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Health Technology Assessment in the Irish Healthcare Setting: Application to Oral Anticoagulants

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A thesis submitted for the degree of Doctor in Philosophy

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2012

DECLARATION

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25th May 2012.

Laura M McCullagh

Date

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SUMMMARY

The objective of this thesis was to examine the application of economic evaluation within the Irish healthcare setting. In so doing, the author sought to develop skills in indirect comparison, economic modelling, value of information analysis and prescribing database analysis. The therapeutic area chosen was the new oral anticoagulants. Rivaroxaban (Xarelto®) and dabigatran (Pradaxa®) were licensed in Ireland in 2008 for the primary prevention of venous thromboembolism (VTE) in adults undergoing elective total hip replacement (THR) and total knee replacement (TKR).

A systematic literature search identified 25 published model based economic evaluations of thromboprophylaxis after THR and TKR. The published models were used to inform the development of two independent thromboprophylaxis models; one with a short-term- and one with a lifetime- horizon.

There are no head-to-head data comparing rivaroxaban and dabigatran after THR or TKR. A Bucher *et al* indirect comparison was performed (enoxaparin is a common comparator across the respective pivotal clinical trials). After THR, the relative risk (RR) (dabigatran vs. rivaroxaban) of developing a: distal DVT=2.797 (95%CI 1.315, 5.946); proximal DVT=6.159 (2.412, 15.725); symptomatic PE=6.657 (0.843, 52.598); major bleed=1.286 (0.091, 18.247). After TKR, the RR (dabigatran vs. rivaroxaban) of developing a: distal DVT=1.908 (1.572, 2.315); proximal DVT=1.226 (0.618, 2.432); major bleed=0.959 (0.447, 2.053). The risk of developing a symptomatic PE with either drug was zero across the trials considered. There is some uncertainty associated with the strength of this indirect comparison.

A 180 day economic model evaluated the cost-effectiveness of rivaroxaban, dabigatran and enoxaparin as VTE prophylaxis. The perspective was that of the Irish Health Service Executive (HSE). The threshold considered was €45,000/QALY. Rivaroxaban dominated both comparators after THR and TKR. The basecase ICER for dabigatran compared to enoxaparin after THR was €33,750/QALY. Dabigatran dominated enoxaparin after TKR. Rivaroxaban has the highest probability of being the most cost-effective strategy after both THR (at 39%) and TKR (at 42%).

A lifetime economic model evaluated the cost-effectiveness of the three strategies. The results of the lifetime- and the 180 day- models were compared. In the lifetime model, rivaroxaban continued to dominate both comparators after THR and TKR. The ICER for dabigatran compared to enoxaparin, after THR, fell to €2,935/QALY. Dabigatran continued to dominate enoxaparin after TKR. The probability that rivaroxaban is the most cost-effective option increased to 69% after THR and to 79% after TKR.

Expected Value of Perfect Information (EVPI) estimates on all four models i.e., the TKR and THR (180 day- and lifetime-) models were calculated. Expected Value of Perfect Parameter Information (EVPPI) analysis indicated that, consistently across the four models, further research should be directed towards the direct medical costs. The THR lifetime model was chosen for further analysis. Assuming a 10 year decision time horizon, the population-EVPI estimate was €11.96 million; the population-EVPPI (direct medical costs) was worth €9.00 million. Updated direct medical costs (deemed to less uncertain than the original costs) were input into the THR lifetime model. All analyses were repeated. Rivaroxaban continued to dominate. The probability that rivaroxaban is the most cost-effective strategy increased from 69% (in the original analysis) to 81% (in the revisited analysis). Population EVPI estimates fell from €11.96 million to €3.43 million.

National General Medical Services (GMS) prescribing trends for both drugs were analysed. During the study period (January 2010 to June 2011 inclusive), rivaroxaban and dabigatran were licensed in Ireland for VTE prophylaxis after THR or TKR only. Both drugs had received a positive HSE reimbursement status for this indication only. Over this time period, both drugs were frequently prescribed for longer than the maximum licensed duration (at that time) of 35 days. Dabigatran was more frequently prescribed for long durations. Analysis of the Eastern Health Board GMS cohort (n=540,221) indicated that patients on rate/rhythm control therapy (commonly used in atrial fibrillation (AF)) were significantly more likely to have received over 90 days (odds ratio (OR) = 17.9; 95%CI 13.6, 23.5) or over 180 days (OR = 16.3; 95%CI 11.5, 23.0) of dabigatran compared to patients not receiving rate/rhythm control therapy. This suggests that, contrary to its license and reimbursement status (at that time) dabigatran may have been prescribed for stroke prevention in AF.

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LIST OF ABBREVIATIONS

ACCP	American College of Chest Physicians
AF	Atrial fibrillation
APTT	Activated partial thromboplastin time
ARIC	Artherosclerotic Risk in Communities
ATC	Anatomical Therapeutic Chemical
BD	Twice daily
BTS	British Thoracic Society
CBA	Cost benefit analysis
CD	Community Drug
CEA	Cost-effectiveness analysis
CEAC	Cost effectiveness acceptability curve
CEAF	Cost effectiveness acceptability frontier
CHS	Cardiovascular Health Study
CI	Confidence interval
CONSORT	Consolidated Standards of Reporting Trials
COSI	Cost of Stroke in Ireland
CoV	Coefficient of variation
CPU	Corporate Pharmaceutical Unit
CrCl	Creatinine clearance
CRD	Centre for Reviews and Dissemination
CrI	Credible interval
CTPA	Computed tomographic pulmonary angiography
CUA	Cost utility analysis
DARE	Database of Abstracts of Reviews of Effects
DDD	Defined daily dose
DES	Discrete event simulation
DOH	Department of Health and Children
DP	Drugs Payment
DRG	Diagnosis related group
DTI	Direct thrombin inhibitor
DVT	Deep vein thrombosis
EC	European Commission
ECG	Electrocardiogram

EMA	European Medicines Agency
ENDORSE	Epidemiologic International Day for the Evaluation of Patients at Risk for Venous Thromboembolism in the Acute Hospital Care Setting
EU	European Union
EVPI	Expected value of perfect information
EVPPI	Expected value of perfect parameter information
EVSI	Expected value of sample information
GDP	Gross domestic product
GI	Gastrointestinal
GMS	General Medical Services
GP	General Practice
GPRD	General Practice Research Database
HIPE	Hospital In-Patient Enquiry
HIQA	Health Information and Quality Authority
HIT	Heparin induced thrombocytopenia
HR	Hazard ratio
HSE	Health Services Executive
HTA	Health Technology Assessment
HTD	High Tech Drugs
ICD-10-AM	International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Australian Modification
ICER	Incremental Cost Effectiveness Ratio
ICH	Intracranial haemorrhage
IMB	Irish Medicines Board
INR	International normalised ratio
IPHA	Irish Pharmaceutical Healthcare Association
ITT	Intention to treat
LITE	Longitudinal Investigation of Thromboembolism Etiology
LMWH	Low molecular weight heparin
LOS	Length of stay
LTI	Long Term Illness
LYG	Life Year Gained
MC	Monte Carlo
mITT	Modified intent to treat

MI	Myocardial infarction
MIMS	Modified Index of Medical Specialities
MOS	Major orthopaedic surgery
mRS	Modified Rankin Score
MTC	Mixed treatment comparison
NB	Net benefit
NCC-AC	National Collaborating Centre for Acute Care
NCPE	National Centre for Pharmacoeconomics
NICE	National Institute for Health and Clinical Excellence
NHS	National Health Service
NHS EED	NHS Economic Evaluation Database
NMB	Net monetary benefit
OAC	Oral anticoagulant
OD	Once daily
OECD	Organisation for Economic Co-operation and Development
OR	Odds ratio
PCRS	Primary Care Reimbursement Services
PE	Pulmonary embolism
PEVPI	Population level expected value of perfect information
PIOED	Prospective Investigation of Pulmonary Embolism Diagnosis
PSA	Probabilistic analysis
PTS	Post thrombotic syndrome
QALYs	Quality adjusted life year
QoL	Quality of life
RCT	Randomised controlled trials
RD	Relative difference
RECORD	REgulation of Coagulation in ORthopedic Surgery to prevent DVT and PE
RR	Relative risk
SA	Sensitivity analysis
SC	Subcutaneous
SD	Standard deviation
SE	Systemic embolism
SPAF	Stroke prevention in atrial fibrillation

SPC	Summary of Product Characteristics
TIA	Transient ischaemic attack
TKR	Total knee replacement
THR	Total hip replacement
UH	Unfractionated heparin
UK	United Kingdom
US	United States
VKA	Vitamin K antagonist
VOI	Value of Information
VQ	Ventilation perfusion
VTE	Venous thromboembolism
WHO	World Health Organisation

Chapter 1

An Introduction to Pharmaceutical Expenditure within the Irish Healthcare Setting and the Concepts of Economic Evaluation

1 AN INTRODUCTION TO PHARMACEUTICAL EXPENDITURE WITHIN THE IRISH HEALTHCARE SETTING AND THE CONCEPTS OF ECONOMIC EVALUATION 3

1 An Introduction to Pharmaceutical Expenditure within the Irish Healthcare Setting and the Concepts of Economic Evaluation

1.1 Background

Economics is the science that deals with the consequences of resource scarcity; health economics specifically deals with the consequence of resource scarcity within the health care setting [1].

For healthcare decision makers, there is a need to assess the value for money, or cost-effectiveness, of health care procedures, services and programmes given the finite resources available. This can be achieved through Health Technology Assessment (HTA). HTA is a multidisciplinary process. It summarises the available information about the medical (clinical effectiveness and safety), social, economic (cost-effectiveness and budget impact), organisational, ethical and medico-legal issues related to the development, diffusion and use of a health technology. Health technologies include pharmaceuticals, devices, diagnostics, procedures, care pathways, public health activities, as well as the systems within which health is protected and maintained.

HTA is a decision support tool. Its purpose is to inform decisions regarding the allocation of healthcare resources to enable healthcare policies that are safe, effective, patient-focused and achieve best value [2]. Pharmacoeconomics is the branch of HTA that focuses on the costs and benefits of drug therapy, in an attempt to provide the best value for money for a given drug budget [3].

The objectives of this chapter are to:

- Provide an overview of the expenditure on pharmaceuticals within the Irish healthcare setting.
- Highlight the year-on-year increase seen in this expenditure and discuss the various strategies which have been introduced to contain it.

- Introduce the concepts of economic evaluation used in this thesis, paying due reference to the use of such evaluations within the context of the Irish healthcare system.

1.2 The Irish Healthcare Setting

In Ireland, healthcare policy and expenditure is governed by the Department of Health (DOH) and administered through the Health Service Executive (HSE). The Board of the HSE is the governing authority of the organisation and is accountable to the Minister for Health. The HSE is the largest employer in the State and employs about 107,000 whole time equivalents. It provides community, hospital and ambulance/emergency response services through the four HSE regions: HSE West, HSE South, HSE Dublin Mid-Leinster and HSE Dublin North East.

Health service funding is derived mainly from taxation (75%) with private funding from health insurance accounting for 11% and patient co-payment accounting for the remainder [4].

Recent figures show that, in Ireland, total health spending in 2009 accounted for 9.5% of Gross Domestic Product (GDP), which equals the 'Organisation for Economic Co-operation and Development' (OECD) countries average. Per capita expenditure on pharmaceuticals in Ireland far exceeded the OECD average and was the highest among OECD countries after the US and Canada [5].

In 2010, the HSE's revenue expenditure was €14.2 billion. Of this, €5.2 billion (37%) was spent on hospital services, €4.5 billion (32%) on community services, €3.2 billion (23%) on primary care and medical card schemes (via the HSE-Primary Care Reimbursement Service (PCRS)) and the remainder on central and clinical support services. A further €370 million was spent on maintaining and developing the capital infrastructure of the health system [6]. The HSE 2011 service plan highlights the current fiscal climate with a reduction in healthcare spending to €13.5 billion [7].

1.2.1 Pharmaceutical Expenditure

The HSE-PCRS manages the reimbursement of medications in the community via the Community Drugs (CD) Schemes. Of the €3.2 billion expenditure by the PCRS in 2010, over 64% (€2 billion) was on pharmaceuticals [6]. The next largest expenditure items were doctors' fees and allowances and capitation payments at 15% (€496m) and 13% (€420m) respectively.

1.2.2 Community Drugs Schemes

There are a number of different reimbursement schemes within the CD Schemes. The largest are the General Medical Services (GMS), the Drugs Payment (DP), the Long-Term Illness (LTI) and the High-Tech Drugs (HTD) Schemes. These four Schemes account for 98% of prescriptions and 99% of expenditure in the community setting [8].

1.2.2.1 The General Medical Services Scheme

The GMS Scheme is the largest of the CD Schemes, it currently accounts for about two-thirds of pharmaceutical expenditure in primary care [9].

This Scheme is means tested and provides free health services to those who are unable, without undue hardship, to arrange medical services for themselves and their dependents. From July 2001 until October 2008, GMS medical cards were automatically issued, without a means test, to all individuals aged 70 years and over. Since October 2008, cards are not automatically issued to this group; however the majority of those over 70 years remain eligible [10]. The number of persons eligible for this Scheme increased from 1,148,055 (30.32% of the population) in 2000 [11] to 1,615,809 (about 40% of the population) in 2010 [6].

Pharmacists are paid a flat fee per item for dispensing on this Scheme [12].

A 50 cent co-payment charge per item was introduced for the GMS Scheme (with a monthly ceiling price of €10 per family) on 1 October 2010 [13].

1.2.2.2 Drugs Payment Scheme

The DP Scheme was introduced on 1 July 1999; it applies to Irish residents who do not have a GMS medical card. Since January 2010, the maximum co-payment is

€120 in any calendar month for approved prescribed medicines for use by that person or his/her family in that month [10]. The number of patients in this Scheme was 942,193 (24.88% of the population) in 2000 [11]; in 2009 it had increased to 1,587,448 (37.44%) of the population [9].

Pharmacists are paid a percentage mark-up (20%) on the ingredient cost as well as a dispensing fee per item on this Scheme [12].

1.2.2.3 Long-Term Illness Scheme

The LTI Scheme entitles patients suffering from any one of 15 specified chronic conditions to reimbursement for medicines relevant to their condition irrespective of income. The medical conditions covered include diabetes mellitus, diabetes insipidus, epilepsy, Parkinson's disease, multiple sclerosis, phenylketonuria, cystic fibrosis, spina bifida, hydrocephalus, haemophilia, cerebral palsy, acute leukaemia, muscular dystrophies, mental handicap and mental illness (for those under 16 years only) [10]. The number of patients eligible for this Scheme increased from 82,619 (2.18% of the population) in 2000 [11] to 127,636 (3.01% of the population) in 2009 [9].

Similar to the DP Scheme, pharmacists are paid a percentage mark-up (20%) on the ingredient cost as well as a dispensing fee per item on the LTI Scheme [12].

A 50 cent co-payment charge per item was introduced on 1 October 2010 (with a monthly ceiling price of €10 per family) [10].

1.2.2.4 High-Tech Drugs Scheme

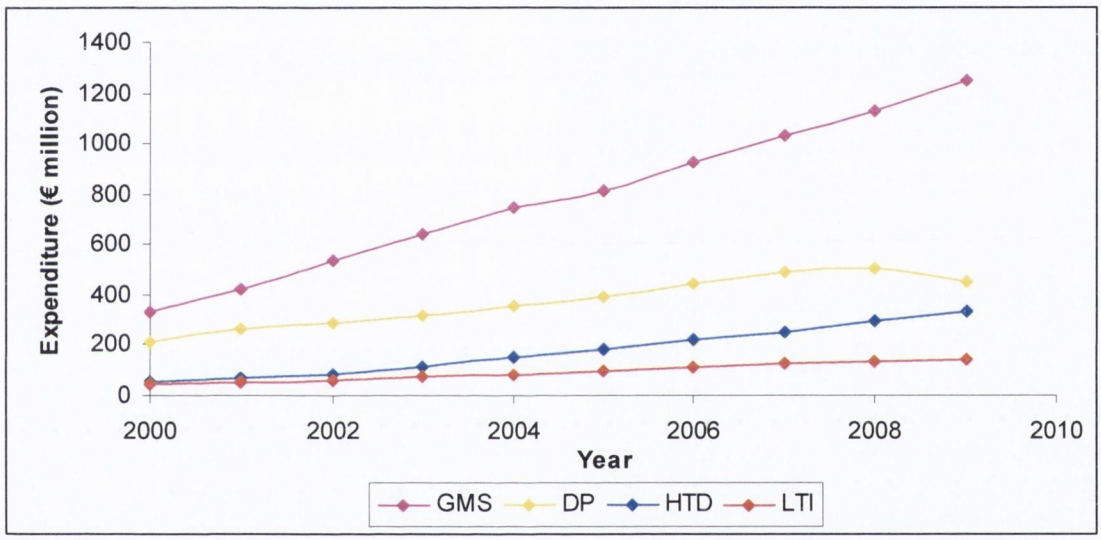
The HTD Scheme was introduced in November 1996 to facilitate the supply by community pharmacies of certain high-cost medicines (e.g. oral chemotherapy, β-interferon and growth hormones), which had previously been supplied mainly in the hospital setting [10]. In 2000, there were a total of 16,247 persons registered under this Scheme [11]; in 2009 a total of 53,515 persons were registered [9]. Patients registered within this Scheme can apply for either a GMS or a DP card depending on their income.

The cost of medicines dispensed under the HTD Scheme is paid (by the PCRS) directly to the wholesalers, medicines are supplied through community pharmacies. Pharmacists are paid a standard monthly patient care fee by the PCRS [12].

1.2.3 Increase in Pharmaceutical Expenditure

There has been a year-on-year increase in pharmaceutical expenditure by the PCRS within each of the four CD Schemes. This increase in expenditure, from 2000 to 2009, is illustrated in Figure 1.

Figure 1: Expenditure on Medicines within the four largest Community Drug Schemes in Ireland



GMS= General Medical Services; **DP**=Drug Payment; **HTD**=High-Tech Drug; **LTI**=Long-Term Illness.

This year-on-year increase is amongst the highest in Europe, and the greater than six-fold increase over the decade to the year-end 2008 occurred despite a price freeze on medications at the introduction price and a price reduction in off-patent medicines in 2007 [10].

Key drivers of this increase in expenditure on medicines are the prescribing of newer, more expensive medicines and the growth in the number of prescription items. A review of the GMS Scheme alone highlights that the 50.7 million items prescribed under this scheme in 2009 [9] is a 2.2-fold increase on the 22.8 million items prescribed in 2000 [11]. Similarly, the cost per item in this Scheme increased from €14.35 in 2000 [11] to €24.56 in 2009 [9].

1.2.4 Strategies Introduced to Contain Pharmaceutical Expenditure

Expenditure is likely to continue to grow should current trends continue and many consider that this level of growth is unsustainable. To ensure the continued provision of innovative and affordable medicines, various strategies have been introduced to ensure greater value for money from pharmaceutical expenditure [14].

1.2.4.1 Payments to Community Pharmacy and Wholesalers

On 18 June 2009, the Minister for Health announced a reduction in payments to pharmacies (including mark-up margins on pharmaceuticals and dispensing fees) and to wholesalers (with regards to mark-up margins on pharmaceuticals) [10].

1.2.4.2 Reference Pricing

The Minister for Health has confirmed that reference pricing will be introduced in 2012. It is widely anticipated that this will be Phase I reference pricing, where pharmaceuticals with the same active ingredient (an original product and its generics) will be subject to a single HSE reimbursement price [10].

1.2.4.3 The Irish Pharmaceutical Healthcare Association Agreement

The supply of medicines to the health services by pharmaceutical companies is governed by a series of agreements between the State and the Irish Pharmaceutical Healthcare Association (IPHA). The agreements cover all medicines reimbursed under the CD Schemes and all medicines supplied to the HSE, State-funded hospitals and State agencies whose functions normally include the supply of medicines [15].

An important component of the IPHA/HSE Agreement (which came into effect on 1 September 2006 and was extended in 2010) was the 35% two-stepped price reduction (20% reduction in 2007 plus an additional 15% reduction in 2009) for patent-expired medicines. From 1 February 2010 there has been a further 40% reduction in the ex-factory price of medicines that have previously undergone price reductions resulting in the price of off-patent medicines being 39% of the price at patent expiry.

Also, following the 2006 IPHA/HSE Agreement, the price of new medicines coming onto the Irish market has been linked to nine European Union (EU) member states; Austria, Belgium, Denmark, Finland, France, Germany, the Netherlands, Spain and

the United Kingdom (UK). These prices are reviewed every two years and adjusted to take account of pricing developments in these markets.

According to the agreement, new medicines granted a marketing authorisation by the Irish Medicines Board (IMB) or European Commission (EC) will become reimbursable under the CD Schemes within 60 days of the reimbursement application date. Where an economic evaluation is requested, this 60 day rule does not apply [15].

Since the 2006 Agreement, the HSE reserves the right to assess the cost-effectiveness of new and existing technologies which may be high cost or have a significant budget impact. [15]. Since September 2009, all new medicines are now considered for a formal pharmacoeconomic assessment prior to reimbursement under the CD Schemes [10]. Such pharmacoeconomic evaluations are conducted by the National Centre for Pharmacoeconomics (NCPE) [10].

