assigned a triangular distribution.

The cost-effectiveness scatter-plot was drawn to represent the uncertainty in the costs and effects, for both the primary prevention and no primary prevention arms of the study. The spread of the points illustrated the range of uncertainty. The cost-effectiveness plane presented the probability that primary prevention statin therapy was cost-effective compared to no primary prevention therapy at an ICER threshold of €45,000/LYG. The cost-effectiveness acceptability curve for primary prevention therapy was presented, including all possible values of the maximum acceptable ICER appropriate for decision making.

5.3 Results

5.3.1 Simple sensitivity analysis

Table 5.2 shows the key results from the one-way simple sensitivity analysis.

Table 5.2 Cost-effectiveness results from the one-way simple sensitivity analysis

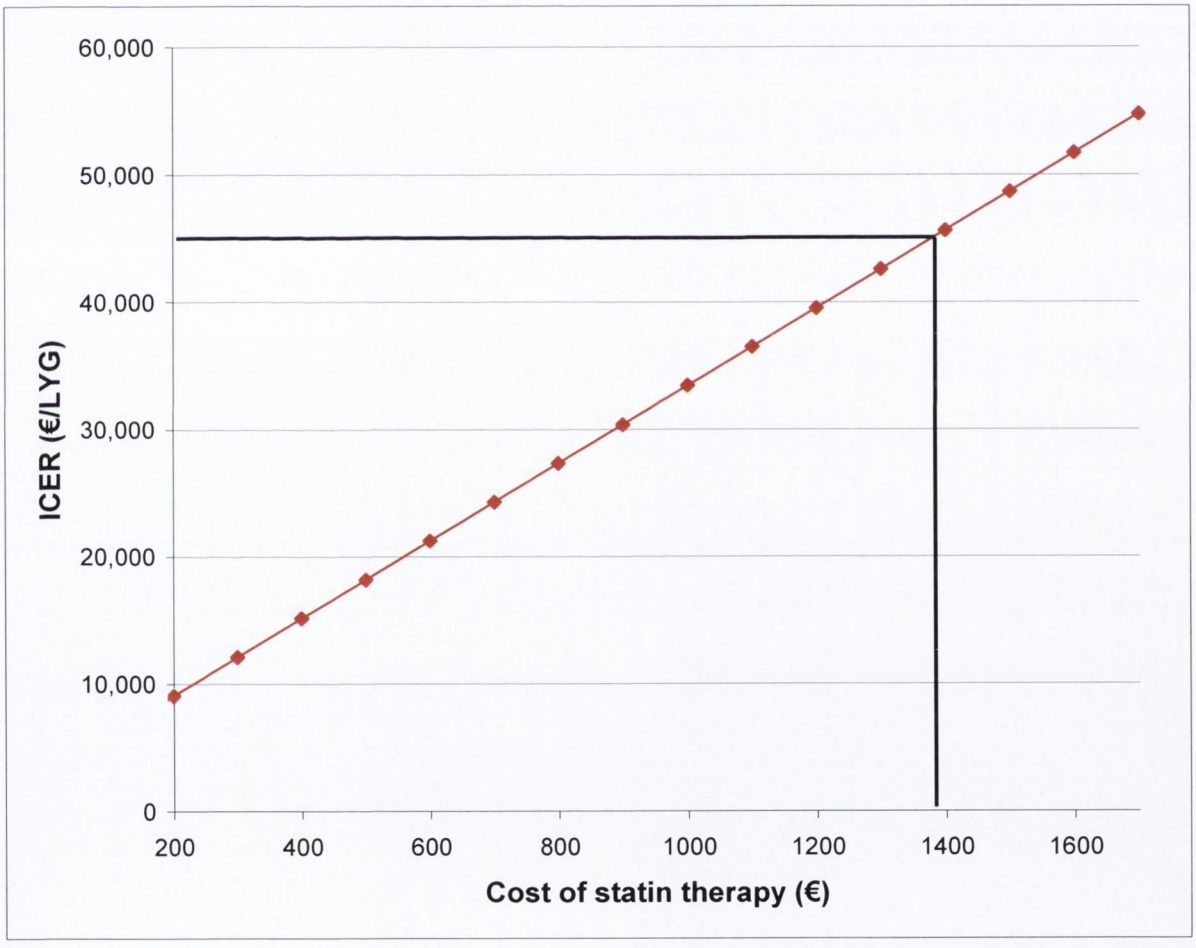
Model variable	Base case	Sensitivity analysis	ICER (€/LYG)
Base Case	-	-	14,165
Model duration	15 years	5 year	83,800
	15 years	10 year	28,931
	15 years	25 year	7,008
Statin cost	€367 per annum	-35% (€239)	10,269
Discount rate	3.5%	0%	13,245
	3.5%	6%	14,762
Half-cycle correction	yes	None	14,559

The model duration had the most significant impact on the ICER. The longer the model was run, the more LYGs collected. This resulted in a smaller ICER representing increased cost-effectiveness. Running the model for 25 years produced a highly cost-effective ICER of €7,008/LYG. Running the model for 5 years restricted the time for potential benefits to occur and resulted in an ICER of €83,800/LYG implying that therapy was no longer cost-effective.

The price of statin therapy also had a substantial impact on the cost-effectiveness results. Lowering drug costs by 35% led to an increase in the effectiveness of statin therapy, with the

ICER reducing from €14,165/LYG to €10,269/LYG. This implied that a 1% decrease in the cost of statin therapy produced a 0.79% decrease in the ICER. For all values of statin therapy in excess of €1,380 per annum, primary prevention statin therapy was no longer cost-effective at an ICER threshold of €45,000/LYG. Figure 5.2 illustrates the impact of changes in the cost of statin therapy on the ICER.

Figure 5.1 Simple sensitivity analysis on the cost of statin therapy



Key results from the multi-way sensitivity analysis are presented in Table 5.3.

Table 5.3 Cost-effectiveness results from the multi-way sensitivity analysis

Model variable	Sensitivity analysis	ICER (€/LYG)
Base case	-	14,165
All costs	Less 35%	9,221
Procedural costs only	Less 35%	16,162
Patient start age	45 years	3,594
	65 years	53,078
All effectiveness data	Less 10%	21,438
	Less 20%	39,339
Cost and effectiveness	Costs less 35%, effectiveness less 10%	13,954
	Costs less 35%, effectiveness less 20%	25,603

Reducing all costs produced a lower ICER as primary prevention therapy became more cost-effective relative to no primary prevention therapy. Reducing procedural costs only, however, increased the ICER, with primary prevention statin therapy becoming less cost-effective as a greater proportion of patients in the no therapy arm benefit from the reduction in procedural costs.

Starting the model with younger patients was more cost-effective than treating older persons, as younger persons are less likely to die from all causes, including CHD. The ICER was only €3,594/LYG for patients entered in the model at a start age of 45 years. The ICER increased to €53,078/LYG for patients beginning the model at 65 years. Incorporation of the impact of quality of life, in addition to mortality, would result in a higher ICER. Therefore, the ICER would exceed the guideline threshold of €45,000/QALY and is thus unlikely to be deemed cost-effective or recommended for reimbursement under the CD schemes.

Effectiveness data from the clinical trials were also subjected to sensitivity analysis. When the relative risk reduction of coronary events, including death, from WOSCOPS was decreased by 10% the ICER increased to €21,438/LYG. A 20% decrease in statin effectiveness resulted in an ICER of nearly €40,000/LYG. This is still below the cost-effectiveness threshold for Ireland, implying that such treatment remains cost-effective under these circumstances. A

simultaneous, 35% decrease in costs and 20% decrease in effectiveness, produced an ICER of €25,603/LYG, implying that primary prevention statin therapy was also cost-effective under these circumstances.

5.3.2 Scenario sensitivity analysis

The best case and worst case scenarios assessed the robustness of the model's findings to more extreme situations and are shown in Table 5.4. These scenarios suggest that primary prevention statin therapy can be extremely cost-effective or cost-ineffective depending on circumstances. However, the likelihood of these extreme scenarios occurring is low.

Table 5.4 Cost-effectiveness results from the scenario sensitivity analysis

Model variable	Sensitivity analysis	ICER (€/LYG)
Base case	-	14,165
Best case	Costs less 35%, duration 25 years	4,562
Worst case	Effectiveness less 20%, duration 5 years	262,162

5.3.3 Probabilistic sensitivity analysis

The probabilistic sensitivity analysis produced cost-effectiveness results similar to the base model. The ICER for the probabilistic analysis was €14,499/LYG compared to an ICER of €14,165/LYG with atorvastatin under the GMS scheme. The key results for the probabilistic analysis are given in Table 5.5. The standard deviations (sd) around the mean cost and LYG illustrate the associated variances and are also shown in Table 5.5.

Table 5.5 Cost-effectiveness results for primary prevention therapy with atorvastatin under the GMS scheme in 2005 using 1,000 simulations

Strategy	Mean Cost (€) (sd)	Mean LYG (sd)
Primary prevention therapy	11,949 (470)	10.60 (0.08)
No primary prevention therapy	8,133 (525)	10.33 (0.09)
Difference	*€3,816*	*0.27 LYG*
ICER	**€14,499/LYG**	

Figure 5.2 presents the cost-effectiveness scatter plot for primary prevention and no primary prevention therapy. The cluster of points for primary prevention therapy is predominantly higher, in terms of cost and effectiveness.