1.2.5 The National Centre for Pharmacoeconomics

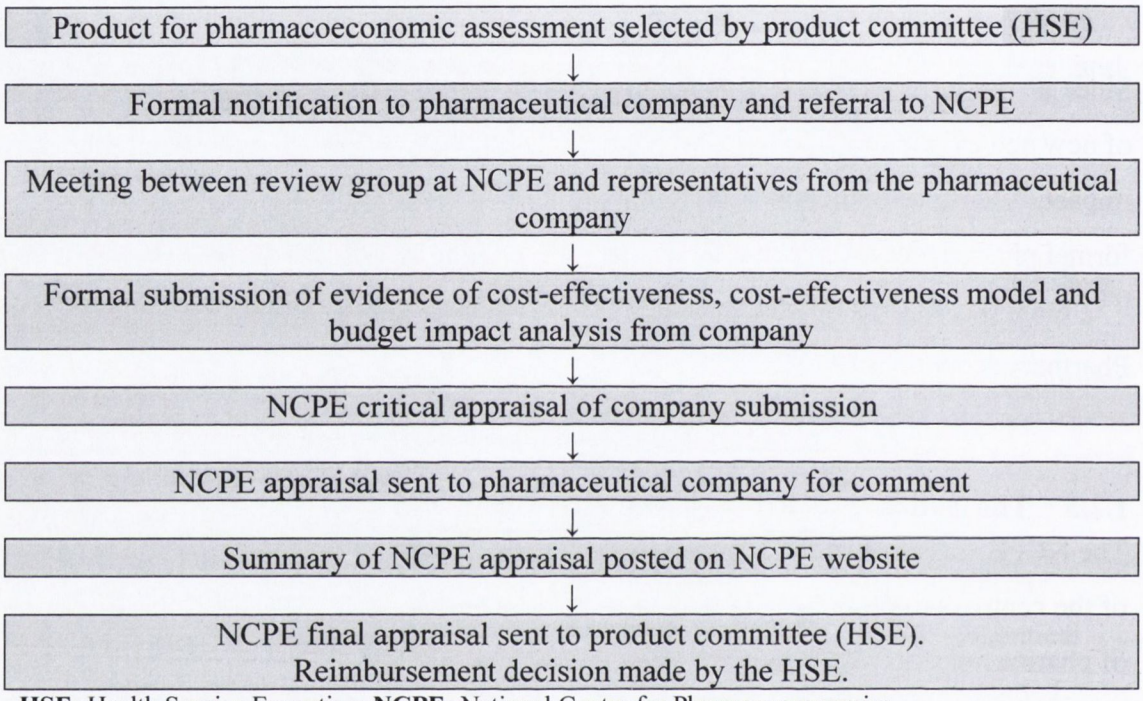
The NCPE was established in Ireland in 1998 with funding from the DOH. The aim of the centre is to promote expertise in Ireland for the advancement of the discipline of pharmacoeconomics through practice, research and education. The NCPE appraises the cost-effectiveness of technologies in response to requests from the HSE or DOH. The centre also conducts pharmacoeconomic evaluations to inform public health policy (e.g. universal infant pneumococcal vaccination) and prescribing in primary care (e.g. use of statins for primary care). The NCPE also analyses drug utilisation and expenditure trends within the various CD Schemes [16].

Since September 2009, all new products undergo a rapid review, which is conducted within a time frame of two to four weeks. Following this review, products may then be referred for a formal HTA or a recommendation may be made for reimbursement. Assessments by the NCPE may be conducted prior to the reimbursement application but must be completed within 90 days [17]. Products subject to an assessment are reimbursed within 40 days of a positive reimbursement decision. Should reimbursement be refused, an appeal process is available [15].

Economic evaluations are conducted in accordance with the existing 'Guidelines for the Economic Evaluation of Health Technologies in Ireland' [18].

The pharmacoeconomic evaluation process includes a number of key steps [8] as depicted in Figure 2.

Figure 2: Summary of the pharmacoeconomics process in Ireland



HSE=Health Service Executive; **NCPE**=National Centre for Pharmacoeconomics

1.2.6 Health Technology Assessment Guidelines

HTA Guidelines outline the principles and methods used in assessing health technologies. Their purpose is to promote the production of assessments that are timely, reliable, consistent and relevant to the needs of decision makers and key stakeholders in Ireland. The first set of Irish HTA Guidelines was introduced in 2000 following collaboration between the IPHA and the NCPE together with input from the DOH [2].

These guidelines have now being updated to take into account developments in pharmacoeconomics and the requirements of key stakeholders. The new guidelines have been produced by the Health Information and Quality Authority (HIQA) and

have been developed in consultation with the Scientific Advisory Group of the Authority [18].

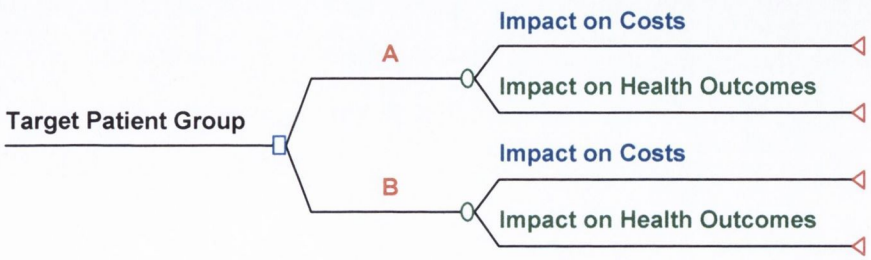
1.2.7 The Health Information and Quality Authority

The HIQA was established in May 2007 as part of the government's Health Service Reform Programme [19]. It reports directly to the Minister for Health and derives its mandate from, and undertakes its functions pursuant to, the Health Act 2007 and other relevant legislation (the Child Care Act, 1991 and the Children Act, 2001). Its mandate extends across the quality and safety of the public, private (within their social care function) and voluntary sectors. The Authority has a statutory responsibility for performing HTAs on health technologies and subsequently provides advice to the Minister and the Executive [2]. The Authority has produced a series of national HTA guidelines; 'Guidelines for the Economic Evaluation of Health Technologies in Ireland' [18], 'Guidelines for the Budget Impact Analysis of Health Technologies in Ireland' [20] and 'Guidelines on Evaluating the Clinical Effectiveness of Health Technologies in Ireland' [21].

1.3 Economic Evaluation

The basic concepts of an economic evaluation are shown in Figure 3. Here intervention 'A' is compared with intervention 'B', which could be an older drug, a non-pharmaceutical intervention or, in the case of a 'breakthrough' drug, no active therapy [22].

Figure 3: Economic evaluation.



The comparative analysis of alternative courses of action in terms of both their costs and outcomes [17]

There are three main forms of economic evaluation.

1.3.1 Cost-Effectiveness Analysis

In a cost-effectiveness analysis (CEA), outcomes are reported in a single unit of measurement and are given in natural units [23]. The outcome must be common to all interventions. For programmes whose main effect is to extend life the usual measure is life-years gained (LYG). Sometimes the benefit measure may be an intermediate marker rather than a final outcome [24]. Where an intermediate marker is chosen it must have a validated, well established link with an important patient outcome [17].

In terms of limitations, a CEA cannot reflect the effects of one intervention on both the quality and quantity of life (QoL). Neither can it reflect the situation where one intervention is superior in some measures of outcome and inferior in others. Also because the measure of primary effectiveness may differ from programme to programme, CEA cannot be used to make comparison across a broad set of interventions. The concept of cost utility analysis (CUA) was developed to address these problems [17].

1.3.2 Cost Utility Analysis

The CUA presents the consequences produced by the interventions in terms of the life-years gained, with each life-year adjusted by a preference (or utility) value. A preference value is the value attached to the health states produced by the interventions. The value is measured on a cardinal scale such that a year of life in perfect health has a score of one and death of zero [25]. The health state valuations should ideally be relevant to the population(s) under study since valuation is believed to be influenced by culture and income [22, 26].

The most widely used outcome measure is the quality-adjusted-life-year (QALY). To calculate QALYs, the duration a person is in a health state is multiplied by the preference value for that state [27]. The use of such a generic measure of outcome makes it possible to compare outcomes of interventions across different activities [28].

There are a number of limitations associated with CUA. Preventive measures, where the impact on health outcomes may not occur for many years, may be difficult to

quantify using QALYs [29]. QALYs do not have the capacity to measure short-term outcomes (for example acute pain relief) which do not affect the QoL. There may also be a lack of good quality preference values available for certain populations [28].

1.3.3 Cost Benefit Analysis

In a cost benefit analysis (CBA), both costs and consequences are measured and valued in monetary terms. A CBA can be used to compare two healthcare interventions that do not have comparable outcome measures. It allows an overall view as to whether the intervention is economically desirable, i.e. whether the total costs of an intervention are justified by the total benefits [22].

The use of CBA is limited by the methods used to translate benefits to monetary values. Two common methods are the 'Willingness to pay' and the 'Human capital' approach. The former involves asking individuals how much they are willing to pay to avoid risk. In the later, the value of a human life is determined by the present value of future earnings, which gives rise to arguments concerning the value of livelihoods rather than lives [30].

1.3.4 The Choice of Evaluation Type

As a CUA has broad applicability, it is frequently considered more useful than a CEA to the decision-maker [17]. Many expert and consensus groups thus have recommended CUA as the gold standard for conducting economic evaluations [30]. CBA is rarely used in healthcare because of the difficulties of expressing health benefits directly in monetary terms [29].

The 'Guidelines for the Economic Evaluation of Health Technologies in Ireland' state that the preferred evaluation type is a CUA with the outcomes expressed in QALYs. The Guidelines state that in exceptional circumstances, a CEA may be used when a CUA is an unsuitable choice [18].

1.3.5 Incremental Cost Effectiveness Ratio

The results of CEA and CUA should be presented in terms of an Incremental Cost Effectiveness Ratio (ICER), which is a measure of the additional cost per unit of outcome. This could be the cost per LYG in a CEA, or the cost per QALY in a CUA. In a CBA, the inputs and outputs of the process are measured in the same units, therefore ICERs are not generated [27].

The ICER is calculated as follows [17]:

$$ICER = \frac{\text{Cost A - Cost B}}{\text{Effect A – Effect B}}$$

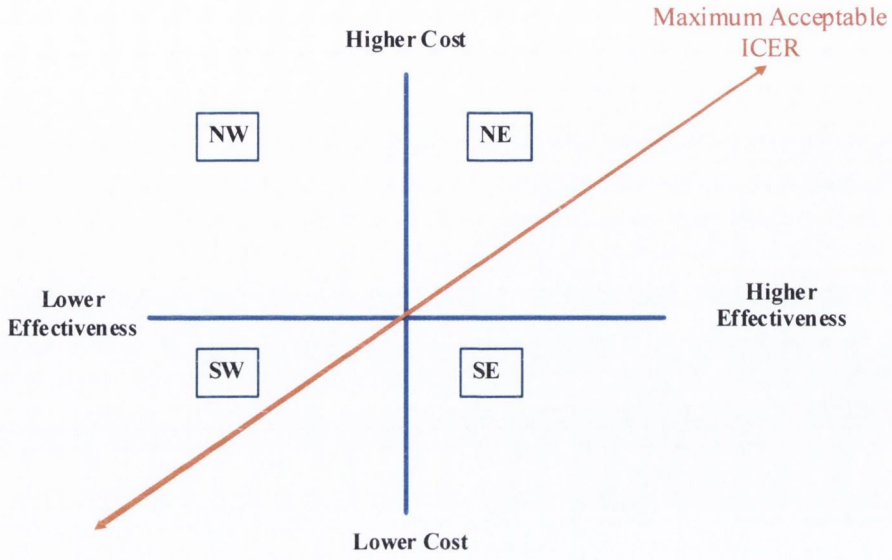
Where: A=Intervention A
B=Comparator B

As the ICER becomes larger the intervention is said to be less cost-effective. The ICER is a frequently applied decision rule for the identification of the most cost-effective strategy. Initially, all possible treatment pathways are ranked with regards to increasing costs of the intervention; ICERS are then calculated. A strategy for which the cost is higher and the effectiveness is lower than another strategy is said to be dominated and would not be considered as an alternative strategy. Extended dominance occurs when the ICER for a strategy under investigation is higher than that of the next most effective strategy. In this instance the strategy under investigation would not be considered a cost-effective option [31].

1.3.6 Cost-Effectiveness Plane

The ICER can be displayed on a cost-effectiveness plane [32-34]. The comparator is placed at the intersection of the x- and y-axis (the origin), and the incremental cost and effectiveness of the new intervention are shown relative to those of the comparator [17].

Figure 4: To illustrate the cost-effectiveness plane



Where: **NW**=north-west; **NE**=north-east; **SW**=south-west; **SE**=south-east; **ICER**=incremental cost-effectiveness ratio.

ICERs with a negative value are in the south-east (SE) or north-west (NW) quadrant. In the SE quadrant the new intervention is more effective and less costly than the comparator; the new intervention dominates. Interventions in this quadrant are always considered cost-effective [17]. In the NW quadrant, the intervention is less effective and more costly; the comparator dominates. Interventions in this quadrant are never considered cost-effective [33].

ICERs with a positive value are in the north-east (NE) or the south-west (SW) quadrants. In the NE quadrant, the new intervention is more effective and more costly [17]. The majority of new interventions fall into this quadrant [17]. In the SW quadrant, the new intervention is less effective and less costly [35]. Whether the new intervention is considered cost-effective is usually determined by the treatment's position relative to the cost-effectiveness threshold (the maximum acceptable ICER) [17]. This threshold is the maximum added cost that society is willing to pay per unit of added benefit from the new treatment. If a new treatment lies below the red line it may be deemed cost-effective. One which lies above the line is not considered to be cost-effective [36].

There is no set cost-effectiveness threshold in Ireland. However the majority of pharmaceuticals which were reimbursed prior to 2009 had an ICER of €45,000 per QALY or less [4]. In recent more economically constrained times, pharmaceuticals with an ICER of greater than €20,000 per QALY are less likely to be reimbursed [37].

1.3.7 Perspective of the Economic Evaluation

Before an economic evaluation begins, the study perspective should be determined in order to establish which costs and consequences are to be considered. The societal perspective is advocated frequently. However, the health-payer perspective is taken by many jurisdictions [38]. This perspective aims to inform the decision maker about the optimal allocation of their budget [17].

The 'Guidelines for the Economic Evaluation of Health Technologies in Ireland' state that the publicly-funded health and social care system in Ireland should be adopted when assessing costs and that all health benefits accruing to individuals should be included in the assessment of outcomes [18].

1.3.8 Costs

Gathering the costs for an economic evaluation normally involves three distinct phases: the identification of the relevant costs, the accurate measurement of the units of resources used and the valuation of these units. In economic evaluations, different categories of costs have been proposed.

Direct medical costs are directly related to the strategy under evaluation and fall within the healthcare sector; they include formal caregivers' time, diagnostic tests and drugs. This cost-category is central in any economic evaluation and relevant when adopting a societal or healthcare perspective.

Direct non-medical costs are also directly related to the strategy, but fall outside the formal healthcare sector (e.g. patient travel costs). These costs are relevant when adopting the societal perspective, but may be considered irrelevant when adopting a healthcare perspective.

Indirect non-medical costs mainly refer to items such as productivity costs, (e.g. absenteeism from work due to illness). The inclusion of these costs is relevant from a societal, but not from a healthcare perspective [39].

1.3.9 Modelling in Economic Evaluation

The most straightforward way to estimate the costs and consequences of a new strategy would be to use resource utilisation and efficacy data from a randomised clinical trial (RCT) [40]. However, for many disease states it would be impossible to perform a RCT with a long enough time horizon to collect the data required to determine cost-effectiveness. Also, some costs associated with a RCT will be protocol-driven and may not be reflective of normal clinical practice. Further, many studies enrol patients in a large number of countries; individual national groups are generally too small to reach significance and to assess country-specific costs [41]. Additionally, it is not uncommon for two interventions being evaluated never to have been trialled against each other [42].

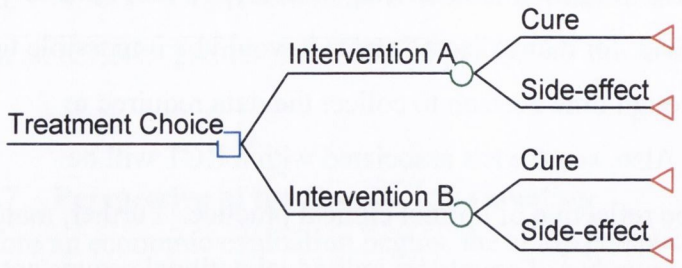
Thus decision-analytical modelling is widely used to estimate the cost-effectiveness of healthcare interventions [18]. A model is a logical mathematical framework that permits the integration of facts and values, and links these data to outcomes that are of interest to healthcare decision makers [43]. Data can be synthesised from different sources, such as epidemiological, clinical and economic sources [43]. Results from RCTs can be extrapolated to a longer time frame. Also different assumptions about risk, effectiveness, safety and costs can be examined [41].

Economic evaluations generally use three different types of models.

1.3.9.1 Decision Tree Models

Decision trees are among the most widely used aggregate level models [44]. They are an appropriate choice in evaluations pertaining to diseases with distinct events that occur with a given probability, within a relatively limited time frame [41]. An example of a simple decision tree is given in Figure 5. The expected cost for each strategy is calculated by multiplying the cost for each branch by the overall probability of that branch occurring [41].

Figure 5: A simple decision tree.

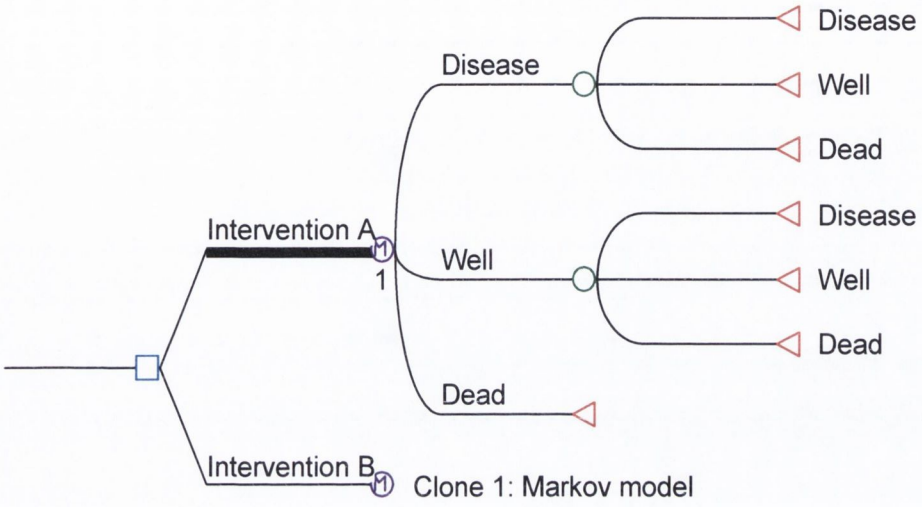


1.3.9.2 Markov Chain Analysis

Markov models can provide a more compact representation than the decision tree when a repeated set of outcomes is possible through time [44]. They are particularly suited to modelling chronic diseases [45]. Figure 6 illustrates the structure of a simple Markov model.

In a Markov model it is assumed that all patients can be classified into a finite number of Markov states. No distinction is made between the different patients within each state [41]. The time period covered by a model is divided into equal increments, referred to as Markov cycles. During each cycle, a transition matrix uses a transition probability for individuals to change from one state to another [44]. Transition probabilities only depend on the health state patients are in and not on how long they have been in this stage and how they got there. Each state is assigned an outcome and a cost, and cumulative outcomes and costs for a given cohort are calculated at the end of the Markov process [41]. In order for a Markov process to terminate, it must have at least one state that the patient cannot leave (absorbing state); the most common absorbing state is death [45].

Figure 6: A simple Markov model.



In this model, patients in the 'Disease' state may remain in this state or progress to the 'Well' or 'Dead' states. Patients in the 'Well' state may remain here or progress to 'Disease' or 'Dead'. Patients in the absorbing 'Dead' state remain here until the end of the simulation

1.3.9.3 Discrete Event Simulation Models

For analyses where the timing and chronology of events is important, discrete event simulation (DES) models are more practical [41]. This is probably the most flexible of all modelling techniques [44].

DES models are analysed as patient level simulations. The experience of individuals is modelled over time in terms of the events that occur and the consequences of those events [46]. Similar to Markovs, patients are classified into states. While in a state, patients can have different characteristics over time, and hence different costs and preferences. They remain in the same state until a certain event happens, such as a change in the disease, change of treatment, death, etc [41]. DES models contain the full range of information available on patients in the data sets used for building the model [41]. Modelling at the patient level is generally computationally expensive [46].

The 'Guidelines for the Economic Evaluation of Health Technologies in Ireland' state that there is no one optimal modelling technique, rather the choice of model should depend on the research question to be addressed [18].

1.3.10 Handling Uncertainty in Economic Models

All economic evaluations will contain some degree of uncertainty [17]. Economic evaluation guidelines have become increasingly concerned with quantifying and presenting this uncertainty [38]. At least three broad types of uncertainty are recognised: parameter, methodological and structural [47]. Parameter uncertainty relates to the fact that we do not know the true value of a given parameter (such as event probabilities, costs and preference values). Methodological uncertainty relates to the choice of analytic methods that underpin an economic evaluation [48], e.g., the perspective of the evaluation. Other sources of uncertainty include the different types of simplifications and scientific judgments that have to be made when constructing and interpreting a model of any sort. These have been classified in a number of different ways but can be referred to collectively as structural uncertainties [49].

Uncertainty is usually handled using some form of sensitivity analysis (SA). The simplest form of SA is a one-way analysis. Here estimates for each parameter are varied one at a time to investigate the impact on the analysis results [17]. This method however is not designed to simultaneously include all the parameters which are subject to uncertainty and will underestimate decision uncertainty [50].

A more sophisticated approach is a multi-way analysis; this recognises that more than one parameter is uncertain [17]. Although multi-way SA is sometimes used to explore combined uncertainty, with a large number of parameters this can be complicated and can be markedly time- and computer-intensive [50].

Probabilistic analysis (PSA) is now becoming widely used in decision-analytic modelling studies [38]. Here probability distributions are applied to ranges for the key parameters [51]. The PSA uses Monte Carlo simulation to repeatedly sample from the prior distributions assigned to the uncertain parameters samples (each Monte Carlo trial run is called a simulation or iteration). The expected costs and the expected effects, for each strategy, are calculated for every PSA iteration row. An empirical distribution of the cost-effectiveness ratio is thus generated [17].