Figure 5.2 Cost-effectiveness scatter plot for primary prevention therapy with atorvastatin under the GMS scheme in 2005

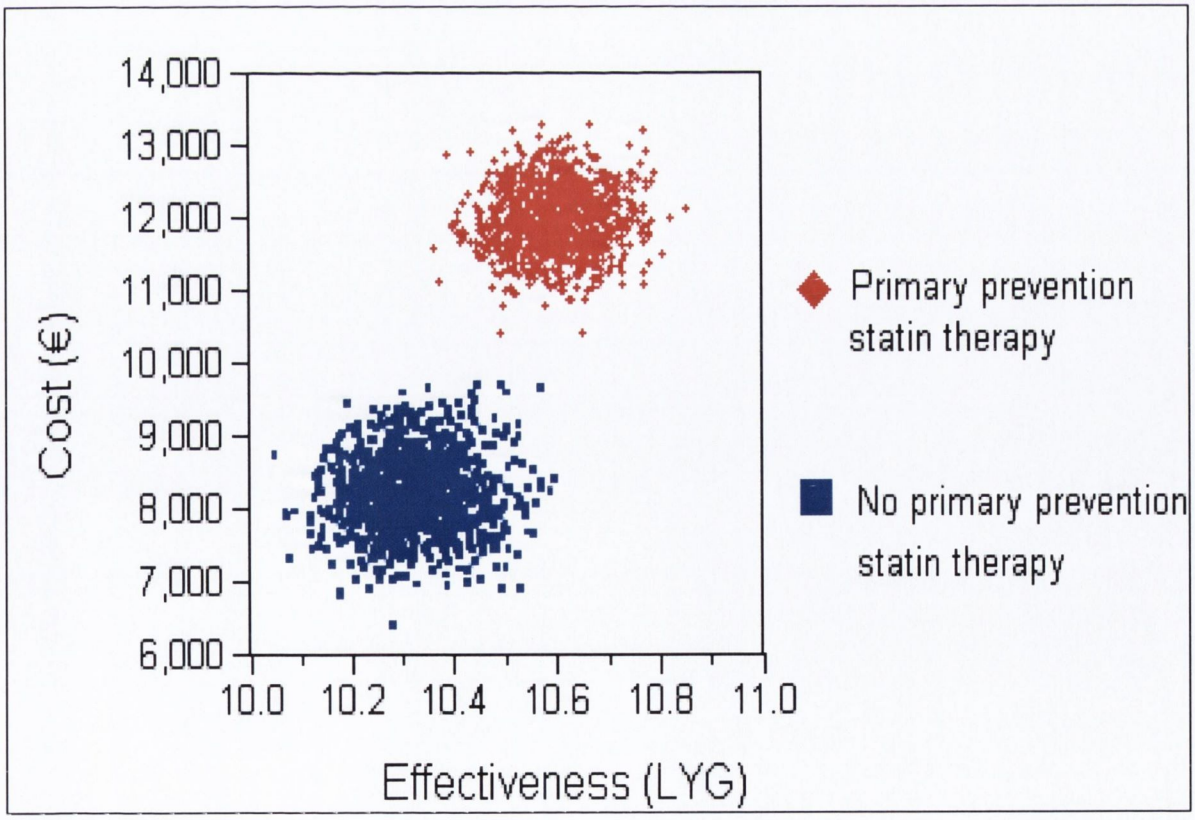
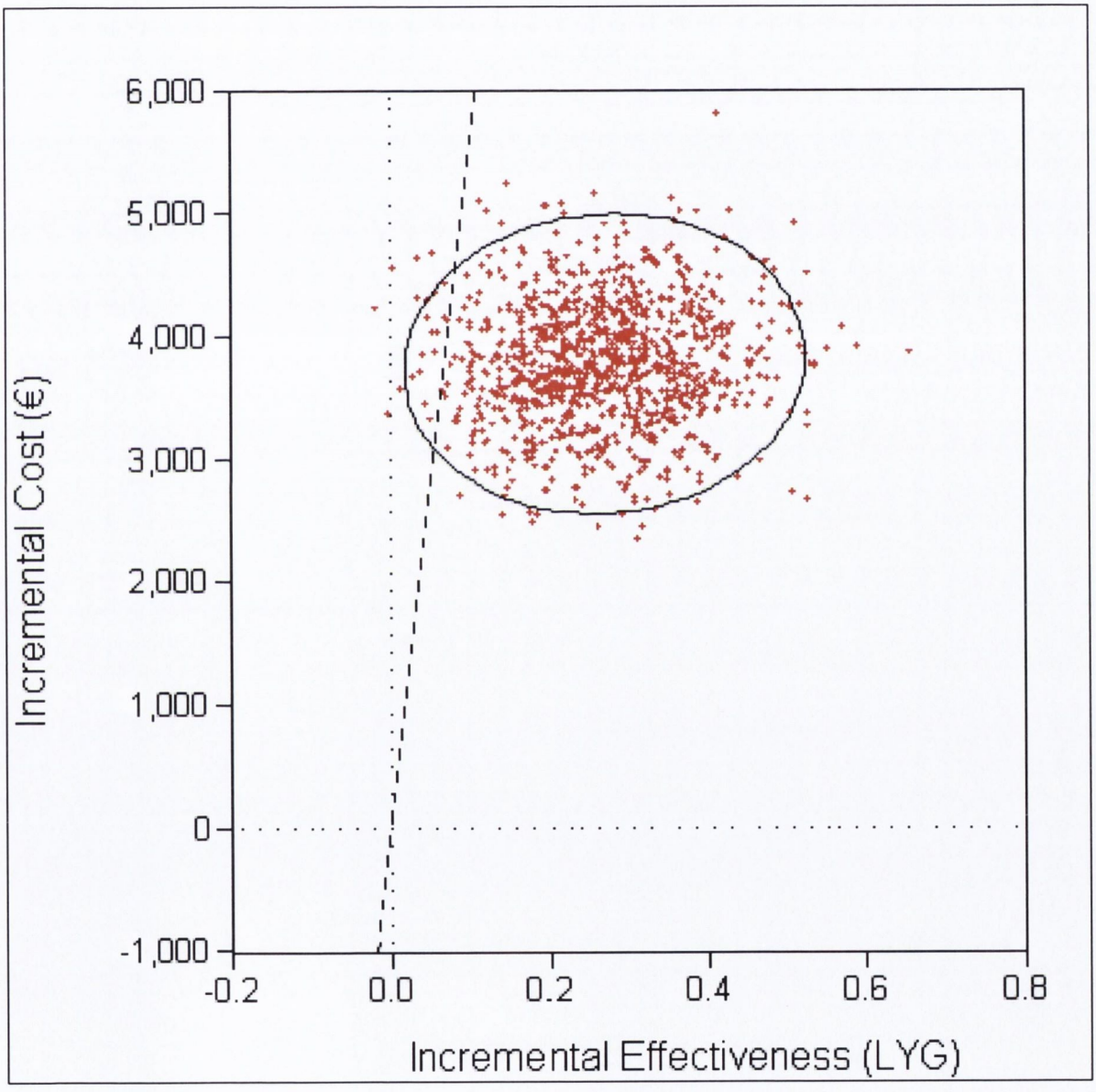