The 'Guidelines for the Economic Evaluation of Health Technologies in Ireland' state that a one-way SA, a multivariate SA and a PSA should be used to assess uncertainty.

Also, the range of values provided for each parameter must be clearly stated and justified [18].

There are a number of techniques available for handling and presenting the results of the PSA.

1.3.10.1 Scatter Plot

A scatter plot of the incremental costs and effect pairs for the intervention under investigation versus the comparator can be presented on the incremental cost-effectiveness plane [52].

1.3.10.2 The Cost-Effectiveness Acceptability Curve

The cost-effectiveness acceptability curve (CEAC) can be generated directly from the PSA [53-55]. It is a graphical method of summarising the decision uncertainty; it plots the probability of a strategy being cost-effective as a function of the cost-effectiveness threshold [56].

In each PSA iteration, the expected costs and expected effects associated with each strategy under consideration is estimated. Then, by explicitly incorporating the cost-effectiveness threshold the net monetary benefit (NMB) for each intervention is calculated: [56, 57]

$$NMB = (E \times \lambda) - (C)$$

Where: λ = cost-effectiveness threshold
E=expected effect
C=expected cost

For each PSA iteration row, the strategy with the maximum expected NMB can be identified. The probability that each alternative strategy is preferred is the fraction of rows in which that strategy has the maximum NMB. Repeating this process for a range of values for the cost-effectiveness threshold yields the CEAC for each of the alternatives [58].

1.3.10.3 The Cost-Effectiveness Frontier

The CEAC details the probability that the intervention is optimal for any particular threshold value; it does not report which alternative has the maximum expected benefit at the given threshold [59]. PSA of decision models may generate skewed distributions of NMB due to skewed prior distributions for model inputs, interactions and non-linearities within the models [56]. If the distribution is asymmetric, the alternative with the maximum probability of having the maximum benefit may not have the maximum expected benefit [56, 60, 61]. The concept of the cost-effectiveness frontier (CEAF) has been presented as a way of overcoming this problem [56]. The CEAF plots the strategy with the highest expected cost-effectiveness (expected NMB) as a function of the cost-effectiveness threshold. It has been suggested that the CEAF presents uncertainty in a format that is more relevant to decision making than the CEAC [56].

Table 1 illustrates the method of calculating the CEAC and the CEAF from a PSA. Each row represents a PSA iteration, with the NMB calculated, for each of the three alternative strategies (A, B and C). In this example, strategy A is the optimal option (highest mean NMB) and strategy C has the highest probability of being cost-effective (has the largest number of PSA iterations where it has the highest NMB). Repeating this process for a range of values for the cost-effectiveness threshold yields the CEAC and the CEAF for each of the alternatives.

Table 1: To illustrate the method for calculating the CEAC and the CEAF at a given threshold.

PSA	NMB (where NMB = (E x λ) – (C))		
Iteration	**Strategy A**	**Strategy B**	**Strategy C**
1	5	2	6
2	5	6	1
3	6	2	1
4	5	2	6
5	5	6	2
6	5	2	6
Expected (mean) NMB	5.17[a]	3.33	3.67
Probability cost-effective	17%	33%	50%[b]

a. CEAF: The optimal option (has the expected mean NMB) is strategy A.

b. CEAC: The option with the highest probability of being cost effective (has the highest percentage of iterations where the NMB is the highest) is strategy C.

CEAC=cost-effectiveness acceptability curve; **CEAF**=cost-effectiveness acceptability frontier; **PSA**=probabilistic analysis; **NMB**= net monetary benefit; **λ**=cost effectiveness threshold; **E**=expected effect; **C**=expected cost.

1.3.10.4 Expected Value of Prefect information

The CEAF plots the option which is optimal [58], however, the importance of uncertainty is not reflected since the consequences of not selecting the 'true' preferred alternative are ignored [61]. The expected value of perfect information (EVPI) estimates the value of simultaneously eliminating all uncertainty of all uncertain parameters related to the decision [62] and provides a measure of the maximum return to further research [63, 64]. It can be determined directly from the PSA, with each iteration representing a possible future resolution of the existing uncertainty for which the optimal decision can be identified [63]. If the EVPI exceeds the expected costs of further investigation, then it is potentially cost-effective to conduct additional research on the technology [65]. If the EVPI suggests that more research is justified, the expected value of perfect parameter information (EVPPI) can identify the key parameters in the economic model whose uncertainty drives the decision uncertainty [62-64, 66].

The 'Guidelines for the Economic Evaluation of Health Technologies in Ireland' state that the results of the PSA should be presented as a scatter plot and a CEAC. The Guidelines make no mention of the CEAF and EVPI analysis [18].

1.3.11 Discounting in Economic Evaluations

Discounting (the valuation of the net present value of a commodity) is performed in order to adjust future costs and outcomes for their differential timing, allowing the decision maker to compare them on the same temporal baseline [67]. Discounting makes current costs and benefits worth more than those occurring in the future because there is an opportunity cost to spending money now and there is desire to enjoy benefits now rather than in the future. This is referred to as 'time preference'. The reason why current spending incurs an opportunity cost relative to delayed spending is that a monetary investment yields a real rate of return and therefore there is a cost to spending money in the present. Failure to discount future health related benefits will tend to show more favourable ICERs compared with discounting [68]. Different interventions may have different time profiles of costs and consequences. For example, the primary benefits of an influenza immunisation programme are immediate while those of a cholesterol screening programme occur well into the future [17].

There is no minimum time period for discounting, however, economic evaluations of healthcare programmes generally do not apply discounting to costs and outcomes occurring less than one year after the initial intervention [69]. Guidelines pertaining to most jurisdictions state that the same discount rate should be applied to both costs and outcomes [38].

The 'Guidelines for the Economic Evaluation of Health Technologies in Ireland' state that a discount rate of 4% per annum should be applied to costs and outcomes occurring beyond one year [18]. This rate is based on guidelines from the Irish Department of Finance [70].

1.3.12 Generalisability and Transferability of Economic Evaluations

In interpreting economic evaluation results from other jurisdictions, decision makers need to form a view on whether the results apply to their own setting [17]. Differences in culture, organisation of healthcare, clinical practice, health state preference values, resource utilisation etc, across jurisdictions, may change the way in which costs and outcomes are accrued [71, 72].

Studies may be considered generalisable if they can be applied to a range of jurisdictions without any adjustment needed for interpretation. In addition, some studies may be transferable if they can be adapted to apply to other settings [72]. Existing economic studies vary in the extent to which issues of generalisability are recognized and explored [25].

The 'Guidelines for the Economic Evaluation of Health Technologies in Ireland' recognise that, in the absence of national data, economic evaluation models developed by manufacturers often rely on international data to develop their recommendations. The Guidelines state that while epidemiological data may also be transferable, any uncertainty should be explored through SA. In addition, they state that undiscounted, disaggregated resource use and unit costs and outcome data should be detailed separately to maximise transparency [18].

1.4 Conclusion

There has been a year-on-year increase in PCRS expenditure on pharmaceuticals within the Irish healthcare system. Expenditure is likely to continue to grow should current trends continue and this level of growth is considered, by many, to be unsustainable. Various strategies have been introduced to ensure greater value for money from pharmaceutical expenditure [14].

Since the introduction of the 2006 HSE-IPHA Agreement, the HSE reserves the right to assess the cost-effectiveness of new and existing technologies which may be high cost or have a significant budget impact [15]. Since September 2009, all new medicines are now considered for a formal pharmacoeconomic evaluation prior to reimbursement under the CD Schemes [10]. Such evaluations are conducted by the NCPE in accordance with the existing 'Guidelines for the Economic Evaluation of Health Technologies in Ireland' [18]. The economic evaluation concepts used in these Guidelines have been introduced.

Chapter 2

Venous Thromboembolism – Incorporating a Review of Published Thromboprophylaxis Pharmacoeconomic Models

2 VENOUS THROMBOEMBOLISM - INCORPORATING A REVIEW OF PUBLISHED THROMBOPROPHYLAXIS PHARMACOECONOMIC MODELS 29

2 Venous Thromboembolism - Incorporating a Review of Published Thromboprophylaxis Pharmacoeconomic Models

2.1 Introduction

Two new orally active anticoagulants, rivaroxaban (Xarelto®; Bayer Ltd) and dabigatran etexilate (Pradaxa®; Boehringer Ingelheim Ltd), became licensed in Ireland in 2008 for the primary prevention of venous thromboembolism (VTE) in adult patients (over 18 years) undergoing elective total hip replacement (THR) and total knee replacement (TKR) [73, 74].

This chapter has three aims:

- To provide an overview of VTE. Where appropriate, a degree of emphasis will be placed towards VTE associated with THR and TKR.
- To discuss the rationale for targeting rivaroxaban and dabigatran etexilate for pharmacoeconomic evaluation.
- To describe published model based economic evaluations of thromboprophylaxis after THR and TKR in order to inform the development of an independent model.

2.2 Venous Thromboembolism

VTE disease represents a spectrum of conditions that includes deep venous thrombosis (DVT) and pulmonary embolism (PE). A DVT is a blood clot (thrombus) in a deep vein. These thrombi may dislodge and travel through the blood stream to lodge in the pulmonary circulation resulting in a PE [75].

DVTs in the legs are proximal when above the knee and distal when below the knee. Approximately 70 to 80% of DVTs involve the proximal veins, whilst 20 to 30% are isolated in distal veins of the calf [76]. The distinction between proximal and distal DVT is important. The clinical relevance of distal DVT is controversial; an isolated distal DVT is rarely symptomatic. However when a distal DVT is both symptomatic and untreated, 25% of cases may extend to the proximal veins [77]. These proximal thrombi are more likely to produce symptoms and result in PE [78]. Up to fifty percent

of people with symptomatic proximal DVT may have PE in lung scans [77]. Mortality from DVT is secondary to PE [79].

The pathological consequence of PE is proportional to the degree of obstruction of the pulmonary arterial tree. A PE results in pulmonary hypertension and right heart failure in up to 70% of cases. Pulmonary infarction is seen in about 10% of cases [80]. The one-week survival rate after a PE is 71% and almost 25% of all cases of PE present as sudden death [79]. Approximately 10% of hospital deaths are attributed to PE [78]. In a Swedish retrospective analysis, among 1,234 hospitalized patients who died and underwent autopsy within 30 days of a surgical procedure, the rate of PE was 32%. In 29% of these cases PE was considered to be the cause of death [81].

VTE is a disease with long term consequences, including the risk of VTE recurrences and the development of the chronic condition post-thrombotic syndrome (PTS) [82-89].

2.2.1 Pathophysiology of Coagulation

Central to the coagulation system is a series of serine proteases, factors XII, XI, IX, X, VII and II (prothrombin) and protein cofactors, factors V and VIII [90]. Endothelial injury can expose collagen, resulting in platelet aggregation which, in the presence of venous stasis or hypercoagulability, triggers the coagulation cascade [80]. There are two pathways involved, the intrinsic and extrinsic pathways [91, 92]. Activation of either pathway triggers a common pathway and results in thrombin production as a result of the activation of a number of proenzymes. Thrombin then converts fibrinogen to fibrin, activates factors V, VIII and XI, which generate more thrombin, and stimulates platelets to form a clot [90]. Natural anticoagulants, such as protein C, protein S and antithrombin, regulate the cascade and help restrict the formation of the haemostatic plugs to the site of injury [90].

2.2.2 Epidemiology

A systematic literature search has revealed a number of prominent epidemiological studies which encompass different jurisdictions in the United States (US) [93-95] and Europe [96-98]. These studies have been summarised in Table 2 [93-99]. No epidemiological studies pertaining to Ireland have been located.

It is difficult to compare incidence rates from the different studies. Some are prospective [93, 95-98] and others are retrospective [94]. The time horizons vary widely and the age ranges of the reference populations differ. The methods of VTE diagnosis vary. Studies are inconsistent in their inclusion or exclusion of recurrent DVTs and in their classification of DVTs diagnosed with or without a concurrent PE. The recent epidemiological studies may convey data that is more reflective of the current population than the older studies.

A review of Table 2 reveals a VTE incidence rate of about 75 to 180 per 100,000 people per year [93-99]. The incidence rate increases with age [93, 96, 98, 99] and is similar in both sexes [93, 94, 97, 99]. Investigations in Sweden [97] and France [98] have revealed incidence rates that are slightly higher than in US studies. This may be explained, in part, by a more ethnically diverse population in the US as racial differences influence the risk of VTE [100]. The relatively low incidence of VTE in Asians and Hispanics has not been explained, but may relate to a lower prevalence of genetic factors predisposing to VTE, such as factor V Leiden in Asian populations (0.5%) compared with Caucasians (5%) [100-103].

Recent data pertaining to Ireland is available from the Hospital In-Patient Enquiry (HIPE) scheme which reports that there were 1,701 venous thrombosis discharges and 1,368 PE discharges from acute public hospitals in Ireland in 2009 [104].

Table 2: Incidence of venous thromboembolism in North America and Europe

Author	Study Setting	Study Population	Annual Incidence (per 100,000) in General Population	Location	Comment
Meta-analysis					
Fowkes *et al* 2003 [99]	Meta-analysis of studies (1976 - 2000)	General population	DVT= 50.4 (95%CI 4.70, 5.38) About 20% of cases were idiopathic Incidence similar in both sexes Incidence increased with age: 30 - 49 yrs = 20 - 30 70 - 79 yrs = 200	Studies conducted in the US, Sweden, France	
US					
Silverstein *et al* 1998 [94]	Retrospective review of medical records of population cohort	2,218 patients with DVT or PE (1966-1990)	VTE = 117 (95%CI 112, 122) DVT = 48 (95%CI 45, 51) PE (± DVT) = 69 (95%CI 65, 73) Male to female ratio=1.2:1 Sub-group analysis (1980 -1990): VTE incidence was 9605 in hospitalised patients versus 71 in community residents [105]	Olmsted County, Minnesota	High incidence of PE might be explained by the high autopsy rate in Olmsted County [94]. A large number were documented at autopsy.
White *et al* 1998 [100]	Retrospective review of discharge data	17,991 patients with idiopathic VTE	African-American=29 Caucasians=23 Hispanics=14 Asians and Pacific Islanders=6	California	Low incidence in Asians/Hispanics may relate to a lower prevalence of genetic factors predisposing to VTE (e.g. factor V Leiden in Asian populations (0.5%) vs. Caucasians (5%) [101, 103].
Spencer *et al* 2006 [95]. The Worcester Venous Thromboembolism Study	Observational study of hospital discharge records of Worchester residents	587 patients with VTE	DVT = 92 (95%CI 84, 101) PE (± DVT)= 29 (95%CI 25, 35)	Worcester, Massachusetts	It was postulated that an improved awareness with respect to VTE diagnosis had resulted in an increased incidence compared to the Olmstead County Study.

Table 2 continued

Author	Study Setting	Study Population	Annual Incidence (per 100,000) in General Population	Location	Comment
Cushman *et al* 2004 [93]. The LITE Study	LITE combined 2 prospective cohort studies; the ARIC Study (1987-1989) and the CHS (1989-1990 and 1992-1993)	21,680 participants Follow up = 7.6 yrs	VTE = 161 (95%CI 143, 181) DVT = 117 PE (± DVT) = 45 Risk of 1st VTE > 3 times greater in ≥ 65 yrs compared to 45-54 yrs Rates similar in both sexes, although in > 75 yrs, the rate in men was higher than in women (550 vs. 270).	Forsyth County, North Carolina; Washington County, Maryland; suburban Minneapolis, Minnesota; Jackson, Mississippi; Sacramento County, California; and Pittsburgh, Pennsylvania	The high incidence of DVT relative to the Olmsted County [94] and Worcester [95] studies may be reflective of the age criteria of the cohort which excluded < 45 yrs. The CHS study only enrolled those ≥ 65 yrs [93].
Europe					
Nordstrom *et al* 1992 [97]	Prospective study of population (1987)	230,835 population	DVT = 160 Equal incidence for both sexes	Malmo city, Sweden	
Oger *et al* 2000 [98] The EPI-GETBO Study Group	Prospective (1 yr) study of Brest population	342,017 population	VTE = 183 (95%CI 169, 198) DVT =124 (95%CI 112, 136) PE = 60 (95%CI 52, 69) Incidence increased with age incidence in >75 yrs = 1000	Brest, France	
Huerta *et al* 2007 [96]	Prospective cohort (1994-2000) using UK GPRD	6,550 patients (20-79 yrs) with VTE. 53% female. median age = 63 yrs	VTE = 74.5 DVT= 40.3 PE (± DVT) = 34.2 Incidence increased with age	UK	The authors commented that the results were likely to be more contemporary than similar studies conducted over longer periods.

VTE=venous thromboembolism; **DVT**=deep vein thrombosis; **PE**=pulmonary embolism; **Yrs**=years; **CI**=confidence interval; **LITE**=Longitudinal Investigation of Thromboembolism Etiology: **ARIC**=Atherosclerotic Risk in Communities Study; **CHS**=Cardiovascular Health Study; **GPRD**=General Practice Research Database.

2.2.2.1 The-Long Term Clinical Course of Venous Thromboembolism

In contrast to the extensive documentation available on the short-term outcome of patients with acute DVT, less information is available on the long-term clinical course of the disease [85]. Recent studies however indicate that VTE is a disease with long-term consequences, including the risk of VTE recurrences and the development of PTS [82-88, 106].

2.2.2.1.1 Recurrent Venous Thrombosis

A systematic literature search has revealed a number of studies which investigate the incidence of recurrent VTE after a symptomatic, confirmed and treated index event [82, 84, 85, 87, 89, 107, 108]. The time horizons of the analyses vary from three to eight years [82, 84, 85, 89, 106, 108]. They are summarised in Table 3.

A review of Table 3 [82, 84, 85, 87, 89] reveals that recurrences are particularly common during the first six to 12 months after an index event, but the risk persists for several years [82, 84, 85, 106, 109, 110]. A recurrence rate of 5 to 10 % per year has been reported, however, the incidence decreases over time [82, 84, 85, 106, 111]. It has been suggested that upper extremity DVT carries a smaller risk of recurrence than a lower extremity event [89]. Patients with transient risk factors such as surgery, recent trauma and fracture are associated with decreased risk of recurrence compared to those with a continuous risk [106]. One study, which compared recurrence rates after different types of surgery, found the lowest risk of recurrence among patients who had undergone orthopaedic surgery [82]. Persistent residual thrombosis has been shown to be a risk factor for recurrence [87]. The risk of recurrence is greater among men with an unprovoked VTE than women with an unprovoked VTE [107, 108]. There is no difference in the risk of recurrence between men and women with an initial provoked VTE event [108]. A lower risk of recurrence has been described in women with hormone associated VTE than in women with an unprovoked VTE [108].

Table 3: Incidence of recurrent venous thromboembolism events after a symptomatic, confirmed and treated index event

Author	Study Setting/Location	Study Population	Cumulative Incidence of Recurrence	Comment
Beyth *et al* 1995 [84]	Prospective cohort Ohio, US	n=124 with DVT Follow-up = 6-8 yrs	3 months = 4% 12 months = 6% 60 months =13%	The 1st recurrence was a DVT in 15 and a PE in 3
Prandoni *et al* 1997 [85]	Prospective cohort Italy	n=528 with 1st DVT Follow-up = 8yrs	3 months =5.6% 6 months =9.5% 2 yrs =17.2% 5 yrs =24.3% 8 yrs =29.7%	In a 1996 report of this study, (n=355) patients with transient risk factors (e.g. surgery, fracture) had decreased recurrence vs. those with continuous risk [106]
Hansson *et al* 2000 [82]	Prospective cohort Sweden	n=738 with 1st or 2nd DVT Follow-up =3.7-8.8 yrs	1 yr =7.0% (95%CI 4.8, 9.1) 2 yrs =12.1% (95%CI 9.3, 14.9) 3 yrs =15% (95%CI 11.8, 18.1) 5 yrs =21.5% (95%CI 17.7, 25.4)	When comparing different types of surgery, the lowest risk of recurrent events was found among patients who had undergone MOS
Prandoni *et al* 2002 [87]	Prospective cohort Italy	n=313 with proximal DVT Follow-up = up to 6 yrs	6 months =4.2% 12 months =7.4% 24 months =12.7% 5 yrs =21.1%	HR (for recurrence) = 2.4 (95%CI 1.3, 4.4 p=0.004) for patients with residual thrombosis vs. those without
Prandoni *et al* 2004 [89].	Prospective cohort Italy	n= 53 with 1st DVT of the arm Follow-up = up to 5 yrs	1yr =2.0% (95%CI 0.0, 5.9), 2yrs =4.2% (95%CI 0.0, 9.9) 5yrs =7.7% (95%CI 0.0, 16.5)	The authors suggested that upper extremity DVT carries a smaller risk than lower extremity event
Kyrle *et al* 2004 [107]	Prospective cohort Austria	n=826 with 1st VTE Follow-up= 36months	Risk of recurrence was greater in men than women; RR= 3.6 (95%CI 2.3, 5.5; p<0.001)	Patients excluded if surgery within the previous 3 months
Douketis *et al* 2011 [108]	Patient level meta-analysis of 7 prospective studies	n=2554 with 1st VTE Follow-up = 27.1 (SD= 19.6) months	1 yr incidence of recurrence: women = 5.3% (95%CI 4.1, 6.7) & men = 9.5% (95%CI 7.9, 11.4%) 3 yr incidence of recurrence: women = 9.1% (95%CI 7.3, 11.3) & men = 19.7% (95%CI 16.5, 23.4)	Unprovoked VTE: men higher risk vs. women (HR= 2.2, 95% CI 1.7 to 2.8). Provoked VTE: no difference in men vs. women (HR=1.2 95%CI 0.6, 2.4) Women with hormone associated VTE had lower risk than women with unprovoked VTE (HR=0.5 95%CI 0.3, 0.8)

US=United States; **DVT**=deep vein thrombosis; **PE**=pulmonary embolism; **VTE**=venous thromboembolism; **HR**=hazard ratio; **yr(s)** =year(s).

2.2.2.1.2 Post-Thrombotic Syndrome

PTS is a chronic condition which may result in ongoing medical resource utilisation and impaired QoL [112, 113]. The pathophysiology is not clearly understood, but it probably involves damage to delicate venous valves and impaired microcirculation due to persistent venous hypertension [114]. The most common symptoms are persistent or intermittent pain, heaviness, swelling, itching, tingling or cramping in the limb. Walking or standing aggravates the symptoms, which tend to improve with rest. Typical clinical signs include oedema, venous dilation, hyper-pigmentation, eczema and varicose collateral veins [113]. In severe cases it can lead to painful leg ulcers, which can limit mobility and require long-term nursing care [88, 113].

A systematic literature search has revealed a number of studies which have investigated the occurrence of PTS in patients with confirmed, symptomatic and treated DVT [83, 85, 88, 115-120]. These are summarised in Table 4 [83, 85, 88, 115-120]. Such studies are difficult to compare. The definition of PTS can vary significantly among authors, there is no standard diagnostic test and three different clinical scales exist for the diagnosis [88, 121, 122]. Published studies often encompass small patient cohorts, may be prospective [85, 89, 115-117, 120] or retrospective [83, 118] and vary in their treatment of the index VTE. The study follow-up periods range from two to 13 years [83, 85, 88, 89, 115-120].

A review of Table 4 reveals that PTS tends to manifest clinically within one to two years of an index VTE event [85, 89, 106, 120]. Incidence rates of 10 to 20% in the first year have been reported [85, 89]. This incidence decreases over time [85, 89]. The location of the index DVT [115-118], extent of the thrombosis [115] and occurrence of ipsilateral recurrence [83, 85] and asymptomatic post-operative DVT [123] may be predictive risk factors for PTS development. A number of studies have suggested that a symptomatic or asymptomatic DVT event secondary to major orthopaedic surgery (MOS) may predispose patients to PTS [119, 123]. In another study, however, patients who had developed postoperative DVT after THR or TKR were not predisposed to PTS development if they had had adequate anticoagulation [88]. The use of compression stockings appears to decrease the risk of PTS development [116, 120].

Table 4: Incidence of post thrombotic syndrome after a symptomatic, confirmed and treated deep vein thrombosis

Author	Study setting/population	Incidence of PTS	Comment
Meta-analysis			
Wille-Jorgensen *et al* 2005 [123]	Meta-analysis of published literature on postoperative DVT and PTS	RR (PTS in patients with asymptomatic postoperative DVT vs. those with no-DVT) =1.58 (95%CI 1.24, 2.02 p<0.0005)	Stratification for MOS demonstrated a significantly higher rate of PTS in the asymptomatic group vs. the no-DVT group (RR=2.36) (95%CI 1.64, 3.41 p<0.00001)
Prospective Studies			
Lindner *et al* 1986 [117] US	n=47 Follow-up = 5-10yrs	Abnormal vascular findings = 83% PTS = 79% Chronic PTS in 47% of distal and 100% of proximal cohorts	Doppler examination of controls (n=28) with no history of DVT revealed valvular competence in all
Monreal *et al* 1993 [115] Spain	n=79 patients (84 limbs) Follow-up=3yrs	Mild PTS in 30 limbs (36%) Severe PTS in 17 limbs (20%) No PTS seen in: 71% where DVT was in 1 venous segment 41% where DVT was in 2 venous segments 20% where DVT was in all 4 segments (iliac, femoral, popliteal and tibial veins)	PTS more common in those with popliteal vein involvement (39/54) vs. those without (8/22)
Prandoni *et al* 1997 [85] Italy	n=528 Follow-up = 8yrs	Cumulative incidence: 1yr =18.0% 2yrs =24.5%, 5yrs =29.6% 8yrs =29.8% incidence remained stable thereafter	Ipsilateral recurrent DVT was associated with an increased risk (RR= 2.4) vs. no ipsilateral recurrence
Brandjes *et al* 1997 [120] The Netherlands	n=194 (proximal DVT) All randomly assigned to either control group (no GCS) (n=98) or active group (GCS) (n=96) for ≥ 2 yrs Median follow-up=76 months	**Moderate PTS** 19 (20%) and 46 (47%) of the active and control groups respectively (p<0·001) **Severe PTS** 11(11%) and 23(23%) of the active and control groups respectively (p<0·001)	Most cases of PTS occurred within 24 months

Table 4 continued

Author	Study setting/population	Incidence of PTS	Comment
Franzeck *et al* 1997 [116] Switzerland	n =39 ultrasonography evaluated the patency and valvular function of veins 12 yrs after DVT	Mild PTS occurred in 28% (15% and 34% of the distal and proximal cohorts respectively) Marked trophic changes occurred in 5% (in none of the distal and 8% of the proximal cohorts respectively) Severe PTS (venous ulceration) in 1 patient	Patients who had used regular GCS had either no or only mild PTS
Prandoni *et al* 2004 [89, 116] Italy	n= 53 with 1st DVT of the arm Follow-up = ≤ 5 yrs	Cumulative incidence: 6 months =20.8% 1 yr = 25.1% 2 yrs = 27.3% incidence remained stable thereafter 13 developed PTS (including 1 severe case)	The authors suggested that upper extremity DVT carries a smaller risk of PTS than a lower extremity event. The small study size, however, makes it difficult to draw definite conclusions
Retrospective Studies			
Janssen *et al* 1997 [118] The Netherlands	n=81 Patients were examined 7-13 yrs after index event	75% PTS (moderate in 31% and ulceration in 2%)	Moderate-severe symptoms in: • 11% of distal cohort • 37% of proximal cohort • 47% of iliac cohort
Ziegler *et al* 2001 [83] Austria	n = 161 Patients who had been followed for ≥ 1 yr after index event were identified via chart review Mean follow-up =160 months	82% PTS (ulceration in 7%)	Occurrence of ipsilateral recurrence was more predictive for developing severe PTS than the extent of the initial thrombosis ($p<0.05$)

Table 4 continued

Author	Study setting/population	Incidence of PTS	Comment
Development of PTS after Major Orthopaedic Surgery - Retrospective Studies			
McNally *et al* 1994 [119] UK	n = 43 All had THR ≥ 5 yrs previously Discharge venography had revealed a new DVT in 8, an old DVT in 3 and no DVT in 32	PTS developed in 4/32 with no DVT and 7/8 with a new DVT	The authors concluded that the high incidence of PTS in those who had developed DVT highlighted the need for effective thromboprophylaxis after elective THR
Ginsberg *et al* 2000 [88] US and The Netherlands	n =255 All had THR or TKR 2-7 yrs previously	PTS occurred in: • 1/25 (4%) with proximal DVT • 4/ • 66 (6.1%) with distal DVT • 7/164 (4.3%) with no DVT Rates were low with no statistical difference between 3 groups	The authors concluded that PTS is an uncommon complication in the 2-7 yrs after THR or TKR and that postoperative DVT does not predispose patients who have received adequate anticoagulation

DVT=deep vein thrombosis; **PTS**=post thrombotic syndrome; **RR**= relative risk; **GCS**=graduated compression stockings; **MOS**=major orthopaedic surgery; **CI**=confidence interval; **THR**=total hip replacement; **TKR**=total knee replacement; **yrs**=years; **UK**=United Kingdom; **US**=United States.

2.2.3 Venous Thromboembolism Risk Factors

Basic understanding of VTE risk factors rests on Virchow's triad, which was proposed over a century ago [124]. The commonly cited risk factors for VTE appear to lead to one or more of the three elements Virchow described: blood stasis, vascular injury and hypercoagulability [125]. Many risk factors have been identified. About 75% of patients with VTE have at least one established risk factor [78] and most hospitalised patients have one or more [126].

The highest risks are associated with increasing age, immobility, major surgery in the previous four weeks, pregnancy and underlying malignancy. Other predisposing conditions include congestive heart failure, sepsis, nephritic syndrome, trauma, vasculitis, high dose oestrogen therapy, haematological conditions affecting the coagulation cascade [80] and ethnicity [127].

The thrombotic risk associated with surgery is dependant on the type of surgery. A US retrospective review investigated the incidence of symptomatic VTE within a three month period after 76 different surgical procedures [128]. Using a large administration database, a total of 1,653,275 cases of surgical procedures between January 1, 1992 and September 30, 1996 were identified. High-risk procedures included MOS.

2.2.3.1 Major Orthopaedic Surgery

A systematic literature search has revealed a number of meta-analyses and studies that have investigated the risk of VTE (symptomatic and asymptomatic) associated with MOS [78, 129-133]. These can be categorised into those which investigated the risk in patients who received thromboprophylaxis [78, 129-131] and those which investigated the risk in patients who did not [129, 132, 133]. These studies have been summarised in Table 5.

In summary, the postoperative risks of VTE vary by surgery type [132]. Patients undergoing MOS are at a particularly high risk for VTE [78, 129-133]. A number of meta-analyses have demonstrated that the rates of DVT and symptomatic PE following MOS in patients who received no thromboprophylaxis are approximately

30% to 80% and 3% to 10% respectively [78, 129-131]. With the routine use of thromboprophylaxis, the risk of total DVT is approximately 17% to 31% and of symptomatic PE is 1.36% [129, 132, 133]. From the thromboembolic perspective, THR differs from TKR. Without prophylaxis, the total DVT rate is greater in TKR [134]. Moreover, prophylactic strategies have a lower efficacy in TKR [134, 135]. Patients continue to be at risk after hospital discharge [133].

The number of THR and TKR surgeries carried out in Ireland is significant. Recent HIPE data reveals that a total of 4,714 THR and 1,736 TKR surgery procedures were performed in acute public hospitals in Ireland in 2009 [104].

Table 5: Venous thromboembolism risk associated with Major Orthopaedic Surgery

Author	Study Setting	Study Conclusions
Venous Thromboembolism Risk with no Thromboprophylaxis		
NICE Clinical Guidance 46 Venous Thromboembolism; April 2007 [131]	Meta-analysis of RCTs (published up to 2006) which assessed VTE risks associated with various surgery types	Estimated that MOS has the highest VTE risk compared to other surgeries. When not on thromboprophylaxis, risk of DVT: • 44% (95%CI 42, 47) in elective hip surgery • 27% (95%CI 22, 32) in elective knee surgery risk of symptomatic PE: • 3% (95%CI 2, 5) in elective hip surgery
The Cardiovascular Disease Educational and Research Trust, European Venous Forum, Int. Surgical Thrombosis Forum, Int. Union of Angiology, 2006 [130]	Meta-analysis of published peer-review papers	Frequency of DVT: 51% (95%CI 48, 54) after THR 47% (95%CI 42, 51) after TKR
Geerts *et al* 2004 [78] 7th ACCP Consensus Conference on Antithrombotic Therapy	Meta-analysis of RCTs, published since 1980, pertaining to the risk of VTE after MOS	After THR, incidences were: • DVT (42 to 57%); proximal DVT (18 to 36%); and PE (0.9 to 28%) After TKR, incidences were: • DVT (41 to 85%); proximal DVT (5 to 22%); and PE (1.5 to 10%)
Freedman *et al* 2000 [129]	Meta-analysis of RCTs, published January 1966-May 1998, which compared the use of various thromboprophylaxis agents vs. placebo in THR	Incidences were: in 947 pooled placebo treated patients: • distal DVT=22.4% (95%CI 18.8, 26.6) • proximal DVT=25.8% (95%CI 21.4, 30.7) • total DVT=48.5% (95%CI 43.4, 53.7) in 860 pooled placebo treated patients: • symptomatic PE=1.51% (95%CI 0.81, 2.57)
Venous Thromboembolism Risk with Thromboprophylaxis		
Sweetland *et al* 2009 [132]	Prospective cohort study n=947,454 middle aged women in the UK (1996-2001)	During follow-up 239,614 admitted for surgery; post-op VTE risk varied by surgery. Highest RR occurred after THR or TKR (RR=220.6 95%CI 118.7, 259.2) in the 1st 6 weeks after surgery vs. no surgery Normal practice dictated that most patients had received prophylaxis
Freedman *et al* 2000 [129]	As Above	With various prophylaxis regimens the risk after THR of: • total DVT=17.7-31.1% • proximal DVT=6.3-19% • distal DVT=7.7-19.7% • symptomatic PE=0.16-1.36%

Table 5 continued

Author	Study Setting	Study Conclusions
White *et al* 1998 [133]	US retrospective study used hospital discharge data to identify cases of symptomatic VTE July 1991-June 1993	Symptomatic VTE seen in 2.8% of 19,568 THR patients and in 2.1% of 24,059 TKR patients within 3 months of surgery Diagnosis was made after discharge in 76% of THR patients and in 47% of TKR patients Data regarding the use of thromboprophylaxis was unavailable, a questionnaire sent to a random sample of orthopaedic surgeons, indicated that 95% had received thromboprophylaxis

NICE=National Institute for Health and Clinical Excellence; **ACCP**=American College of Chest Physicians; **RCT**=randomised controlled trial: **MOS**=major orthopaedic surgery; **VTE**=venous thromboembolism; **DVT**=deep vein thrombosis; **PE**=pulmonary embolism; **RR**=relative risk; **THR**=total hip replacement; **TKR**=total knee replacement; **RR**=relative risk; **UK**=United Kingdom; **US**=United States.

2.2.4 Prevention of VTE

The need for preventative measures depends on a patient's risk factors for VTE[136]. The mortality, acute and long-term morbidities and resource utilisation associated with un-prevented VTE support effective preventive strategies [78, 128, 137].

General measures used to prevent VTE include:

- Early mobilisation

- Adequate hydration (haemoconcentration results in increased blood viscosity and reduced blood flow)

- Mechanical prophylaxis including graduated compression stockings (GCS), intermittent pneumatic compression devices and the venous foot pump. All methods have been shown to reduce the risk of DVT but are generally less efficacious for the prevention of DVT than anticoagulants. No mechanical option has been shown to reduce the risk of death or PE [78].

- Pharmacological agents, which may be used alone or in combination with compression methods. Options include:

    1. Aspirin and other antiplatelet drugs. These are effective at reducing major thrombotic vascular events in patients who are at risk for or have atherosclerotic disease [138]. They also provide some protection against VTE in hospitalised patients [139, 140]. Their use alone as VTE prophylaxis, however, is not recommended primarily because more effective strategies exist [134].

    2. Vitamin K antagonists (VKAs) of the coumarin type are orally active agents which inhibit the synthesis of factors dependent on vitamin K (prothrombin; factors VII, IX, and X; protein C; protein S). There is a considerable inter-patient variability in effectiveness, which is influenced by age, racial background, diet and co-medications. Frequent laboratory monitoring is required, the prothrombin time being compared with a standard to produce the international normalised ratio (INR). Adverse effects include haemorrhage,

hypersensitivity, alopecia and purpura [141]. Warfarin is the most commonly prescribed VKA in Ireland [142].

3. Heparin increases the inactivation of the coagulation enzymes thrombin (IIa), factor IXa, and factor Xa by binding to antithrombin III and causing a conformational change in the molecule. Unfractionated heparin (UH) consists of a heterogeneous mixture of polysaccharides with an average molecular weight of 15000 Da. Due to its extensive first pass metabolism it must be given parenterally. The effect on the intrinsic clotting cascade is monitored by measuring the activated partial thromboplastin time (APTT) [141]. Adverse effects include haemorrhage, osteoporosis, alopecia, thrombocytopenia and hypersensitivity [141].

Many advances have been made in anticoagulant therapy since the 1930s and 1940s when parenteral UH and the VKA warfarin were the primary options for treating patients [143].

4. Low molecular weight heparins (LMWHs) (4000-6000 Da) were introduced in the 1980s [144]. LMWHs are weaker inhibitors of thrombin relative to UH but inhibit factor Xa to a similar extent. The advantages of LMWH over UH are higher availability and longer half-life, which allows once daily (OD) subcutaneous (SC) administration and more predictable anticoagulant responses that obviate the need of laboratory monitoring. LMWHs only need dosage tailoring based upon patient weight [145].

5. Fondaparinux became available in the 1990s [144]. It is a synthetic analogue of the antithrombin-binding pentasaccharide sequence found in UH and LMWH. It binds antithrombin and enhances its reactivity with factor Xa [146]. It is at least as effective as UH and LMWH, employing a standard dosing regimen that offers a uniform approach of patient management (SC injection OD with no body-weight tailoring) [147]. Fondaparinux is not available in Ireland.

Non-anticoagulant side-effects of UH such as thrombocytopenia and osteoporosis have been substantially reduced with the advent of LMWHs and fondaparinux but are still a potential risk [145, 148].

Research into the development of new anticoagulants has focused on the identification of synthetic compounds that act directly on distinct serine protease enzymes that drive clot propagation and fibrin deposition [149]. Two principal targets are thrombin and factor Xa [149, 150]. Of the new drugs in clinical development, approximately two thirds are factor Xa inhibitors and one-third direct thrombin inhibitors [145]. Research has mainly concentrated on the development of agents suitable for oral administration at a fixed dose, without the need for laboratory monitoring [145]. The first approved oral direct thrombin inhibitor (DTI), ximelagatran (Exanta®; AstraZeneca), was withdrawn from the market in 2006 owing to its link to liver toxicity [151]. The mechanisms of unexpected and sometimes fatal acute liver injury observed with ximelagatran remain unexplained [152].

In 2008, two oral anticoagulants, dabigatran etexilate (Pradaxa®; Boehringer Ingelheim Ltd) and rivaroxaban (Xarelto®; Bayer Ltd) were licensed in Ireland for the prevention of VTE in adult patients (over 18 years) undergoing elective THR or TKR [73, 74]. Both are licensed in Europe, Canada and the US for this indication [153-155].

6. Rivaroxaban is a highly selective oral direct factor Xa inhibitor that interrupts both the intrinsic and extrinsic pathways of the coagulation cascade [73]. It has a high oral bioavailability (80-100%), a rapid onset of action (maximum concentrations appear 2-4 hours after dosage) and a half-life of 7-11 hours. It is metabolised by hepatic cytochrome P450 isoenzyme 3A4 and is a substrate for P-glycoprotein [73].

   The recommended dose is 10mg OD, with the first dose taken 6-10 hours after surgery completion, provided haemostasis has been established. Treatment should be continued for five weeks after THR and for two weeks after TKR [73].

7. Dabigatran etexilate is a small molecule prodrug. After oral administration, it is rapidly absorbed and converted to dabigatran by esterase-catalysed hydrolysis in plasma and in the liver. Dabigatran is a potent, competitive, reversible DTI and is the main active principle in plasma. It inhibits free thrombin, fibrin-bound thrombin and thrombin-induced platelet aggregation. The bioavailability is approximately 6.5% after oral administration. Peak plasma concentrations are achieved 6 hours after administration. The mean half-life is 12-17 hours. It is a substrate for the transporter P-glycoprotein [74].

   There are two licensed doses of dabigatran etexilate, a standard dose of 220mg OD and a reduced dose of 150mg OD reserved for special patient populations (moderate renal impairment, elderly aged over 75 years and concomitant use of amiodarone). The first dose should be taken 1- 4 hours after surgery completion, provided that haemostasis has been established and should be continued for 28 to 35 days post THR and for ten days post TKR [74].

Both drugs are administered in fixed doses without the need for coagulation monitoring during routine clinical practice [73, 74].

There are a number of limitations to the use of these new agents.

- One of the major complications of anticoagulation therapy is bleeding. In contrast to VKAs, LMWHs and UH, there is no specific antidote for DTIs and factor Xa inhibitors [156].

- Oral factor Xa inhibitors and DTIs have variable effects on the current standard tests of coagulation [73, 74]. Without appropriate coagulation monitoring, drug compliance is more difficult to assess.

- The long term safety of these new drugs is unknown.

2.2.4.1 Prevention of Venous Thromboembolism after Total Hip- and Total Knee- Replacement

Risk stratification of patients is an important step to determine the appropriate thromboprophylaxis strategy. Both the American College of Chest Physicians (ACCP) and the National Institute for Health and Clinical Excellence (NICE) categorise patients undergoing MOS as belonging to the highest risk group [134, 157].

From the thromboembolic perspective, THR differs from TKR. Without prophylaxis, the total DVT rate is greater in TKR [134]. Moreover, prophylactic strategies have a lower efficacy in TKR [134, 135].

The NICE recommendation is that patients undergoing elective THR or TKR should receive mechanical prophylaxis and either LMWH or fondaparinux. The recommendations were updated in January 2010 to also include rivaroxaban and dabigatran etexilate as options. THR patients should continue prophylaxis for 28 to 35 days. TKR patients should continue pharmacological prophylaxis for ten to 14 days [157].

The ACCP recommend that patients undergoing elective THR or TKR should receive either LMWH, fondaparinux, or a VKA. TKR patients should receive prophylaxis for a minimum of ten days and THR patients for a minimum of ten days and for up to 35 days. Mechanical prophylaxis should be used primarily for patients at high bleeding risk or possibly as an adjunct to pharmacological prophylaxis [134]. The guidelines were updated in 2012 to include rivaroxaban and dabigatran etexilate as options [158].

In Ireland, local guidelines classify MOS patients as having a high risk for VTE [159, 160]. It is recommended that patients undergoing THR or TKR receive prophylaxis with LMWH. Graduated compression stockings may be combined with pharmacological prophylaxis in patients with multiple risk factors. In 2007, the St James's University Teaching Hospital Prescribing Guidelines recommended that prophylaxis be continued for seven to ten days [159]. The Guidelines were updated in 2009; it is now recommended that prophylaxis be continued until the patient is mobile or discharged and extended prophylaxis may be considered for up to 35 days after THR and TKR surgery [160].