Figure 5.3 presents the cost-effectiveness plane for the 1,000 simulations in the probabilistic sensitivity analysis.

Figure 5.3 Cost-effectiveness plane for primary prevention therapy with atorvastatin under the GMS scheme in 2005

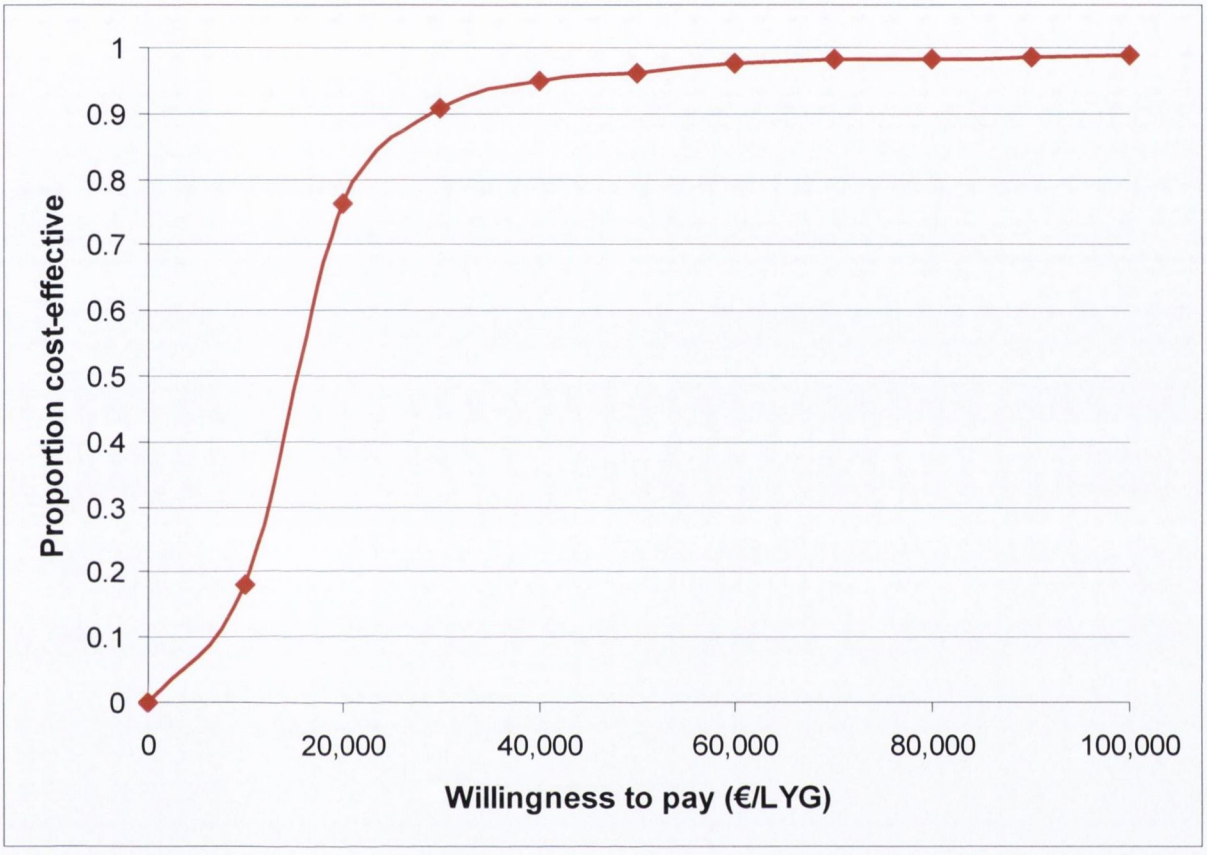


The cost-effectiveness plane, in Figure 5.3 illustrates that primary prevention statin therapy has higher costs and effectiveness in over 99.7% of the simulations. This was evident from the concentration of points in the upper right quadrant. Primary prevention statin therapy was

more costly and less effective than no primary prevention therapy 0.3% of the time. The number of points in the upper left quadrant represents this. None of the simulations were in the lower quadrants implying that primary prevention statin therapy was never less costly than no primary prevention therapy. An Irish ICER threshold, of €45,000/LYG, is represented by the line through the origin. Over 97% of all points were to the right of this line. This means that primary prevention statin therapy was cost-effective 97% of the time at this threshold.

Figure 5.4 presents the cost-effectiveness acceptability curve for primary prevention therapy. Similar to the cost-effectiveness plane it shows that for a cost-effectiveness threshold of €45,000/LYG the probability that primary prevention statin therapy was cost-effective is 0.97. It also illustrates the proportion of therapies that are likely to be cost-effective given various ICER thresholds. The probability of primary prevention statin therapy being cost-effective increased most dramatically between the €10,000 and €20,000 thresholds, with 16% of therapies being cost-effective at the €10,000 threshold, increasing to 77% for an ICER of €20,000/LYG. At the €30,000/LYG threshold the probability of primary prevention statin therapy being cost-effective rose to 90.7%

Figure 5.4 **Cost-effectiveness acceptability curve for primary prevention therapy with atorvastatin under the GMS scheme in 2005**



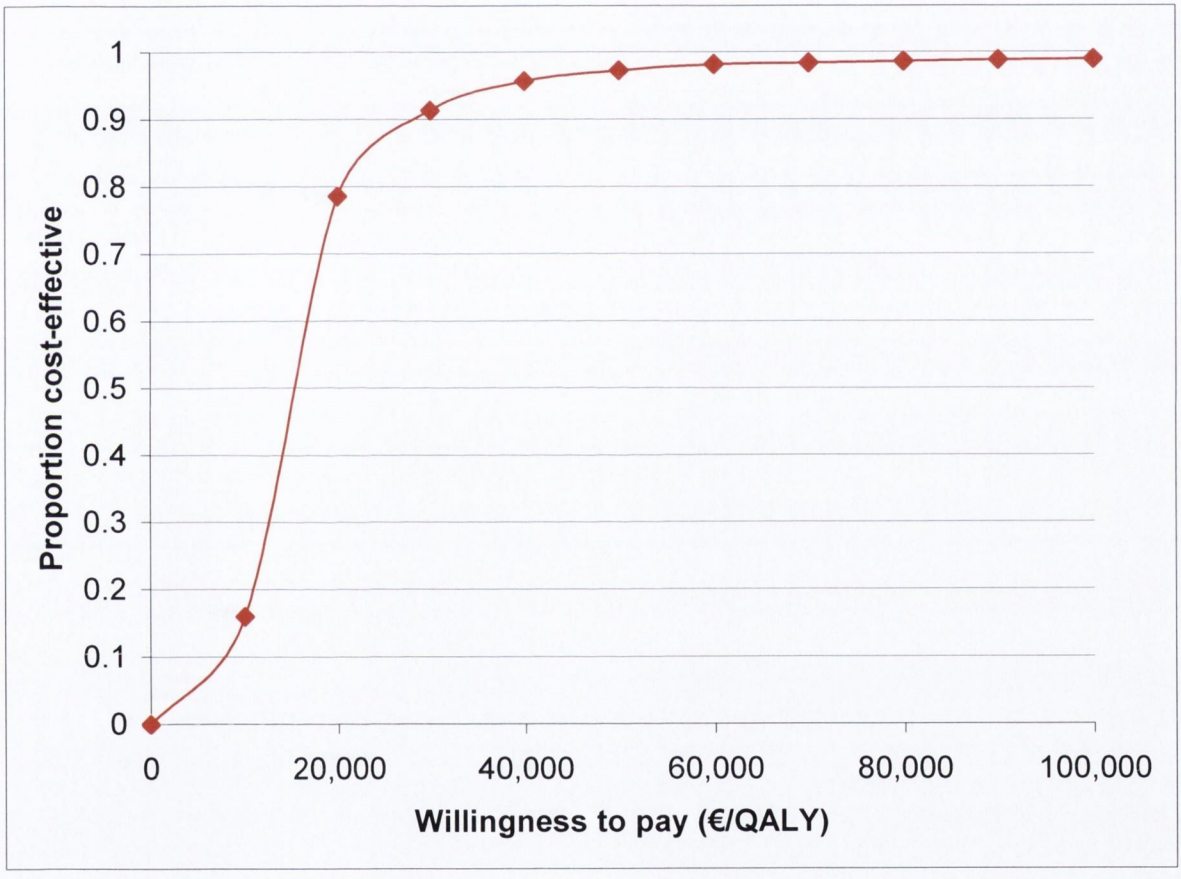
As sensitivity analysis on the cost-utility model produced results similar to the cost-effectiveness model, only selected probabilistic sensitivity analysis cost-utility results are provided here. The ICER for the probabilistic cost-utility analysis was €19,136/QALY for atorvastatin under the GMS scheme as can be seen from Table 5.6.