The multinational cross-sectional ENDORSE study assessed the proportion of at-risk patients who receive effective VTE prophylaxis in 358 hospitals across 32 countries [161]. In total, 88% of patients undergoing THR or TKR received prophylaxis. Although specific data for hip and knee surgery in Ireland was not presented, 112 out of 175 (64%) at risk surgical patients in Ireland received ACCP-recommended prophylaxis.

2.2.5 Diagnosis of Venous Thromboembolism

2.2.5.1 Diagnosis of Deep Vein Thrombosis

Clinical Signs

Symptoms include swelling, pain and discoloration in the affected extremity. Physical examination may reveal unilateral oedema, warmth and superficial venous dilation [162].

Probability Scoring

Symptomatic patients should have a pre-test probability determination using an established prediction model such as The Wells' Score (see Table 6) [76, 163, 164]. Over 14 studies have demonstrated the reproducibility of this model [164].

Table 6: Wells' Rule for determining the probability of deep vein thrombosis

Clinical Feature	Score
Active Cancer (treatment within 6 months or palliation)	1
Paralysis, paresis or immobilisation of lower extremity	1
Bedridden for more than 3 days because of surgery (within 4 weeks)	1
Localised tenderness along distribution of deep veins	1
Entire leg swollen	1
Unilateral calf swelling of greater than 3cm	1
Unilateral pitting oedema	1
Collateral superficial veins	1
Previously documented DVT	1
Alternative diagnosis at least as likely as DVT	-2

Adapted from Wells *et al* 2003 [164]. **DVT**=deep vein thrombosis

A Wells' score of 2 or higher indicates that the probability of DVT is 'likely'; a score of less than 2 indicates that the probability is 'unlikely' [76].

After a pre-test probability is determined, a D-dimer blood test should be performed [165].

Blood Tests

D-dimer fibrin fragments are present in fibrin clots and fibrin degradation products. D-dimer levels may be elevated in any condition where clots form and represent a low specificity for DVT. Therefore they should be used to rule out and not to confirm DVT [76]. Where there is a moderate or high clinical suspicion of DVT, diagnostic imaging should be performed [125].

Diagnostic Imaging

Doppler Ultrasound Study: This is the most widely used modality for evaluating suspected DVT [166]. The non-invasive technique combines ultrasonographic imaging with Doppler flow studies. DVT is confirmed when the vascular lumen cannot be compressed due to an occluding thrombus. The absence of normal Doppler signals from venous flow provides further evidence of occlusion [125]. This is accurate in the prediction of DVT, however, a normal ultrasound in a high-probability patient requires additional investigation [125]. There are a number of limitations: accuracy depends on the operator; it cannot distinguish between old and new clots; it is not accurate in detecting DVT in the pelvis or small calf vessels, or in the presence of obesity or significant oedema. Causes of false positive examination include superficial phlebitis and abscess [125, 167].

Contrast Venography: The patient is injected with contrast material and the veins in the calf and thigh are imaged. Although it is not performed routinely, it remains the gold standard as it is considered to be the most sensitive and specific test [168]. Its use is limited by the risk of pain, phlebitis, hypersensitivity and DVT. Oedema or obesity may make the test difficult or impossible to perform in approximately 10% of patients. It is often used for DVT diagnosis in RCTs [167], however the clinical significance of asymptomatic DVT detected venographically is controversial [124]. In such trials, patients with detected asymptomatic DVT typically receive anticoagulant therapy which alters the natural history of the disease and undoubtedly results in lower rates of symptomatic events [125].

2.2.5.2 Diagnosis of a Pulmonary Embolism

Clinical Signs
Patients classically present with acute onset chest pain (80 to 90%), dyspnoea (75 to 85%) and haemoptysis (13 to 20%); but all three of these symptoms are only seen in 20% of patients. Other symptoms include cough, abdominal pain and cardiac arrhythmias. Patients may have signs and symptoms of underlying DVT. Life-threatening PE may present with cardio-respiratory arrest due to acute occlusion of the pulmonary arteries or with syncope, hypotension and cyanosis [77].

Low Probability Diagnostic Tests/Non-Diagnostic Tests
Tests that are not sensitive for PE but can be diagnostic include the chest X-ray, arterial blood gas measurements and electrocardiogram (ECG). These are frequently used to establish a high, intermediate or low risk of PE.

Probability Scoring
Scoring algorithms have little impact on PE risk stratification.

Blood Tests
D-dimer levels may be elevated but are not sensitive or specific enough to diagnose a PE [80]. A number of blood tests can be used to exclude important secondary causes of PE. These include a full blood count, clotting status and some screening tests: erythrocyte sedimentation rate, renal function, liver enzymes and electrolytes.

Diagnostic Imaging
Ventilation Perfusion (V/Q) Scanning: This is a pair of nuclear scans and is the most useful non-invasive diagnostic procedure [77]. The ventilation scan scans the lungs while the patient inhales radioactive gas. In the perfusion scan, radioactive albumin is injected into the arm and the lungs are scanned as blood flows through [125]. A high-probability scan provides evidence for the presence of PE. A normal scan excludes PE. Fifty to 70% of scans are indeterminate [169]. In the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) study, 40% of patients with confirmed PE had a high-probability, 40% had an intermediate-probability and 14% had a low-probability scan [169]. A low-probability scan does not rule out PE [80]. If there is a

discrepancy between clinical suspicion and the scan, computed tomographic pulmonary angiography (CTPA) is warranted [126].

Computed Tomographic Pulmonary Angiography: This relies on radionuclide imaging of the pulmonary arteries [170]. It is regarded as highly sensitive and specific and is the most definitive diagnostic test [171]. Studies indicate that CTPA detects large PEs with a sensitivity and specificity of nearly 90%, but is generally unable to detect smaller PEs [124].

2.2.6 Treatment of Venous Thromboembolism

Treatment of suspected or confirmed VTE involves the use of anticoagulant therapy to prevent further clot development and to reduce the risks of mortality and recurrent VTE [172, 173]. For most patients, treatment of a DVT consists of the same treatment regimens as treatment of a PE [172].

2.2.6.1 Acute Treatment of Venous Thromboembolism

Initial therapy must involve therapeutic doses of either UH, LMWH or fondaparinux [174]. Historically, UH had been the standard treatment for acute VTE, however, LMWHs are more effective than UH for the initial treatment of VTE and are associated with less bleeding [175]. Fondaparinux has been shown to be as effective and safe as LMWH for the acute treatment of VTE [173]. As a consequence, LMWHs and fondaparinux have replaced UH in the treatment of acute VTE [173, 175].

The currently recommended approach is to start both a heparin (or fondaparinux) and a VKA at the time of diagnosis [176]. A threefold-higher rate of recurrent VTE has been reported in patients who received a VKA only [176]. Heparin (or fondaparinux) treatment should be continued for at least five days and until the INR is > 2 for at least two consecutive days [160].

2.2.6.2 Long-Term Treatment of Venous Thromboembolism

For the majority of patients with VTE, oral therapy with VKAs (target INR= 2.0-3.0) is very effective for the long-term prevention of recurrent thrombosis [174, 177].

Although the initial treatment of VTE is similar for most patients, the duration of long-term anticoagulation treatment differs according to guidelines, location of the thrombosis and the risk-benefit ratio of long term anticoagulation treatment in an individual patient [172, 174, 178].

The British Society for Haematology (2011) recommends that patients with proximal DVT or PE should be treated for at least three months. Also, if a diagnostic strategy that identifies isolated distal DVTs is employed, treatment of such clots can be restricted to six weeks [179]. The previous edition of these guidelines stated that a distal DVT should be treated for at least six weeks [180].

2.2.7 The Economic Cost of Venous Thromboembolism

A systematic literature search has revealed a number of studies which report the direct medical costs associated with VTE from a health payer perspective [181-184]. No Irish studies were located. The studies are summarised in Table 7.

On review of Table 7, a number of prospective and retrospective studies of various time horizons, across different jurisdictions consistently conclude that VTE, and in particular the long-term complications associated with VTE, such as recurrent VTE and PTS, confer a significant economic burden [181-191]. Indeed, a number of US studies which investigated the costs associated with readmission for the treatment of VTE complications were consistent in that the readmission costs were higher than that of the index event [185-187]. A multi-centre European study concluded that the total one-year cost of managing a VTE patient was about 30% higher than the acute care cost alone [190]. In a Swedish 15-year retrospective study which investigated the economic burden of the long-term complications of VTE, the average additional long-term cost of treating DVT complications were about 75% of the cost of a primary event [191].

VTE represents a large financial burden for the Irish HSE. The estimated cost in Ireland in 2011 of hospitalisation for a DVT (Diagnosis Related Group (DRG) codes F63A, F63B) is €3,900 and for a PE (DRG codes E61A, E61B) is €6,630 [192, 193].

The estimated burden of illness in Ireland for 2011 for DVT and PE hospital admissions is €14.56 million [192, 193].

Table 7: The per-patient cost of venous thromboembolism

Author	Costing Year	Study design	Costing period/ Perspective	Costs
Acute Events				
Knight *et al* 2005 [182] US	1999 - 2000	Retrospective observational cohort; patients with primary DVT (n=953) or PE (n=3,933) admission	NS/acute events only Health payer	Inpatient cost: • DVT =$3,018 - $5,040 • PE = $5,198 - $6,928
Backman *et al* 2004 [183] Sweden	1997	Prospective study, patients with acute DVT randomised to inpatient (n=66) or outpatient treatment (n=65)	3 months Health payer & patient	• Outpatient group = €1,405 • Inpatient group= €1,899
Annemans *et al* 2002 [184] Belgium	1998	Retrospective chart review; inpatient cost of treating PE (n=54)	Inpatient stay (mean=14.6 days) Health payer	Inpatient cost: • PE = €3,394 (SE=€323)
Tillman *et al* 2000 [181] US	1996 - 1998	Prospective study; patients (n=391) in outpatient DVT treatment program vs. potential inpatient costs	3 months Health payer	• Outpatient group=$1,868 (SD=$2,197) • Inpatient group=$2,828 (SD=$2,270)
VTE and Long Term Consequences				
Spyropoulos and Lin 2007[185] US	1998 - 2004	Retrospective review; National Discharge Database: Primary DVT (n=5,348); Secondary DVT (n= 4,593); Primary PE (n=2,984); Secondary PE (n=1,119)	12 months Health payer	• Primary DVT= $10,804 • Secondary DVT=$7,594 • Primary PE =$16,644 • Secondary PE =$13,018 Cost per readmission for recurrent DVT =$11,862 vs. $9,805 for initial hospitalisation Cost per PE readmission =$14,722 vs. $14,146, for initial hospitalisation
Mac Dougall *et al* 2006 [188] US	1997 - 2004	Retrospective observational study: patients with DVT or PE (n=26,958, median follow-up =280 days), PTS sub-analysis (n=17,634, median follow-up =558 days)	12 months Health payer	• DVT = $33,200 • PE = $31,300 • DVT & PE = $38,300 • Control (no VTE) = $2,800 Mean cost =$47,596 in PTS group vs. $35,929 in DVT/PE non-PTS group

Table 7 continued

Author	Costing Year	Study design	Costing period/ Perspective	Costs
Ramacciotti *et al* 2006 [189] Brazil	2000 - 2002	Prospective observational multicentre study; patients (n=90) with PTS (18.8% with mild-to-moderate and 81.1% with severe PTS)	12 months Health payer	• Mild-to-moderate PTS =$426 • Severe PTS=$1,188 Cost difference primarily due higher hospitalisation costs in severe cohort
Bullano *et al* 2005 [187] US	1997 - 2001	Retrospective observational cohort study; patients (n= 2,147) admitted for DVT (69.8%), PE (17.4%) or DVT & PE (12.8%) Health payer	21.3 months Health payer	• DVT =$7,712 (SD=$18,339) • PE =$9,566 (SD=$13,512) • DVT & PE =$12,200 (SD=$24,038) Readmissions: Recurrent event= $14,975 ($12,326 per recurrent VTE; $15,339 per bleed; $24,085 per recurrent VTE & bleed) Recurrent non hospitalised bleeds = $239
O'Brien *et al* 2002 [186] US	1997	Retrospective observational cohort; patients discharged with DVT (n=29,295) Health payer	6 months Health payer	• DVT =$5,102 • DVT & minor bleed= $12,142 • DVT & HIT=$13,469 • DVT & PE=$14,649 • DVT & major bleed=$17,169
Levy *et al* 2001 [190] France and Italy	N/S	Retrospective study; patients with DVT using Inpatient Diagnosis Group Data. Risk of PE and DVT recurrences were modelled from published data	1 year Health payer	Inpatient cost in: France = €3,220 Italy = €2,865 In both countries, the total one-year cost of managing a patient was 30% higher than the acute care cost alone
Bergqvist *et al* 1997 [191] Sweden	1997	15-year retrospective study to determine costs of long-term complications of DVT. (n= 257) patients with DVT (diagnosed 1970-1985) vs. controls (n=241) without DVT	15 year period Health payer	After 15 years of follow-up, average expected health care cost of treating DVT complications = $4,659 in DVT patients = $375 in controls Most expensive complication = venous ulcer ($7,933) In control group, primary DVT = $6,000

US=United States; **DVT**=deep vein thrombosis; **PE**=pulmonary embolism; **NS**=not stated; **SD**=standard deviation; **PTS**=post thrombotic syndrome; **VTE**=venous thromboembolism; **HIT**=heparin induced thrombocytopenia. (All dollars are US$)

2.2.7.1 The Cost of VTE Secondary to Major Orthopaedic Surgery

Several studies have examined the direct medical costs, from a health payer perspective, of VTE in patients after MOS. Four studies are from the US [194-197] and one is European [198] and they comprise of both short and long time horizon investigations. These studies are summarised in Table 8 [194-198].

In summary, a mixture of retrospective and model based cost of illness studies conclude that MOS confers a significant VTE risk. The development of VTE secondary to MOS has been associated with an increase in the length of stay (LOS) [196] and cost of the index admission [195, 196] and an increase in the cost of long-term follow-up care [194, 195]. Patients who develop a VTE after MOS have been shown to be at a significantly increased risk of hospital readmission, bleeding and mortality compared to those who do not develop a VTE after MOS [194]. The risk of development of VTE after MOS continues after hospital discharge [195].

Table 8: The per-patient cost of venous thromboembolism secondary to major orthopaedic surgery

Author	Costing Year	Study Design	Costing period/perspective	Cost	Comments
Acute Events					
Ollendorf *et al* 2002 [196] US	NS	Retrospective study; (n=105,562) patients who had TKR, THR or hip fracture repair between 1998-1999 with or without VTE	Inpatient stay Health payer	Mean inpatient costs: DVT=$17,114 PE=$18,521 No VTE = $9,345	During inpatient stay, DVT occurred in 0.7% and PE in 0.4% Mean LOS = 11.5days (DVT), 12.4 days (PE) & 5.4 days (no VTE), ($p < 0.0001$ for both comparisons)
VTE and Long Term Consequences					
Baser *et al* 2010 [194] US	2005-2007	Retrospective analysis; healthcare provider database (2005-2007) identified n=170,047 patients (51,961 THR & 118,086 TKR). Postoperative VTE occurred in 3,014.	1 year Health payer	**THR cohort** Mean cost of 1 year follow-up inpatient care $8,382 higher in the VTE group vs. no VTE group ($p<0.0001$) **TKR cohort** Mean cost of 1 year follow-up inpatient care $9,244 higher in the VTE group vs. no VTE group ($p<0.05$)	• VTE occurred 1.77% during inpatient stay • Mortality rates for those with VTE vs. without (OR for THR = 2.95, $p< 0.0001$; OR for TKR = 5.0, $p< 0.0001$) • Patients with VTE more likely to be re-hospitalised within 30 days, 90 days, 180 days, 1 yr, 2yrs ($p<0.05$ each period) • Patients with VTE more likely to bleed ($p<0.05$ each period)
Tilleul *et al* 2006 [198] France	1999	Decision tree model estimated costs of prophylaxis & treatment of VTE. Incidence of MOS, VTE & LOS derived from DRG database	1 year Health payer	Annual cost of VTE associated with MOS =€8,265 per patient Total annual cost for health payer = €60 million (€28 million for inpatient care and €30 million for recurrences & PTS)	Estimated incidence of inpatient VTE after • TKR =2.4% • THR = 1.4%

Table 8 continued

Author	Costing Year	Study Design	Costing period/perspective	Cost	Comments
Oster *et al* 2004 [195] US	1999	Retrospective study; (n=11,960) patients who had THR, major knee surgery or hip fracture repair from 1993-1998. Within 90-days of surgery, 259 developed VTE. Two controls matched to each VTE case.	90 days Health payer	**In-hospital VTE diagnosis** At discharge VTE case =$52,037 Control =$34,485 At day 90 VTE case =$54,480 Control =$35,646 **Post-discharge diagnosis** At day 90 VTE case =$41,411 Control =$35,646	61.8% of VTE events occurred post-discharge **In-hospital VTE diagnosis** Mean LOS = 11.1 days vs. 6.6 days for controls Day 90: 5.4 day difference in LOS reflected a 10% readmission rate **Post-discharge diagnosis** Day 90: mean LOS = 10.2 vs. 6.8 days reflecting readmissions
Caprini *et al* 2003 [197] US	2000	Markov model used to estimate lifetime economic burden of DVT secondary to THR. The model simulated natural history of DVT. Patient care pathways were defined by the literature.	1 year Health payer	Annual cost of: • Mild-to-moderate PTS $839 in 1st & $341 in subsequent years • Severe PTS $3,817 in 1st & $1,677 in subsequent years • Recurrent DVT=$3,798 • Recurrent PE=$6,404	Difference in PTS costs from 1st to subsequent years was due to surgery costs

US=United States; **NS**=not stated; **TKR**=total knee replacement; **THR**=total hip replacement; **VTE**=venous thromboembolism; **DVT**=deep vein thrombosis; **PE**=pulmonary embolism; **LOS**=length of stay; **OR**=odds ratio; **MOS**=major orthopaedic surgery; **DRG**=diagnosis related group; **PTS**=post thrombotic syndrome.

2.3 Targeting New Oral Anticoagulants for Pharmacoeconomic Evaluation

LMWHs and VKAs have been the cornerstone of thromboprophylaxis for the last two decades [152]. Two new orally active anticoagulants, rivaroxaban (Xarelto®; Bayer Ltd) and dabigatran etexilate (Pradaxa®; Boehringer Ingelheim Ltd), were licensed in Ireland in 2008 for the primary prevention of VTE in adult patients (over 18 years) undergoing elective THR or TKR surgery [73, 74].

The global anticoagulant market is projected to grow from around $6 billion in 2008 to over $9 billion in 2014. The growth will be driven by demographics of the ageing population and by the approval of new agents which may offer improvements over the current standards of care. It has been predicted that the direct oral anticoagulants are likely to take more than half of the anticoagulant market share between 2010 and 2014 [151].

The cost of these new agents will be a potential obstacle to their usage and it is pragmatic therefore to target these novel anticoagulants for pharmacoeconomic evaluation.

In order to proceed with this evaluation, a primary objective is to describe the structure of published model based economic evaluations of thromboprophylaxis after THR and TKR.

2.4 Review of Cost Effectiveness Models used to Evaluate Thromboprophylaxis after Total Hip- and Total Knee-Replacement

2.4.1 Introduction

Several studies have evaluated the cost-effectiveness of thromboprophylatic agents in patients undergoing THR or TKR. Economic evaluation results will vary depending on various factors including time horizon, model structure, economic perspective and outcome analysed.

2.4.2 Objective

The objective of this study was to describe published model based economic evaluations of thromboprophylaxis after THR and TKR in order to inform the development of an independent model.

2.4.3 Method

A systematic literature search identified a number of economic evaluations. The search was limited to literature published in the English language since 1985. Inclusion criteria incorporated pharmacoeconomic analyses that used decision analytic models to evaluate the primary prevention of VTE following THR or TKR. Additional references were identified from the reference lists of published articles. Combinations of the following search terms were used:

For Pubmed MeSH: arthroplasty, replacement, knee; arthroplasty, replacement, hip; venous thrombosis; pulmonary embolism; thromboembolism; economics; costs and cost analysis; anticoagulants; drug therapy; warfarin.

For Embase Thesaurus: deep vein thrombosis; venous thromboembolism; leg thrombosis; lung embolism; prothesis; hip prothesis; knee prothesis; knee arthroplasty; hip arthroplasty; economic evaluation; pharmacoeconomics; health economics.

Centre for Reviews and Dissemination (CRD): databases including DARE (Database of Abstracts of Reviews of Effects), NHS EED (NHS Economic Evaluation Database), and HTA (Health Technology Assessment) were searched for relevant references on thromboprophylaxis relating to TKR and THR.

For NICE: completed HTAs were searched; appraisals of thromboprophylaxis were retrieved.

2.4.4 Results

Twenty-five evaluations were identified, these have been summarised in Table 9 [199-223]. One model compared dabigatran etexilate to enoxaparin sodium after both THR

and TKR [206]. One model, published in 2011 (subsequent to completion of the analysis in this thesis), evaluated rivaroxaban or dabigatran etexilate compared with LMWH after THR and TKR [223]. The other models compared various different thromboprophylaxis regimens.

2.4.4.1 Time Horizon

The time horizon of the analyses ranged from 35 days to lifetime. Some analyses covered the acute phase only (usually up to three months after surgery) [204, 209, 213, 214]. Others combined the acute phase with a chronic phase (usually up to five years) [211, 212, 215]. The remainder had a lifetime horizon [200-202, 205-207, 210, 219, 223].

Sullivan *et al* [124] performed a review of pharmacoeconomic evaluations of thromboprophylaxis in MOS which had been published between 1984 and 2000. The authors concluded that since VTE manifests as both an acute and chronic disease, evaluations of VTE related costs and outcomes should be conducted over a time horizon which allows both the acute and chronic phases of the disease to be evaluated.