Table 5.6 **Cost-utility results for primary prevention therapy with atorvastatin under the GMS scheme in 2005 using 1,000 simulations**

Strategy	**Mean Cost (€) (sd)**	**Mean QALY (sd)**
Primary prevention therapy	9,188 (734)	10.70 (0.09)
No primary prevention therapy	4,343 (1,004)	10.45 (0.10)
Difference	*4,845*	*0.25*
ICER	**€19,136/QALY**	

The QALY cost-effectiveness acceptability curve shows that primary prevention statin therapy was cost-effective 89.6% of the time given a cost-effectiveness threshold of €45,000/QALY. This is marginally lower than the acceptability at the €45,000/LYG threshold.

Figure 5.5 Cost-utility acceptability curve for primary prevention therapy with atorvastatin under the GMS scheme in 2005



5.4 Discussion

5.4.1 Drivers of cost-effectiveness

The cost of statin therapy plays a key role in determining the cost-effectiveness of statin therapy. This study found a 1% decrease in the annual cost of statin therapy resulted in a 0.79% decrease in the ICER. This is similar to findings by previous research[162, 191]. The effectiveness of therapy was also a key driver of cost-effectiveness. In this study a 1% decrease in statin effectiveness resulted in a 5% increase in the ICER. Effectiveness was

reduced by up to 20% in the sensitivity analysis in an attempt to address issues such as poorer compliance, however, in line with previous research significant changes in effectiveness did not alter the key cost-effectiveness results[179].

The duration of the model greatly influenced the ICER. Statin models run for a shorter timeframe often give rise to less cost-effective results, as they do not allow sufficient time for benefits to accrue[196]. Also younger patients have a lower probability of cardiovascular events and death, and therefore are often associated with more favourable results.

The CHD risk targeted by statin therapy has a substantial impact on the cost-effectiveness findings. Treatment is better targeted at estimated CHD risk as opposed to cholesterol levels or lipid fractions alone, which are very weak predictors of CHD risk[197, 198, 199]. Cost-effectiveness clearly improves with increasing baseline CHD risk. However, this study, and others[200], show that targeting 1.5% annual CHD risk with primary prevention statin therapy can be cost-effective.

5.4.2 Developing treatment policy

When developing treatment policy, cost-effectiveness is only one consideration. The proportion of the population that requires treatment must also be considered. Treatment of all patients above the 1.5% CHD risk threshold at which benefit is proven would involve treating significantly more patients. In the UK, estimates range from 11.4% to 24.4% for the 35-69 year old population. Applied to the Irish setting this could result in 400,000 people eligible for statin therapy. In 2005, the total CD schemes statin expenditure was €99m. Assuming that all patients were only prescribed the most cost-effective statin (atorvastatin), the additional annual cost of treatment could be as much as €100m. If pravastatin branded was prescribed, the costs could range from an additional €91m to €308m per annum.

It has been advocated that all cost-effective treatments should be made available in collectively funded health systems[201]. Primary prevention statin therapy was found to be cost-effective at the 1.5% CHD risk threshold and would be as cost-effective as many other treatments in wide use[202]. This presents the Irish DoHC and the HSE with a dilemma as to

adopt such a policy may not be sustainable given the current level of funding and healthcare resources.

5.4.3 Modelling uncertainty

Economic models can be used to reflect uncertainty. By now, clinical trials are well established with validated processes and procedures. Designing economic models can be more complex than designing clinical trials, due to the lack of information and the requirement for various assumptions. There may even be a complete absence of formal evidence regarding an element of the intervention, and therefore, informed judgements may be required.

Economic models may have to deal with lack of head-to-head randomised controlled trial results to compare interventions. Trials regularly use intermediate end points as an indicator for the ultimate health goal of concern to policy makers. Modelling beyond the clinical trial period is frequently required due to a shorter follow-up in the clinical trial than the period of interest to the policy maker. This means that costs and benefits may have to be extrapolated, via the use of economic modelling.

5.5 Conclusion

Sensitivity analysis, and in particular probabilistic sensitivity analysis, is increasingly being used to assess uncertainty in economic evaluations. This chapter used various types of sensitivity analysis to examine the uncertainty in the primary prevention statin therapy model developed in chapter 4.

A 1% decrease in the cost of statin therapy resulted in a 0.79% decrease in the ICER. A similar decrease in statin effectiveness increased the ICER by 5%. The model duration was the single variable with the most significant impact on the cost-effectiveness results producing an ICER of €7,008/LYG. Altering the start age to 65 years resulted in primary prevention statin therapy no longer being cost-effective.