2.4.4.2 Model Structure

Nineteen of the 25 evaluations used decision trees to model costs and events [199, 201, 203-205, 209-222]. Others combined a decision tree with a Markov model to extrapolate results from clinical studies to a longer time frame [200, 202, 206, 207, 223]. One evaluation used a short-term Markov model [208].

The decision tree model described, in 1987, by Oster *et al* [222] was similar in structure to many subsequent analyses [200-207, 209, 211, 212, 215-219, 221]; in all subsequent models the structure was expanded to varying extents.

The beginning of the Oster *et al* [222] tree has four branches:

Branch 1: True-positive clinical diagnosis of DVT (symptomatic VTE)

Patients are assumed to undergo tests to confirm diagnosis and receive treatment.

Branch 2: False-negative clinical diagnosis of DVT (asymptomatic VTE)

Of those with undetected DVT, some will develop a PE and some of these will die suddenly before treatment can be initiated. Survivors may receive a clinical diagnosis, which will be confirmed and treated. Others with undetected PE may survive, receive no treatment and may experience recurrence. Of those who do not have PE, some may receive a clinical diagnosis of PE, which is not confirmed. The remaining patients with undetected VTE are assumed to undergo no additional tests or treatment.

Branch 3: False-positive clinical diagnosis of DVT
Patients who do not have DVT may nevertheless receive a clinical diagnosis of DVT. Because the diagnosis is incorrect, it will not be confirmed and treatment will not be initiated. Since VTE has been ruled out, it is assumed there will be no PE diagnosis.

Branch 4: True-negative clinical diagnosis of DVT (no VTE)
Most patients undergo no additional tests or treatment. However, some may receive a clinical diagnosis of PE. This will not be confirmed and treatment will not be initiated.

Thus, events included in the Oster *et al* [222] model were DVT, PE, and VTE-related death. Haemorrhage and the long-term consequences of VTE, such as PTS, were not modelled.

The Menzin *et al* [221] model is patterned on Oster *et al* [222] with adjustments to Branch 1. There is a probability that the diagnosis of DVT will be incorrectly ruled out in some. Most of this cohort will not undergo further tests or treatment and will remain at risk of PE.

The Gordois *et al* [216] model is similar to Oster *et al* [222] but with the addition of thromboprophylaxis related haemorrhage, recurrent VTE and PTS events. Haemorrhage is added as the first event so that all patients are at risk. In this model VTEs may occur pre- or post-discharge (between discharge and day 30). The risk of recurrence was assumed to begin immediately after a DVT or PE. The risk of PTS was assumed to begin at day 91 (the chronic phase of the model) with different estimates depending on whether the patient had initially developed a symptomatic or

an asymptomatic VTE. The time horizon was five years [216]. Bjorvatn *et al* [211] and Lundkvist *et al* [215] both used this model. Dranitsaris *et al* [204] used the model but restricted it to 90 days, considering it pragmatic from a health payers perspective, to include only acute events.

Levin *et al* [200, 202] adopted the Oster *et al* [222] model by combining it with a simple Markov model to simulate an annual mortality risk over 18 years. The Markov process accommodated the long-term complications of VTE (recurrent DVT, superficial thrombophlebitis, superficial infection, venous leg ulcer, varicose veins, venous insufficiency and PE) [200, 202].

Botteman *et al* [207] used an Oster *et al* [222] based model to accommodate the period immediately after surgery and added a Markov process to extrapolate to lifetime. The Markov process depicts the natural history of post-DVT complications (i.e. PTS, VTE events and death). Patients enter the Markov as those who had survived surgery either with or without experiencing a primary DVT. Those who had survived a primary DVT could remain in this post-DVT state or develop signs and symptoms of mild-moderate PTS or severe PTS or die. Patients who did not experience a primary DVT were also assumed to experience idiopathic VTE and PTS events at less frequent rates. The model established a distinction between the first and subsequent years of PTS to allow for differences in diagnostic and treatment patterns and associated costs, as recommended by Caprini *et al* [197]. Once patients entered the PTS states, they remained in these states until they died or reached 100 years. Due to limited epidemiologic data, the model assumed no movements between the mild-moderate PTS and severe PTS states. Recurrent or idiopathic VTEs were treated as isolated clinical events rather than health states. Haemorrhage was not modelled [207].

The structure of the Wolowacz *et al* [206] model was similar to that of Botteman *et al* [207] but was modified by the addition of the 'Untreated DVT' and the 'Post Stroke' health states. Distal and proximal DVTs were also included as separate events to allow different costs and consequences to be attached to these. The decision tree accommodated the initial ten-week period. Adverse events were modelled simultaneously so that all patients were at risk for major and minor bleeding events and heparin-induced thrombocytopenia (HIT). The Markov component simulated

events (mild to moderate PTS, severe PTS, recurrent VTE, death from other causes) occurring over a 60 year horizon [206].

The Ringerike *et al* [223] model combined a decision tree with a Markov module. The decision tree component modelled the acute phase (up to 90 days after surgery) and considered major bleeding, DVT (symptomatic or asymptomatic) and PE events. The Markov simulated events occurring over patient lifetime (until the patient died or reached 100 years). The Markov contains three health states 'symptom-free ', 'PTS' and 'dead'. In each cycle, patients could develop recurrent VTE or PTS or could die from other causes. Once patients entered the PTS state, they could experience a recurrent VTE event or remain in this state until death or the end of the simulation. The risk of stroke associated with major bleed was not considered.

Sarasin *et al* [208] used a short-term Markov model with weekly cycles extending over three months. During each cycle, recurrent chance events (DVT, major bleed) lead to transition between health states. VTE-related death and all cause mortality were not modelled [208].

2.4.4.3 Outcome Analysed

All economic models have included DVT and PE. A number included only proximal DVT and excluded distal DVT assuming that these tend to be asymptomatic and untreated [200, 202, 213]. Skedgel *et al* [210] classified DVT as symptomatic DVT only. Some models combined distal and proximal DVT as a single event and assumed equivalent costs and outcomes for both [205, 212, 214-216, 218, 221-223]. Others included them as separate events attaching different costs and outcomes [199, 201, 203, 206, 208, 217, 219]. All extrapolated models included PTS and recurrent VTE. Most extrapolated models included VTE-related death, however, there were exceptions to this [201, 208, 220].

A number of evaluations did not incorporate a bleeding risk [200, 202, 205, 207, 218, 221, 222]. Although thromboprophylaxis associated major bleeding was included in most models, two also included minor bleeding associated with thromboprophylaxis [206, 213]. Other evaluations included haemorrhage secondary to the treatment of VTE events [199, 203, 215]. Most analyses treated bleeds as gastrointestinal (GI) bleeds, only a small number included intracranial haemorrhage (ICH) and the probability of

surviving such an event with either no sequelae or with a permanent disability [203, 206]. Marchetti *et al* [203] demonstrated that stroke (a surrogate for ICH) was a major component of both the costs and the quality of life in their economic analysis of thromboprophylaxis after THR.

HIT was included in two analyses [206, 213].

2.4.4.4 Perspective

Most of the economic analyses were conducted from the health payer's perspective and considered only direct medical costs. Although the analysis by Detournay *et al* [205] considered only direct medical costs, it was conducted from a societal perspective since total values (reimbursed and out of pocket) were considered. Marchetti *et al* [203] considered both direct and indirect costs (represented by absences from work incurred by patients with long-term complications of VTE).

2.4.4.5 Analysis Type

Most analyses were CEAs. Wolowacz *et al* [206] and Davies *et al* [218] presented the results of a CEA and a CUA. Six analyses were CUAs [199, 203, 207, 209, 210, 223].

2.4.5 Discussion

Based on a review of the structure of published model based economic evaluations of thromboprophylaxis after THR and TKR, it is recommended that two economic models be constructed, as suggested by Sullivan *et al* [124]. One model should have a short-term time horizon to capture the acute costs and outcomes associated with VTE disease. A second model with a longer time horizon will also determine the impact of the long-term consequences of VTE such as recurrent VTE and PTS.

The following recommendations will inform the development of two independent economic models which will evaluate the cost-effectiveness of rivaroxaban and dabigatran etexilate. These models will be presented in subsequent chapters of this thesis.

2.4.5.1 Model Structure Recommendations

Short-Term Time Horizon Model

- To consider the structure of the economic models by Oster *et al* [222] and Gordois *et al* [216] and those models whose structure is patterned on these.
- To construct different branches for distal and proximal DVT.
- To make a distinction between symptomatic and asymptomatic DVT.
- To include a risk of thromboprophylaxis related major haemorrhage.
- To include a risk of stroke associated with major haemorrhage.
- To make a distinction between pre- and post-discharge VTE. A pre-discharge event would result in a prolonged hospitalisation followed by outpatient anticoagulant visits; post-discharge events would require readmission followed by outpatient anticoagulant visits.
- To present the results of both a CEA and a CUA.

Long-Term Time Horizon Model

- To construct a hybrid model combining the acute phase model with a lifetime Markov process module to investigate the impact of recurrent VTE and PTS events.
- To consider the structure of the models reported by Botteman *et al* [207] and Wolowacz *et al* [206].
- To establish a distinction between the first and subsequent years of PTS [197].
- To assume no movements between the mild-moderate PTS and severe PTS.
- To include annual risks of idiopathic VTE in those cohorts who had not experienced a primary VTE.
- To include an annual risk of PTS in those cohorts who had not experienced a primary DVT.
- To consider the long-term costs and consequences of stroke secondary to major bleed.
- To include an annual mortality risk.
- To present the results of both a CEA and a CUA.

2.5 Conclusion

VTE disease represents a spectrum of conditions that includes DVT and PE. Epidemiology studies have revealed a VTE incidence rate of about 75 to 180 per

100,000 people per year [93-99]. VTE is a disease with long-term consequences, including the risk of VTE recurrences and the development of the chronic condition PTS. A recurrence rate of 5 to 10 % per year has been reported [82, 84, 85, 106, 111]. Recurrences are particularly common during the first six to 12 months after an index event, but the risk persists for several years [82, 84, 85, 106, 109, 110]. PTS incidence rates of 10 to 20% in the first year have been reported, however, the incidence decreases over time [85, 89].

Many risk factors for VTE have been identified; patients undergoing MOS represent a group that has a particularly high risk for VTE [78, 129-131]. Indeed, both the ACCP [134] and NICE [157] Guidelines categorise patients undergoing MOS as belonging to the highest risk group.

A number of prospective and retrospective studies have shown that VTE, and in particular the long-term complications associated with VTE, confer a significant economic burden [181-191]. Specifically, the development of VTE secondary to MOS has been associated with an increase in the cost of the index admission [195, 196] and the long-term follow-up care [194, 195].

Two new orally active anticoagulants, rivaroxaban and dabigatran etexilate, were licensed in Ireland in 2008 for the primary prevention of VTE in adult patients undergoing elective THR or TKR [73, 74]. The cost of these new agents will be a potential obstacle to their usage and it is pragmatic therefore to target them for pharmacoeconomic evaluation.

It is recommended that two pharmacoeconomic models be constructed to assess the cost-effectiveness of rivaroxaban and dabigatran etexilate for THR and TKR. One model, with a short-term time horizon, will capture the costs and consequences associated with acute VTE disease. A second model, with a lifetime horizon, will consider the long-term costs and outcomes associated with VTE.

Table 9: Summary of cost-effectiveness studies comparing thromboprophylaxis regimens after total hip replacement and total knee replacement

Author	Comparators	Indication	Analysis Type	Time Horizon	Model Outcomes	Location
Decision Tree/Markov Combinations						
Ringerike *et al* 2011 [223]	Rivaroxaban or dabigatran vs. LMWH	THR & TKR	CUA	life	DVT, PE, recurrent VTE, PTS, bleed, VTE related death	Europe
Wolowacz *et al* 2009 [206]	Dabigatran vs. enoxaparin	THR & TKR	CEA, CUA	life	Proximal & distal DVT, non-fatal PE, bleed, VTE related death, HIT, recurrent VTE, PTS, all cause mortality	Europe
Botteman *et al* 2002 [207]	Enoxaparin vs. warfarin	THR	CUA	life	DVT, PE, recurrent VTE, PTS, VTE related death	US
Levin *et al* 2001 [200]	Desirudin vs. enoxaparin	THR	CEA	life	DVT, PE, recurrent VTE, PTS, VTE related death	Europe
Levin *et al* 1998 [202]	Desirudin vs. UH	THR	CEA	life	DVT, PE, recurrent VTE, PTS, VTE related death	Europe
Markov Models						
Sarasin *et al* 2002 [208]	Enoxaparin & tinzaparin vs. warfarin	THR	CEA	3 mnths	Proximal & distal DVT, PE, bleed, recurrent DVT	Europe
Decision Trees						
Dranitsaris *et al* 2009 [209]	10 day & 35 day dalteparin vs. warfarin	THR, TKR & HFS	CUA	Short-term	DVT, PE, bleed	Canada
Skedgel *et al* 2007 [210]	LMWH vs. warfarin	THR	CUA	costs: 90 days, life expectancy: lifelong	DVT, PE, bleed, survival, death	Canada
Bjorvatn *et al* 2005 [211]	Fondaparinux vs. enoxaparin	THR, TKR &HFS	CEA	7 days, 30 days, 5 years	DVT, PE, PTS, survival, bleed, death	Europe
Dranitsaris *et al* 2004 [204]	Fondaparinux vs. enoxaparin	THR, TKR & HFS	CEA	90 days post surgery	DVT, PE, PTS, bleed, death	Canada
Sullivan *et al* 2004 [212]	Fondaparinux vs. enoxaparin	THR, TKR & HFS	CEA	acute phase-90 days chronic phase-5 yrs	VTE, bleed, PTS, recurrent VTE, PE related death	US
Haentjens *et al* 2004 [199]	12 days vs. 42 days enoxaparin	THR, TKR	CUA	1 year	Proximal & distal DVT, PE, recurrent DVT & PE, PTS, bleed, VTE related death	Europe
Honorato *et al* 2004 [213]	Bemiparin vs. enoxaparin	TKR	CEA	6 weeks	DVT, PE, VTE related death, bleed, HIT, death (other causes)	Europe
Dahl *et al* 2003 [214]	Short- & long-term LMWH vs. warfarin	THR	CEA	35 days	DVT, PE, bleed	Europe
Lundkvist *et al* 2003 [215]	Fondaparinux vs. LMWH	THR, TKR & HFS	CEA	acute phase: 3 mnths chronic phase: 3mnth-5yrs	DVT, PE, bleed, recurrent VTE, PTS, VTE related death	Europe

Table 9 continued

Author	Comparators	Indication	Analysis Type	Time Horizon	Model Outcomes	Location
Gordois *et al* 2003 [216]	Fondaparinux vs. LMWH	THR, TKR & HFS	CEA	acute phase: 3 mnths chronic phase: 3 mnths-5 yrs	DVT, PE, bleed, recurrent VTE, PTS, VTE related death	Europe
Nerurkar *et al* 2002 [217]	Enoxaparin vs. warfarin	TKR	CEA	NR (short-term events)	Proximal & distal DVT, PE, bleed, VTE related death	US
Davies *et al* 2000 [218]	Short- vs. long-term enoxaparin	THR	CEA, CUA	NR (short-term events)	DVT, PE, VTE related death	Europe
Marchetti *et al* 1999 [203]	Short- & long-term LMWH vs. UH	THR	CUA	NR (long term events)	Proximal & distal DVT, PE, PTS, bleed, stroke, PE related death, all cause mortality	Europe
Hawkins *et al* 1998 [201]	Enoxaparin vs. warfarin	TKR	CEA	costs: short-term events outcomes: life	Proximal & distal DVT, non-fatal PE, bleed	US
Detournay *et al* 1998 [205]	Short- vs. long-term LMWH	THR	CEA	costs: short-term events outcomes: life years	DVT, PE, VTE related death	Europe
Abdool-Carrim *et al* 1997 [219]	LMWH vs. Aspirin	THR	CEA	costs: short-term events outcomes: life years	Proximal & distal DVT, PE, bleed, VTE related death	S. Africa
Borris & Lassen 1996 [220]	LMWH vs. no prophylaxis, dextran 70 or UH	THR	CEA	NR (short-term events)	DVT, PE, bleed	Europe
Menzin *et al* 1995 [221]	Warfarin or enoxaparin vs. no prophylaxis	THR	CEA	NR (short-term events)	DVT, PE, PE related death, death due to treatment	US
Oster *et al* 1987 [222]	No prophylaxis vs. warfarin vs. UH vs. IPC vs. GCS vs. UH & dihydroergotamine mesylate vs. UH & GCS.	THR, TKR & HFS	CEA	NR (short-term events)	DVT, PE, VTE related death	US

THR = total hip replacement; **TKR**=total knee replacement; **HFS**=hip fracture surgery; **CEA**=cost effectiveness analysis, **CUA**=cost utility analysis; **DVT**=deep vein thrombosis; **PE**=pulmonary embolism; **VTE**=venous thromboembolism; **PTS**=post thrombotic syndrome; **LMWH**=low molecular weight heparin; **UH**=unfractionated heparin; **NR**=not reported; **IPC**=intermittent pneumatic compression; **GCS**=graduated compression stockings; **US**=United States.

Chapter 3

Introduction to Indirect Comparisons - Incorporating an Indirect Comparison of Rivaroxaban and Dabigatran etexilate as Thromboprophylaxis after Total Hip- and Total Knee- Replacement

3 Introduction to Indirect Comparisons - Incorporating an Indirect Comparison of Rivaroxaban and Dabigatran etexilate as Thromboprophylaxis after Total Hip- and Total Knee- Replacement

3.1 Introduction

Rivaroxaban and dabigatran etexilate, are licensed in Ireland for the prevention of VTE in adult patients (over 18 years) undergoing elective THR or TKR [73, 74]. The rationale for targeting these new drugs for economic evaluation has previously been discussed (section 2.3). There are no head-to-head efficacy data available comparing these drugs [224].

Estimating the effectiveness of alternative healthcare interventions is the core of both clinical and economic technology assessments [225]. It has become widely recognised that well designed and implemented head-to-head RCTs provide the most rigorous and valid research evidence on the relative efficacy and safety of different interventions [226]. RCTs are designed to minimise bias by techniques such as: randomised allocation to the different interventions, matched patient populations and the blinding of patients and investigators to the interventions [227].

It is not uncommon for two interventions being evaluated never to have been trialled against each other [42]. RCTs of new pharmaceuticals are invariably designed for licensing; pharmaceutical licensing authorities may accept partial comparisons, often against placebo. Also, RCT evidence on non-pharmaceutical technologies, such as medical devices and surgical procedures, is not typically required before such interventions are routinely used on patients [228]. Additionally, it is rarely the case that a single RCT will represent the entirety of information about the relative effectiveness of different interventions for a particular disease state [229].

A decision that recommends one or more of treatments as preferable should be based on a simultaneous comparison of all relevant alternatives. If no attempt is made to synthesise data from the individual RCTs, a set of discrete trial-based cost-effectiveness analyses will be insufficient to inform a decision maker of the best

option [230]. A pragmatic solution here is the use of indirect comparisons of interventions to assess the comparative effectiveness of all options [42, 231].

This chapter has three aims:

- To introduce the concepts of indirect comparison.
- To discuss the pivotal clinical trial data for rivaroxaban and dabigatran etexilate and to highlight the need for an indirect comparison of these drugs.
- To perform an indirect comparison of rivaroxaban and dabigatran etexilate as thromboprophylaxis after THR and TKR. (This work will provide certain parameter inputs to the economic models in subsequent chapters of this thesis).

3.2 Introduction to Indirect Comparisons

Indirect comparisons vary in complexity. The simplest form is where two head-to-head RCTs with common comparator arms (A vs. C and B vs. C) are combined to provide an indirect estimate of the comparative treatment effect for A vs. B. A more complicated situation is where one or both sides of the indirect comparison consist of a direct head-to-head meta-analysis (meta-analyses of A vs. C and B vs. C). More complex investigations can involve multiple comparisons of more than two treatment options, rather than just a pair-wise comparison [232]. Indirect comparisons can also be combined with direct head-to-head comparisons, non-randomised data and observational data in a mixed treatment comparison (MTC) approach [233].

Although there are situations in which indirect comparisons may be performed and can provide useful information, such analyses present with several limitations and their application is not always appropriate. Deciding when it is or is not appropriate to combine trials is inevitably a subjective decision [225].

In recent years indirect comparisons have become a widespread method to improve clinical decision-making [234]. However, it is generally accepted that well-conducted RCTs provide the most valid estimates of the relative efficacy of competing healthcare interventions [235, 236]. The precision of an indirect estimate of the relative effect of B vs. C is generally lower than that of the direct estimate obtained from RCTs comparing B and C [237].

3.2.1 Assumptions Pertaining to Indirect Comparisons

An indirect comparison requires inference or extrapolation from known results to situations in which a study has not been done and, therefore, the validity of estimates obtained may be uncertain [236]. For the estimates of an indirect comparison to be valid the following assumptions must hold:

Homogeneity Assumption

In a standard meta-analysis, it is assumed that different trials estimate the same constant treatment effect (in a fixed effect model) or different treatment effects distributed around a common distribution (in a random effects model) [238, 239]. For a meta-analysis to be valid, results from different trials should be sufficiently homogeneous. Heterogeneity in results across studies can be statistically tested using the Chi^2 test and quantified using I^2 [240].

Similarity Assumption

In addition, for an adjusted indirect comparison to be valid, a similarity assumption is required. Trial similarity consists of clinical and methodological similarity. Clinical similarity includes similarities in trial populations, trial settings, length of follow-up and outcomes measured [232]. Methodological similarity refers to the aspects of trials which are associated with the risk of bias [238].

Consistency Assumption

When both direct and indirect evidence is available, a further assumption of evidence consistency is required to quantitatively combine the direct and indirect estimates in a MTC. In this instance, direct estimates should be compared to indirect estimates to examine whether the estimates are consistent. Possible causes of discrepancy between the direct and indirect evidence, (such as invalid indirect comparison, bias in head-to-head comparative trials, and clinically meaningful heterogeneity across trials) should be investigated [241].

The trial similarity assumption for adjusted indirect comparison is relevant only if the homogeneity assumption is valid. Similarly, the consistency assumption needs the prerequisite of both the homogeneity and the similarity assumptions [238].

3.2.1.1 Assessing the Trial Similarity Assumption

No well-established methods exist to determine when the similarity assumption holds. It has been proposed that comparing patient or trial characteristics across the trials may indicate whether similarity is reasonable [242]. A similarity in the event rates in the common reference groups across the trials, might also indicate that trial similarity is likely [243]. Variation in the treatment effects between trials within pair-wise contrasts is likely to occur where trials have been undertaken on different patient groups in different settings and/or methodological differences exist in the design and conduct of the trials [242].

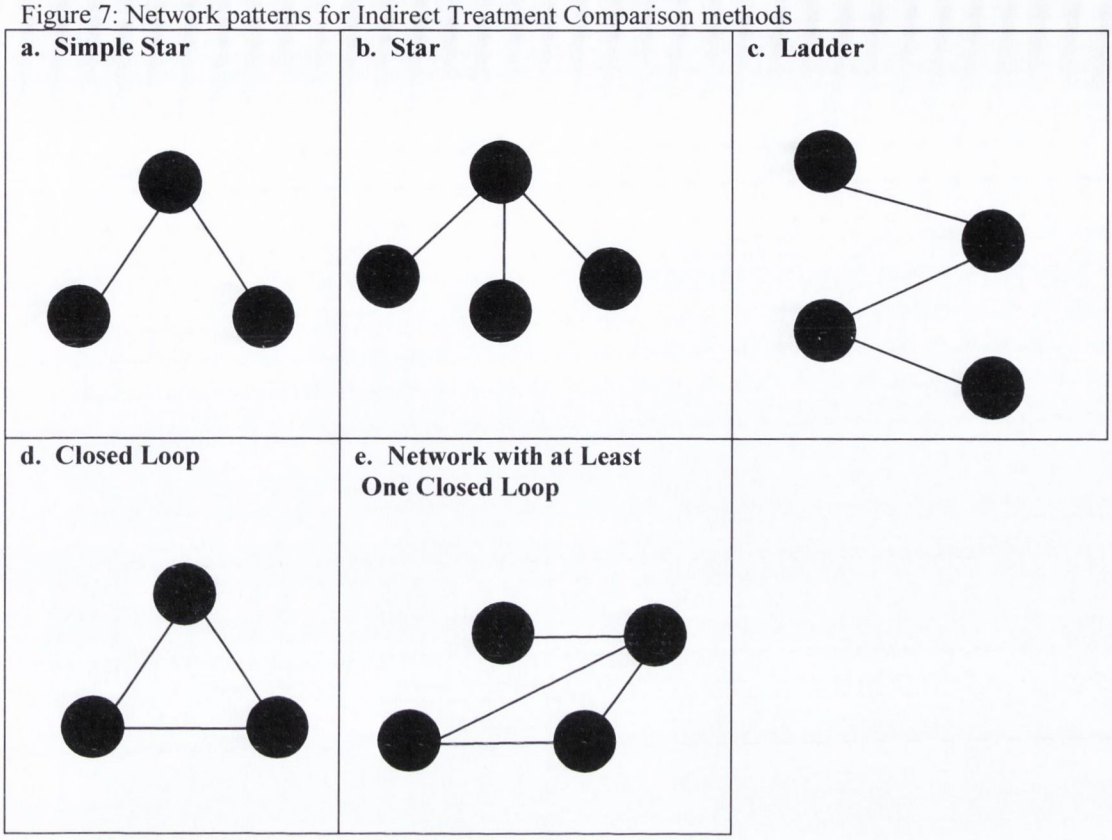
The CONSORT (Consolidated Standards of Reporting Trials) statement was first published in 1996; the most up to date version was made available in 2010 [244]. It provides guidance for all RCTs but mainly focuses on pair-wise, parallel trials.

The statement comprises of an evidence-based checklist and a flow diagram which displays the progress of all participants through the trial. The checklist includes 25 items, chosen because empirical evidence has indicated that not reporting them is associated with biased treatment effect estimates, or in the readers' inability to judge the reliability or relevance of the findings. The checklist specifically focuses on reporting how the trial was designed (e.g. randomisation methods, eligibility criteria, sample size determination), analysed (e.g. statistical methods) and interpreted (e.g. the balancing of benefits and harms) [245].

3.2.2 Network of Evidence

Studies available for indirect comparisons or MTCs form a network of evidence. The range of networks is illustrated in Figure 7. Depending on the method of indirect comparison used, there are restrictions on the types of networks that can be analysed.

Figure 7: Network patterns for Indirect Treatment Comparison methods



3.2.3 Methods for Making Indirect Comparison

3.2.3.1 Naïve Unadjusted Indirect Comparison

A simple, but inappropriate statistical method, is to compare the results of individual arms from different trials as if they were from the same RCT. This naïve or unadjusted indirect comparison however discards the within trial comparison, increasing liability to bias and over precise estimates. When compared with direct estimates, unadjusted indirect comparisons result in a large number of discrepancies in the significance and direction of relative effectiveness [231].

In contrast to an unadjusted indirect comparison, the adjusted indirect comparison can take advantage of the strength of RCTs in making unbiased comparisons [246]. Randomisation is not broken since comparative estimates are derived from each trial prior to synthesis [238].

3.2.3.2 Bucher Adjusted Indirect Comparison

Bucher *et al* [234] suggest a simple method of indirect comparison, in which the indirect comparison of A vs. B is adjusted according to the results of their direct comparisons with a common intervention C (star design in Figure 7a). This method provides a summary estimate and 95% CI for the difference between the treatments [234].

The principal assumption of this model is that the relative efficacy of a treatment is the same in all trials included in the indirect comparison; such that if an A arm had been included in the BC trial, the estimate of the relative risk of A vs. C would be consistent with those produced by the AC trial [225].

This method is relatively simple to implement and superior to an unadjusted indirect comparison. However, its limitations are that it can only be applied to data generated from two arm trials, it can only incorporate a single indirect comparator and cannot integrate any direct comparative data that may be available from RCTs of the comparison of interest [42].

To improve statistical power, evidence generated by indirect comparison can be combined with evidence from head-to-head trials [102, 247]. The combination of direct and indirect evidence has been facilitated by the development of network meta-analysis [248] and Bayesian hierarchical models for MTCs [239]. These techniques are useful when the relevant trials have considered many different treatments [238].

3.2.3.3 Lumley Network Meta-analysis for Indirect Treatment Comparisons

Lumley [248] has described a network meta-analysis, which allows an indirect comparison between the two treatments of interest to be obtained through more than one common comparator.

Where numerous trials exist which separately compare A vs. C, C vs. B, A vs. D and B vs. D, the results of the trials in which the common comparator was C, as well as trials in which the common comparator was D can be incorporated in order to obtain an indirect comparison of A vs. B [236].

The network meta-analytic approach may also be valuable when an indirect comparison between two treatments can occur through multiple paths, which require indirect comparisons within indirect comparisons [248].

If the indirect comparison between two treatments generates the same result regardless of the common comparator, there is a greater likelihood that the indirect comparison represents the true relationship between the interventions. However, if these results disagree, the discrepancy is referred to as incoherence; this incoherence can be estimated [248].

In addition to the homogeneity and similarity assumptions, the fundamental assumption underlying the network meta-analysis is that the indirect comparison between two interventions will occur through a closed loop (Figure 7d and e) [236]. A closed loop design is necessary for calculating the estimate of incoherence, which is then used to construct a 95% CI for the indirect estimate [248].

The network meta-analysis approach has a number of strengths. Similar to the Bucher *et al* technique, it partially preserves the randomisation of the trials from which data are derived [236]. Further, it also simultaneously combines direct and indirect evidence and provides an estimate of the agreement between different results. Direct evidence is not required for this technique.

The technique has a number of inherent limitations. Open loop networks, such as those which follow a star or a ladder design cannot be used in the network meta-analysis. The method does not automatically account for correlations that may exist between different effect estimates when they are obtained from a single multi-armed trial [236].

3.2.3.4 Mixed Treatment Comparison

The MTC technique can be seen as an extension of the traditional pair-wise meta-analysis to a simultaneous analysis of multiple pair-wise comparisons. Any combination of studies can be combined as long as every study is connected to at least one other study [247]. Analyses are based on the pooling of effect estimates across trials rather than individual treatment groups [236]. It can integrate direct and indirect

evidence within the network of trials and there is no restriction on the number of arms in any given trial [225]. The results obtained through combining both direct and indirect evidence in the evaluation of two interventions may provide more precise estimates, as indicated by narrower CIs, than results based on direct evidence alone [239].

There are two roles for MTC: one is to strengthen inference concerning the relative efficacy of two treatments by including both direct and indirect comparisons. The other is to facilitate simultaneous indirect comparisons among treatments for which results from direct comparisons do not exist. In this way, it is possible to obtain effect estimates for all possible pair-wise comparisons and to rank the efficacy of these various competing treatments [239].

Lu and Ades have described a multivariate statistical model for performing MTC within a Bayesian framework [239]. Bayesian meta-analysis provides more flexibility than classical methods to include more data and handle more complex modelling structures [239, 249]. The complexity of this method may limit its use. Also, it is a Bayesian technique and thus involves judgments in specifying prior distributions. These judgments may or may not be valid [236].

3.2.3.5 Summary of Methods for Making Indirect Comparison

It is generally accepted that well-conducted RCTs provide the most valid estimates of the relative efficacy of competing healthcare interventions [235, 236]. In the absence of such comparisons, a pragmatic solution is the use of indirect comparisons. Various approaches for indirect comparisons exist. The Bucher *et al* [234] method has been designed to apply to the common indirect treatment comparison involving a simple star design (Figure 7a). The Lumley [248] network meta-analysis method can compare treatments in a network that contains at least one closed loop (Figure 7d and e). The MTC method can be used to obtain measures of effect for all network patterns (Figure 7a, b, c, d and e).

3.3 Efficacy Data pertaining to Rivaroxaban and Dabigatran etexilate as Thromboprophylaxis

3.3.1 Rivaroxaban Pivotal Clinical Trials

The phase III randomised, double blind, active-comparator-controlled, parallel group RECORD (REgulation of Coagulation in ORthopedic Surgery to prevent DVT and PE) programme consists of four studies which evaluate rivaroxaban 10mg OD for the prevention of VTE after THR and TKR. The primary outcome for all trials was a composite of the incidence of venographically confirmed DVT, non-fatal PE and all cause deaths. RECORD 1, RECORD 3 and RECORD 4 were all designed with a non-inferiority comparison (in the per-protocol population) followed by a superiority comparison (in the Modified intent to treat (mITT) population) as the primary efficacy assessment [250-252]. RECORD 2 only had a superior comparison [253]. In all trials the mITT analysis included patients who had undergone planned surgery, had taken a study drug, and had undergone an adequate assessment for thromboembolism [250-253].

Total Hip Replacement

RECORD 1 and RECORD 2 were both multicentre, prospective trials comparing rivaroxaban 10mg OD with enoxaparin sodium 40mg OD for the prevention of VTE in patients after THR [252, 253].

RECORD 1 (n = 4541 randomised): the treatment duration of both rivaroxaban (10mg OD) and enoxaparin sodium (40mg OD) was 31 to 39 days. In the mITT analysis the primary efficacy outcome occurred in 1.1% (18/1595) in the rivaroxaban group and in 3.7% (58/1558) in the enoxaparin sodium group (absolute risk reduction, 2.6%; (95%CI 1.5, 3.7); $p<0.001$). Superiority was demonstrated. Major bleeding occurred in 6 of 2209 patients (0.3%) in the rivaroxaban group and in 2 of 2224 patients (0.1%) in the enoxaparin sodium group ($p=0.178$) [252].

RECORD 2 (n = 2509 randomised): the treatment duration was 31 to 39 days for rivaroxaban (10mg OD) and ten to 14 days for enoxaparin sodium (40mg OD). In the mITT analysis the primary efficacy outcome occurred in 2.0% (17/864) in the rivaroxaban group and in 9.3% (81/869) in the enoxaparin sodium group (absolute risk reduction, 7.3%; (95%CI 5.2, 9.4); $p<0.001$). Superiority was demonstrated. The incidence of major bleeding was <0.1% in both groups ($p=0.980$) [253].

Total Knee Replacement

RECORD 3 and RECORD 4 were both multicentre, prospective trials comparing rivaroxaban 10mg OD with enoxaparin sodium for the prevention of VTE in patients after TKR [250, 251]. The dose of enoxaparin sodium was the European Union (EU) licensed dose of 40mg OD in RECORD 3 [251] and was the non-EU licensed dose of 30mg BD in RECORD 4 [250]. The 30mg BD dose regimen is more consistent with North American practice [254].

RECORD 3 (n = 2531 randomised): the treatment duration was ten to 14 days for both rivaroxaban (10mg OD) and enoxaparin sodium (40mg OD). In the mITT analysis the primary efficacy outcome occurred in 9.6% (79/824) in the rivaroxaban group compared with 18.9% (166/878) in the enoxaparin sodium group (absolute risk reduction, 9.2% (95%CI 5.9, 12.4); $p<0.001$). Superiority was demonstrated. The incidence of major bleeding was 0.6% (7/1226) and 0.5% (6/1239) in patients receiving rivaroxaban and enoxaparin sodium respectively ($p=0.774$) [251].

RECORD 4 (n= 3148 randomised): the treatment duration was 10 to 14 days for both rivaroxaban (10mg OD) and enoxaparin sodium (30mg BD). In the mITT, the primary efficacy outcome occurred in 67 (6.9%) of 965 patients in the rivaroxaban group and in 97 (10.1%) of 959 patients in the enoxaparin sodium group (absolute risk reduction 3.19%, (95%CI 0.71, 5.67; $p=0.0118$). Superiority was demonstrated. Ten (0.7%) of 1526 patients receiving rivaroxaban and four (0.3%) of 1508 patients receiving enoxaparin sodium had major bleeding ($p=0.1096$) [250].

In summary, three pivotal phase III RCTs (RECORD 1 (THR) [252], RECORD 2 (THR) [253] and RECORD 3 (TKR) [251]) compared rivaroxaban with enoxaparin sodium 40 mg OD as VTE prophylaxis. One further phase III trial, RECORD 4 (TKR), [250] compared rivaroxaban to enoxaparin sodium at the non-EU licensed dose of 30mg BD. All showed the superior clinical-effectiveness of rivaroxaban. In all trials, rivaroxaban was associated with a small but non-statistically significant increase in the rate of major bleeding.

3.3.2 Dabigatran etexilate Pivotal Clinical Trials

Three phase III multicentre, prospective, double-blind, parallel-group design RCTs (RE-NOVATE, RE-MODEL and RE-MOBILIZE) compare dabigatran etexilate with enoxaparin sodium for the prevention of VTE after THR or TKR [255-257]. The dose of enoxaparin sodium was 40mg OD in RE-NOVATE and RE-MODEL and was 30mg BD in RE-MOBILIZE [255-257]. In all trials, patients were randomised to 150mg OD or 220mg OD of dabigatran etexilate irrespective of age or renal function. The primary outcome for all trials was the composite of the incidence of venographically confirmed DVT, non-fatal PE and all cause deaths. All were designed to accept non-inferiority of dabigatran etexilate for the primary outcome in the mITT population (those who had undergone planned surgery, had taken a study drug, and had undergone an adequate assessment for thromboembolism) [255-257].

Total Hip Replacement

RE-NOVATE (n = 3494 randomised): the treatment duration for both drugs was 28 to 35 days. The mITT showed a non-statistically significant difference in the incidence of the composite primary endpoint; 6% (53/880) of the 220mg cohort, 8.6% (75/874) of the 150mg cohort and 6.7 % (60/897) of the enoxaparin sodium cohort. This represented an absolute risk difference of -0.7 (95% CI -2.9, 1.6) and 1.9 (95% CI: -0.6, 4.4) for the 220mg and 150mg doses respectively vs. enoxaparin sodium. The incidence of major bleeding was 2.0% (23/1146) and 1.3% (15/1163) in the dabigatran etexilate 220mg and 150mg groups respectively and 1.6% (18/1154) in the enoxaparin sodium group (p=0.44 for 220mg and p=0.60 for 150mg). Both doses met the pre-defined criteria for non-inferiority [255].

Total Knee Replacement

RE-MODEL (n = 2076 randomised): the treatment duration for both drugs was six to ten days [256]. The mITT showed a non-statistically significant difference in the incidence of the composite primary endpoint; 36.4% (183/503) of the 220mg cohort, 40.5% (213/526) of the 150mg cohort and 37.7% (193/512) of the enoxaparin sodium cohort. This represented an absolute risk difference of -1.3 (95%CI -7.3, 4.6) and 2.8 (95%CI -3.1, 8.7) for the 220mg and 150mg doses respectively vs. enoxaparin sodium. The rate of major bleeding was 1.5% (10/679) and 1.3% (9/703) in the dabigatran etexilate 220mg and 150mg groups respectively and 1.3% (9/694) in the

enoxaparin sodium group (p=0.82 for 220mg and p=1.0 for 150mg). Both doses met the pre-defined criteria for non-inferiority [256].

RE-MOBILIZE (n= 2615 randomised): the treatment duration for both drugs was 12 to 15 days [257]. In the mITT, the primary outcome occurred in 31.1% (188/604) of the 220mg cohort, 33.7% (219/649) of the 150-mg group and 25.3% (163/643) of the enoxaparin sodium group. This represented an absolute risk difference of 5.8 (95%CI 0.8, 10.8) and 8.4 (95%CI 3.4, 13.3) for the 220mg and 150mg doses respectively vs. enoxaparin sodium. The rate of major bleeding was not significantly different among the three groups: 0.6% (5/857) for the 220 mg dose, 0.6% (5/871) for the 150 mg, dose and 1.4% (12/868) for enoxaparin sodium. Both dosage regimens failed to show non-inferiority to enoxaparin [257].

In summary, RE-NOVATE (THR) [255] and RE-MODEL (TKR) [256] supported the EU-regulatory submission, whilst RE-MOBILIZE (TKR) [257] supported the North America regulatory submission for dabigatran etexilate. All trials compared two doses of dabigatran etexilate (220mg and 150mg OD) with enoxaparin sodium. In both RE-NOVATE and RE-MODEL, dabigatran etexilate was statistically non-inferior to enoxaparin sodium for the primary efficacy outcome (total VTE and all-cause mortality). Dabigatran etexilate failed to show non-inferiority to enoxaparin sodium in RE-MOBILIZE. There was no statistically significant difference in the rates of bleeding events across all treatment groups in the three trials.

3.4 Indirect Comparison of Pivotal Clinical Trials: Rivaroxaban versus Dabigatran etexilate as Thromboprophylaxis

3.4.1 Introduction

There are no head-to-head data available comparing rivaroxaban and dabigatran etexilate as VTE prophylaxis after THR or TKR [224]. A practical solution here is the use of indirect comparisons to assess their comparative effectiveness and safety. The use of the Bucher *et al* [234] method is appropriate in this instance; the indirect comparison of rivaroxaban vs. dabigatran etexilate can be adjusted according to the results of their direct comparisons with the common intervention enoxaparin sodium (the network is in a star design).

The dabigatran etexilate and rivaroxaban pivotal trials are summarised in Table 10. The trials chosen for the indirect comparisons are shown in the shaded text boxes. The approach taken in choosing the trials for the indirect compassion is now described:

Total Hip Replacement-Choice of Trials for Indirect Comparison

In both RECORD 1 [252] and RE-NOVATE [255] enoxaparin sodium was given for four to five weeks. The duration of enoxaparin sodium (ten to 14 days) in RECORD 2 [253] was more reflective of clinical practise, in Ireland, at the time of this analysis [160].

Thus, for this analysis, efficacy and bleeding rate point estimates pertaining to rivaroxaban and enoxaparin sodium (after THR) were obtained from RECORD 2 [253]. Those pertaining to dabigatran etexilate were derived from an adjusted indirect comparison using the RE-NOVATE trial. The assumption here is that the treatment effect seen in RE-NOVATE would be the treatment effect seen in RECORD 2 had a dabigatran etexilate arm been included.

Total Knee Replacement- Choice of Trials for Indirect Comparison

In both RECORD 4 [251] and RE-MOBILIZE [257] enoxaparin sodium was given at a dose of 30mg BD. Neither trial was thus considered for this indirect comparison. In contrast, the EU-licensed dose (40mg OD) was given in both RECORD 3 [250] and RE-MODEL [256]. In RECORD 3, enoxaparin sodium was given for ten to 14 days [251]. The shorter duration of six to ten days given in RE-MODEL [256] was more reflective clinical practise, in Ireland, at the time of this analysis [160].

Thus, for this analysis, efficacy and bleeding rate point estimates pertaining to dabigatran etexilate and enoxaparin sodium (after TKR) were derived from RE-MODEL [256]. Those pertaining to rivaroxaban were derived from an adjusted indirect comparison using the RECORD 3 trial. The assumption is that the treatment effect seen in RECORD 3 would be the treatment effect seen in RE-MODEL had a rivaroxaban arm been included.

3.4.1.1 Dose of Dabigatran etexilate Chosen for Evaluation

There are two licensed doses of dabigatran etexilate; 220mg OD and 150mg OD. The 150mg dose is reserved under the license for patients with moderate renal impairment, those over 75 years and those who are co-prescribed amiodarone [88]. In neither RE-NOVATE nor RE-MODEL was there a subgroup analysis to determine the efficacy and safety in these populations [255, 256]. Therefore, in this analysis, an indirect comparison (and subsequently an economic evaluation) was performed for the 220 mg OD dose only.

Table 10. The rivaroxaban and dabigatran etexilate pivotal clinical trials.