The best case scenario, assessing a 35% decrease in all costs and extending the model for 25 years, produced highly cost-effective results. However, the worst case scenario, which

involved reducing effectiveness by 20% and only running the model for 5 years, was highly ineffective.

The probabilistic sensitivity analysis produced an ICER of €14,499/LYG for atorvastatin (Lipitor®) under the GMS scheme. It found primary prevention statin therapy to be cost-effective 97% of the time at an Irish ICER threshold of €45,000/LYG. Probabilistic analysis on the cost-utility model produced similar, though marginally less effective results, due to the inclusion of utility measures, with therapy being cost-effective 90% of the time at the current Irish guideline threshold of €45,000/QALY.

Chapter 6

Findings, recommendations and future research

Chapter 6

This chapter has 3 aims:

- First, to present a summary of the findings from the economic evaluations undertaken in this thesis;
- Second, to make recommendations for the Irish health service arising from these findings; and,
- Third, to outline areas for future research highlighted by this thesis.

6.1 Summary findings

A summary of the findings from the three economic evaluations undertaken in this thesis is presented in this section.

6.1.1 CVD cost-of-illness analysis

In chapter 2, a cost-of-illness analysis for the cost of CVD from the Irish health service perspective in 2005 was undertaken. The findings from this chapter include:

- The cost of treating CVD was estimated at €648m;
- Hospital costs were estimated at €426m;
- Inpatient CVD costs were estimated at €323m, day case costs at €19m, outpatient costs at €50m and A&E costs at €34m;
- Community medication costs were estimated at €222m with the GMS scheme contributing €162m; and,
- Serum lipid reducing agents, including statins, were the highest cost CVD drug group dispensed under the Community Drugs schemes.

6.1.2 PPI triple therapy cost-effectiveness analysis

In chapter 3, an evaluation of the cost-effectiveness of PPI triple therapy for the eradication of H. pylori infection in the community setting in Ireland in 2003 was undertaken. The findings from this chapter include:

- The overall effectiveness of PPI triple therapy, in terms of no further maintenance anti-secretary therapy during the one-year follow-up period, was 40%-46% depending on the PPI prescribed;
- The majority of prescriptions resulted in the prescribing of PPI maintenance therapy;

- Rabeprazole (Pariet®) was the most cost-effective PPI regimen, even when subjected to extensive sensitivity analysis;
- The annual cost of treating patients with PPI triple therapy varied from under €100 to nearly €900, depending on the PPI prescribed, the patients' symptoms and the strategy adopted; and,
- Prescribing only the most cost-effective PPI regimen, rabeprazole, has the potential to result in annual savings of €8.7m under the GMS scheme alone.

6.1.3 Primary prevention statin therapy analysis

In chapter 4, a cost-effectiveness and cost-utility analysis of statin therapy for the primary prevention of CHD in 2005 was undertaken. Irish males with an average annual CHD risk of 1.5% were examined. The findings from this chapter include:

- Primary prevention statin therapy increased survival rates by 6% with only 31% in the primary prevention arm, versus 37% in the no primary prevention arm dying over the 15-year timeframe of the model;
- All statins prescribed under the GMS and DP schemes were found to be cost-effective at the current Irish guideline ICER thresholds. The cost-effectiveness of individual statins, however, varied greatly depending on the statin prescribed and the Community Drugs scheme used; and,
- Atorvastatin (Lipitor®) was found to be the most cost-effective statin, producing an ICER of €14,165/LYG. Atorvastatin also had the most favourable cost-utility results.

In chapter 5, sensitivity analysis was used to address uncertainty in the primary prevention statin therapy model. The findings from this chapter include:

- Primary prevention statin therapy was found to be cost-effective 97% of the time at an ICER threshold of €45,000/LYG. The cost-utility analysis found statin therapy to be cost-effective 90% of the time at the Irish guideline threshold of €45,000/QALY;
- The probabilistic sensitivity analysis produced a highly cost-effective ICER of €14,499/LYG for atorvastatin under the GMS scheme;
- A 1% decrease in the cost of statin therapy decreased the ICER by 0.79%; and,
- A 1% decrease in statin effectiveness increased the ICER by 5%.

6.2 Recommendations

The recommendations for the Irish health service arising from the analysis undertaken in this thesis are outlined in this section.

6.2.1 Development of Irish data sources

All evaluations require comprehensive, accurate data sources. One of the main deficiencies in Irish healthcare, highlighted in the 2001 Health Strategy, is inadequate Irish healthcare information[69]. This limits the capacity for prioritisation, planning, evidence-based decision making and efficient service delivery. The Casemix database and the CD prescribing databases demonstrate the value of good information sources. These databases can be used to plan, monitor and assess the effects of health policies. Gathering, synthesising and scrutinising data, however, is a costly exercise[203].

Arising from the economic analysis undertaken in this thesis I would advocate the following recommendations regarding Irish data sources:

- Health service decision makers should make better use of all information sources to inform decisions regarding the efficient allocation of resources;
- Irish epidemiological and costing data need to be further developed;
- Information systems within the community setting should be developed and expanded;
- The classification of outpatient and A&E activity by disease category should be included in the Casemix programme;
- The inclusion of patient outcomes in the Irish CD schemes database should be considered; and,
- Linking the Casemix and the CD databases should be considered enabling the tracking of patients across the hospital and community settings.

6.2.2 Development of Irish health economic capacity

HIQA has been charged with the development and management of health economic capacity in Ireland, specifically, to evaluate the clinical and cost-effectiveness of health technologies including drugs and to provide advice arising out of the evaluations to the Minister and the

Executive (HSE)[204]. The contribution economic analysis can make to the provision of cost-effective healthcare in Ireland has been highlighted by this thesis. The main challenges facing HIQA regarding the expansion of health economic capacity in the Irish health service include:

- Gaining recognition for the contribution health economics can make in the development and delivery of cost-effective health services;
- Identifying and developing health economic skills and resources;
- Developing international linkages and collaborations with exposure to the best international expertise in areas such as HTA and pharmacoeconomic evaluations; and,
- Communicating to decision makers, in a meaningful way, the results of economic evaluations.

6.2.3 Application of economic evaluations

A number of recommendations arise from the development and application of the economic evaluations applied in this thesis including:

- Economic evaluations should be updated when new evidence becomes available;
- The disease-specific costing framework developed in chapter 2 should be applied to various disease categories in the Irish healthcare setting including diseases and disorders of the digestive system and the nervous system;
- The cost-effectiveness and cost-utility analysis undertaken in this thesis should be used as a template for a range of therapeutic areas and classes of medications focusing initially on other high cost therapeutic areas such as hypertension, depression and asthma; and,
- The type of sensitivity analysis undertaken in chapter 5 should be used to assess the uncertainty surrounding all economic evaluations undertaken in the Irish healthcare setting. This approach should also be applied to submissions of evidence from pharmaceutical companies in advance of a decision on product reimbursement by the Irish health service.

6.2.4 Promotion of cost-effective prescribing

Following on from the economic analysis undertaken in this thesis, I suggest that the following cost-effective prescribing recommendations be implemented:

- National therapeutic prescribing guidelines, specific to the Irish healthcare setting, incorporating Irish cost-effectiveness data should be issued regularly by the Irish health service;
- The results of economic evaluations, similar to those undertaken in this thesis should also be published, so that they are fully accessible and understood, facilitating the prescribing of the most cost-effective preparations;
- The HSE should implement and carefully monitor all price reductions negotiated in the IPHA agreement. The 35% post-patent price reduction can be applied to the PPIs, omeprazole (Losec®) and lansoprazole (Zoton®), and the statins, pravastatin (Lipostat®) and simvastatin (Zocar®). This has the potential to result in annual savings under the CD schemes in excess of €18m for the PPIs and of nearly €14m for statin therapy;
- The cost-effectiveness of hospital and community drug prescribing should be reviewed simultaneously. The vast majority of prescriptions continued in the community setting originate in the hospital environment and may not be the most cost-effective community setting preparation. The HSE, as the purchasers of medications in the hospital and the community settings should consider aligning the most cost-effective preparations in both settings;
- Only the most cost-effective preparations should be prescribed under the CD schemes. Prescribing only rabeprazole (Pariet®) triple therapy for the eradication of H. pylori infection could result in annual savings of €8.7m under the GMS scheme. Prescribing only the most cost-effective statin, atorvastatin (Lipitor®) for the primary prevention of CHD in Ireland may also generate substantial savings;
- Generic preparations should only be prescribed if they are the most cost-effective regimen. Poorer cost-effectiveness results are often found for the generic preparations in Ireland as the pricing of generics can be greater than the price of other similar branded products. Of the nine PPI regimens examined the generic preparations ranked third, fifth, seventh, and eighth in terms of cost-effectiveness. In the primary prevention statin therapy model the generic preparations ranked fourth, fifth, seventh and eighth in terms of cost-effectiveness; and,

- The Irish health service should review the use of the DP scheme as the cost-effectiveness of therapy is significantly influenced by the reimbursement mechanism. In both the PPI and statin therapy analysis the GMS scheme produces more favourable results than the DP scheme due to the inclusion of a 50% mark up on the acquisition costs of medicines under the DP scheme.

6.3 Further research

This thesis highlighted a number of areas for further research including:

- The approach required to implement national therapeutic prescribing guidelines for all medications dispensed under the CD schemes;
- The feasibility of including patient outcomes in the CD schemes database;
- A review of PPI triple therapy prescribing patterns focusing on patient outcomes, the duration of the maintenance phase and the appropriate maintenance phase dose; and,
- The implications of revising Irish guidelines recommending primary prevention statin therapy at the 1.5% annual CHD risk.

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List of Publications

1. 'Best practice' for Helicobacter pylori eradication in the primary care setting

Walshe V, O'Morain C, Bennett K, Keeling PWN, Barry M.

Irish Medical Journal 2006; 99: (1) 11-12.

2. Cost effectiveness of statin therapy for the primary prevention of coronary heart disease.

Walshe V, Nash A, Barry M.

Irish Medical Journal 2006; 100: (3) 144-145.