Clinical Trial	Intervention	Comparator	Indirect Comparison	Limitation to Indirect Comparison
Total Hip Replacement				
[a] RECORD 2 [253] (n=2509)	Rivaroxaban 10mg OD for 31-39 days	Enoxaparin 40mg OD for 10-14 days	**RECORD 2 & RE-NOVATE chosen for Indirect Comparison.** Point estimates for rivaroxaban & enoxaparin were obtained from RECORD 2. Estimates for dabigatran derived from an adjusted indirect comparison. It was assumed that the treatment effect seen in RE-NOVATE would be the same as that seen in RECORD 2 had a dabigatran arm been included.	Duration of enoxaparin is different in RECORD 2 and RE-NOVATE. This treatment-effect modification might bias the results of an indirect comparison towards demonstrating superior efficacy with rivaroxaban.
[a] RE-NOVATE [255] (n=3494)	Dabigatran 220mg OD or 150mg OD for 28-35 days [c]	Enoxaparin 40mg OD for 28-35 days		
[b] RECORD 1 [252] (n=4541)	Rivaroxaban 10mg OD for 31-39 days	Enoxaparin 40mg OD for 31-39 days	**RECORD 1 not considered for Indirect Comparison;** duration of enoxaparin considered to be inconsistent with practice in Ireland	
Total Knee Replacement				
[a] RE-MODEL [256] (n=2076)	Dabigatran 220mg OD or 150mg OD for 6-10 days [c]	Enoxaparin 40mg OD for 6-10 days	**RE-MODEL & RECORD 3 chosen for Indirect Comparison.** Point estimates pertaining to dabigatran & enoxaparin derived from RE-MODEL. Estimates for rivaroxaban derived from an adjusted indirect comparison. It was assumed that the treatment effect seen in RECORD 3 would the same as that seen in RE-MODEL had a rivaroxaban arm been included	Duration of anticoagulation is different in RE-MODEL and RECORD 3. This treatment-effect modification might bias the results of an indirect comparison towards demonstrating superior efficacy with rivaroxaban.
[a] RECORD 3 [251] (n=2531)	Rivaroxaban 10 mg OD for 10-14 days	Enoxaparin 40mg OD for 10-14 days		
[b] RE-MOBILIZE [257] (n=2615)	Dabigatran 220mg OD or 150mg OD for 12-15 days	Enoxaparin 30mg BD for 12-15 days	**RE-MOBILIZE not considered for Indirect Comparison;** enoxaparin dose not licensed in the EU	
[b] RECORD 4 [250] (n=3148)	Rivaroxaban 10 mg OD for 10-14 days	Enoxaparin 30mg BD for 10-14 days	**RECORD 4 not considered for Indirect Comparison;** enoxaparin dose not licensed in the EU	

a. The trials chosen for the indirect comparisons are shown in shaded text.
b. These trials where not considered for indirect comparison.
c. An indirect comparison (and subsequently an economic evaluation) was performed for the 220 mg dose of dabigatran etexilate only

Where: **OD**=once daily; **EU**=European Union.

In summary, the trials considered for indirect comparison are RECORD 2 and RE-NOVATE (for the THR disease state) and RECORD 3 and RE-MODEL (for the TKR disease state).

3.4.2 Objective

The initial objective of this study was to check the degree of similarity between the dabigatran etexilate and rivaroxaban trials chosen for the indirect comparison, in order to examine the validity of performing an adjusted indirect comparison [238].

The subsequent objective was to perform a Bucher *et al* indirect comparison [234] for the outcomes of distal DVT, proximal DVT, symptomatic PE and major bleed for both THR and TKR. (This work will provide efficacy and bleeding risk parameter inputs to the economic models in subsequent chapters).

3.4.3 Method

3.4.3.1 Assessment of Similarity between Trials Chosen for Indirect Comparison

The CONSORT statement [245] was considered when assessing trial similarity. The criteria examined included:

- Description of trial design/randomisation/blinding
- Statistical methods used to compare groups for primary/secondary/safety outcomes
- Statistical methods used to determine sample size
- Study population/cohort size/eligibility criteria/settings and locations where data was located
- Interventions for each group/dose/administration/duration of treatment
- Definition of pre-specified primary/secondary/safety outcomes; including how/when they were assessed.

3.4.3.2 Adjusted Indirect Comparison

RECORD 2 [253] compared rivaroxaban and enoxaparin sodium and RE-NOVATE [255] compared dabigatran etexilate and enoxaparin sodium after THR. An adjusted indirect comparison of rivaroxaban vs. dabigatran etexilate (after THR) was determined by the Bucher *et al* method [234].

1. The RR of an event occurring on rivaroxaban vs. enoxaparin sodium (from RECORD 2) can be calculated [258]:

$$RR_{RE} = \frac{n/N \text{ (Rivaroxaban)}}{n/N \text{ (Enoxaparin)}}$$

Where: RR_{RE} = Relative risk (rivaroxaban vs. enoxaparin)
n= number of individuals with event of interest (extracted from RECORD 2 [253])
N= number of individuals under observation (extracted from RECORD 2 [253])

Likewise the RR of dabigatran vs. enoxaparin sodium (RR_{DE}) can be extracted from RE-NOVATE [255].

2. The log RR of the adjusted indirect comparison for dabigatran etexilate vs. rivaroxaban is calculated as [42, 234]:

$$\log RR_{DR} = \log RR_{DE} - \log RR_{RE}$$

Where: RR_{DR} = Relative risk (dabigatran etexilate vs. rivaroxaban)
RR_{DE} = Relative risk (dabigatran vs. enoxaparin) from RE-NOVATE [255]
RR_{RE} = Relative risk (rivaroxaban vs. enoxaparin) from RECORD 2 [253]

The exponential of log RR_{DR} gives the RR for dabigatran vs. rivaroxaban

3. Assuming that there is similarity across evidence, such that if a dabigatran arm had been included in RECORD 2 [253], the point estimate for dabigatran (the probability (absolute risk) of an event occurring while on dabigatran) for inclusion in the economic model is calculated as:

$$\text{Dabigatran point estimate} = RR_{DR} \times [n/N \text{ (Rivaroxaban)}]$$

Where: n= number of individuals with event of interest (extracted from RECORD 2 [253])
N= number of individuals under observation (extracted from RECORD 2 [253])

4. The standard error (SE) for the log RR is obtained as [258]:

$$SE(\log RR_{DR}) = \sqrt{[1/(n(dab)) - 1/(N(dab)) + 1/(n(riv)) - 1/(N(riv))]}$$

Where n(dab) = N(dab) x Dabigatran point estimate (as previously calculated)
N(dab) = number of individuals (on dabigatran) under observation in RE-NOVATE [255]
n(riv) = number of individuals (on rivaroxaban) with event of interest in RECORD 2 [253]
N(riv) = number of individuals (on rivaroxaban) under observation in RECORD 2 [253]

5. Combining logRR_{DR} and SE (logRR_{DR}) yields a 95%CI for log RR_{DR} [42, 237]:

$$95\%CI = \text{Exponential } [(\log RR_{DR}) \pm 1.96 \times SE (\log RR_{DR})]$$

Likewise, for the TKR economic model, point estimates for dabigatran etexilate and enoxaparin were derived from RE-MODEL [256]. Point estimates for rivaroxaban were derived by an indirect comparison assuming that the RR_{RE} seen in RECORD 3 [251] would be the same as in RE-MODEL [256] had a rivaroxaban arm been included.

3.4.4 Results

3.4.4.1 Assessment of Similarity between Trials Chosen for Indirect Comparison

The rivaroxaban and dabigatran etexilate trials (which were chosen for the indirect comparison) have a number of similarities:

- All trials were international, multi-centre, randomised (computer generated randomisation) and double-blind in design [251, 253, 255, 256].

- Participants were very similar across all trials with similar mean age (60 to 68 years), equivalent body weights and proportion of females. Exclusion criteria were similar across all trials [251, 253, 255, 256].

- The numbers of patients included in the primary efficacy analyses in the THR pivotal trials were similar. Of the randomised patients in RECORD 2, 864 and 869 were considered in the rivaroxaban and enoxaparin sodium arms respectively [253]. In RE-NOVATE, 880 and 874 were included in the dabigatran etexilate 220mg and 150mg arms and 897 were included in the enoxaparin sodium arm [255].

- In all trials SC enoxaparin sodium 40 mg OD was a common control [251, 253, 255, 256].

- All trials were designed to assess the same pre-specified composite primary outcome; the composite of DVT (venographic or symptomatic), non-fatal symptomatic PE and all-cause mortality. The same pre-specified secondary

outcomes were defined. In all, the primary and secondary outcomes were adjudicated by blinded independent monitoring committees [251, 253, 255, 256].

- In all trials the primary efficacy endpoint was measured in the mITT population [251, 253, 255, 256]. It is noted that, in view of the high compliance with the protocol, the mITT is unlikely to be different from an as-treated or per-protocol analysis, usually deemed to be more conservative for non-inferiority designs [244].

Despite these similarities, there are important differences in the design of the studies:

- The rivaroxaban and dabigatran etexilate trials followed a different statistical concept. The rivaroxaban trials tested both the non-inferiority and superiority hypotheses. Rivaroxaban was found to be superior to enoxaparin sodium in efficacy and comparable in safety [251, 253]. The dabigatran etexilate trials were non-inferiority trials, dabigatran etexilate showed non-inferior efficacy and comparable safety to enoxaparin sodium [255, 256].

- The number of patients considered in the primary efficacy analysis differed between the TKR trials. Of the randomised patients in RECORD 3, 824 and 878 were included in the rivaroxaban and enoxaparin sodium arms respectively [251]. In RE-MODEL, 503 and 526 patients were included in the dabigatran etexilate 220mg and 150mg arms and 512 were included in the enoxaparin sodium arm [256].

- Methods of ascertaining VTE outcomes were similar amongst the trials, with DVT diagnosed by venography and PE diagnosed by VQ scanning, CTPA, spiral computerised tomography or by autopsy. However, different independent venogram adjudication committees were used to interpret the venograms [251, 253, 255, 256]. It has been recognised elsewhere that the frequency of asymptomatic DVT in clinical trials is influenced by the centre in which the venograms are adjudicated thus potentially introducing heterogeneity [134].

- All the trials excluded patients who were at high risk of haemorrhage. All trials also used pre-specified definitions to capture haemorrhagic adverse events, which were divided into two main categories; major bleeds and clinically relevant, non-major bleeds. Trial investigators considered major bleed to be those that led to death, or bleeding into a critical organ, or bleeding necessitating reoperation, or blood transfusion of ≥ 2 units, or bleeding with a ≥ 2 g/l fall in haemoglobin [251, 253, 255, 256]. Beyond this however, the definitions of major bleeding events differed between trials. In RE-NOVATE and RE-MODEL, surgical site bleeding that fulfilled the criteria of a major bleeding event was categorised as a major bleed [255, 256]. By contrast, surgical site bleeding was not included in the major bleeding category in RECORD 2 and RECORD 3 unless they required re-operation or were fatal [251, 253]. Rather, it was grouped with excessive wound haematoma in the composite endpoint 'haemorrhagic wound complications' which was categorised as non-major bleeding. The RECORD 2 investigators acknowledged that this may have been responsible for the relatively low overall bleeding rates observed with rivaroxaban [253].

- The duration of enoxaparin sodium was different across the THR trials chosen for indirect comparison. In RECORD 2, enoxaparin sodium was given for ten to 14 days and rivaroxaban was given for 31 to 39 days [253]. In RE-NOVATE the duration of both dabigatran etexilate and enoxaparin sodium was 28 to 35 days [255].

  The risk of having a primary outcome event on enoxaparin sodium was lower in RE-NOVATE [255] than in RECORD 2 [253]; this is likely to reflect the longer duration of enoxaparin sodium. The risks of having a major bleed whilst on enoxaparin sodium were lower in RECORD 2 [253]; this is likely to reflect both the shorter duration of enoxaparin sodium and the differences in the definition of major bleeding between the pivotal trials.

- In the TKR trials chosen for indirect comparison, the difference in duration of anticoagulation given was less pronounced. Rivaroxaban and enoxaparin sodium were both given for ten to 14 days in RECORD 3 [251], whilst

dabigatran etexilate and enoxaparin sodium were given for six to ten days in RE-MODEL [256].

These differences in trial design highlight some of the challenges in performing an indirect comparison between dabigatran etexilate and rivaroxaban.

3.4.4.2 Adjusted Indirect Comparison

The calculations and results of the Bucher Method of Indirect Comparison are illustrated in Table 11 and Table 12.

Table 11. The Bucher Method of Indirect Comparison to determine point estimates for the total hip replacement economic model.
The relative risk (±95%CI) of dabigatran vs. rivaroxaban was calculated assuming that the relative risk of dabigatran vs. enoxaparin in RE-NOVATE would be the same as that observed in RECORD 2 had a dabigatran arm been included.

	RE-NOVATE [255] [a]			RECORD 2 [253]			INDIRECT COMPARISON	
Parameter	**Strategy**	**n/N (point estimate)**	**RR_{DE} (95% CI) [c]**	**Strategy**	**n/N (point estimate)**	**RR_{RE} (95% CI) [d]**	**RR_{DR} [e] (95% CI) [f]**	**Dab point estimate [g]**
Distal DVT	Dab [b] Enox	22/874 (0.025) 24/894 (0.027)	0.938 (0.530, 1.660)	Riv Enox	9/864 **(0.010)** [h] 27/869 **(0.031)** [h]	0.335 (0.159, 0.709)	2.797 (1.315, 5.946)	**0.029** [h]
Proximal DVT	Dab [b] Enox	23/905 (0.025) 33/914 (0.036)	0.704 (0.417, 1.189)	Riv Enox	5/864 **(0.006)** [h] 44/869 **(0.051)** [h]	0.114 (0.046, 0.287)	6.159 (2.412, 15.725)	**0.036** [h]
Symptomatic PE	Dab [b] Enox	5/1137 (0.004) 3/1142 (0.003)	1.674 (0.401, 6.998)	Riv Enox	1/864 **(0.0012)** [h] 4/869 **(0.005)** [h]	0.251 (0.028, 2.245)	6.657 (0.843, 52.598)	**0.008** [h]
Major Bleed	Dab [b] Enox	23/1146 (0.020) 18/1154 (0.016)	1.287 (0.698, 2.37)	Riv Enox	1/1228 **(0.0008)** [h] 1/1229 **(0.0008)** [h]	1.001 (0.063, 15.983)	1.286 (0.091, 18.247)	**0.001** [h]

a. Distal thrombi are rarely symptomatic [137]; therefore it was assumed that all symptomatic DVT events are proximal
b. Only 220mg OD (and not 150mg OD) of dabigatran etexilate was considered for analysis
c. Where 95%CI = Exponential [($logRR_{DE}$) ± 1.96*S.E ($logRR_{DE}$)]
d. Where 95%CI = Exponential [($logRR_{RE}$) ± 1.96*S.E ($logRR_{RE}$)]
e. Where RR_{DR} = Exponential ($logRR_{DE} - logRR_{RE}$)
f. Where 95%CI = Exponential [($logRR_{DR}$) ± 1.96*S.E ($logRR_{DR}$)]
g. Calculated so that dabigatran point estimate = rivaroxaban point estimate x RR_{DR}
h. Point estimates in bold type are to be input into the THR economic models.

THR=total hip replacement; **Dab**=dabigatran etexilate; **Enox**=enoxaparin sodium; **Riv**=rivaroxaban; **n**=number of individuals with events; **N**=the number of individuals under observation; **RR_{DE}**=relative risk (dabigatran vs. enoxaparin); **RR_{RE}**=relative risk (rivaroxaban vs. enoxaparin); **RR_{DR}**=relative risk (dabigatran vs. rivaroxaban); **DVT**=deep vein thrombosis; **PE**=pulmonary embolism; **CI**=confidence interval; **SE**=standard error.

Table 12. The Bucher Method of Indirect Comparison to determine point estimates for the total knee replacement economic model.
The relative risk (±95%CI) of rivaroxaban vs. dabigatran was calculated assuming that the relative risk of rivaroxaban vs. enoxaparin in RECORD 3 would be the same as that observed in REMODEL had a rivaroxaban arm been included.

	RECORD 3 [251]			REMODEL [256] [a]			INDIRECT COMPARISON	
Parameter	**Strategy**	**n/N (point estimate)**	**RR_{RE} (95% CI)[c]**	**Strategy**	**n/N (point estimate)**	**RR_{DE} (95% CI)[d]**	**RR_{RD}[e] (95% CI)[f]**	**Riv point estimate[g]**
Distal DVT	Riv Enox	70/824 (0.085) 140/878 (0.159)	0.533 (0.406, 0.698)	Dab[b] Enox	168/503 **(0.334)**[h] 168/511 **(0.329)**[h]	1.016 (0.853, 1.210)	0.524 (0.432, 0.636) **RR_{DR}**=1.908 (1.572, 2.315)[i]	**0.175** [h]
Proximal DVT	Riv Enox	9/824 (0.011) 20/878 (0.023)	0.479 (0.220, 1.047)	Dab[a] Enox	14/506 **(0.028)**[h] 24/510 **(0.047)**[h]	0.588 (0.308, 1.123)	0.815 (0.411, 1.617) **RR_{DR}**=1.226 (0.618, 2.432)[i]	**0.023** [h]
Symptomatic PE	Riv Enox	0/842 (0) 4/878 (0.005)		Dab[a] Enox	0/675 **(0)**[h] 1/685 **(0.001)**[h]			**0** [h]
Major Bleed	Riv Enox	7/1220 (0.006) 6/1239 (0.005)	1.185 (0.399, 3.515)	Dab[a] Enox	10/679 **(0.015)**[h] 9/694 **(0.013)**[h]	1.136 (0.464, 2.777)	1.043 (0.487, 2.235) **RR_{DR}**=0.959 (0.447, 2.053)[i]	**0.015** [h]

a. Distal thrombi are rarely symptomatic [137]; therefore it was assumed that all symptomatic DVT events are proximal
b. Only 220mg OD (and not 150mg OD) of dabigatran etexilate was considered for analysis
c. Where 95%CI = Exponential [($LnRR_{RE}$) ± 1.96*S.E ($LnRR_{RE}$)]
d. Where 95%CI = Exponential [($LnRR_{DE}$) ± 1.96*S.E ($LnRR_{DE}$)]
e. Where RR_{RD} = Exponential ($LnRR_{RE} - LnRR_{DE}$)
f. Where 95%CI = Exponential [($LnRR_{RD}$) ± 1.96*S.E ($LnRR_{RD}$)]
g. Calculated so that rivaroxaban point estimate = dabigatran point estimate x RR_{RD}
h. Point estimates in bold type are to be input into the TKR economic models.
i. Where RR_{DR}(95%CI) = 1/(RR_{RD}(95%CI))

TKR=total knee replacement; **Dab**=dabigatran etexilate; **Enox**=enoxaparin sodium; **Riv**=rivaroxaban; **n**=number of individuals with events; **N**=the number of individuals under observation; **RR_{DE}**=relative risk (dabigatran vs. enoxaparin); **RR_{RE}**=relative risk (rivaroxaban vs. enoxaparin); **RR_{RD}**=relative risk (rivaroxaban vs. dabigatran); **DVT**=deep vein thrombosis; **PE**=pulmonary embolism; **CI**=confidence interval; **SE**=standard error.

3.4.5 Discussion

Estimating the effectiveness of alternative healthcare interventions is the core of both clinical and economic technology assessments [225]. Since there are no head-to-head efficacy data comparing rivaroxaban and dabigatran etexilate as thromboprophylaxis after THR or TKR, an indirect comparison has been used to assess their comparative effectiveness. The Bucher *et al* [234] method was an appropriate choice given that enoxaparin sodium is a common comparator across the individual pivotal clinical trials. It is noted that this indirect comparison will inform the efficacy and bleeding risk parameter inputs for the economic evaluations in subsequent chapters of this thesis.

The trials chosen for the indirect comparisons were RECORD 2 and RE-NOVATE (for the THR disease state) and RECORD 3 and RE-MODEL (for the TKR disease state) (see Table 10). The choice of trials for the indirect comparisons was made based upon the dose of enoxaparin sodium (only those trials which used the EU licensed dose of 40mg OD were considered). It was also considered important that the duration of enoxaparin sodium given in the trials should reflect clinical practice in Ireland.

Table 11 illustrates the calculation of the RR (efficacy and safety) of dabigatran etexilate vs. rivaroxaban after THR. The adjusted indirect comparison indicates that rivaroxaban offers better efficacy (distal DVT, proximal DVT and symptomatic PE) with less accompanying haemorrhage. Only the 95% CIs pertaining to distal DVT and proximal DVT do not cross the value '1' and therefore only these results are statistically significant [258]. The wide CI associated with each calculated estimate, and in particular those pertaining to proximal DVT, symptomatic PE and major bleeding preclude any definite conclusions being made with regards to relative efficacy and safety.

Table 12 indicates that, after TKR, rivaroxaban is associated with a significant decrease in the risk of distal DVT and a non-significant decrease in the risk of proximal DVT (compared to dabigatran etexilate). There were no instances of symptomatic PE in the dabigatran etexilate and rivaroxaban arms of the respective

trials. Rivaroxaban is associated with a non-significant risk in major bleeding when compared to dabigatran etexilate. The 95% CI here are narrower than the THR indirect comparison suggesting improved certainty.

Of note, the incidence of VTE events is higher in the TKR pivotal trials compared to the THR trials. This is not unexpected. Without prophylaxis, the total DVT rate is greater in TKR [134]. Moreover, prophylactic strategies have a lower efficacy in TKR [134, 135].

There are a number of limitations to this indirect comparison.

Indirect comparisons between RCTs are not always appropriate. The CONSORT statement [245] was considered here to assess trial similarity. Although the pivotal trials (chosen for the indirect comparisons) were deemed similar in many respects, the similarity assumption does not hold for all features of the trials. This raises the concern that the validity of point estimates obtained via the indirect comparison may be uncertain.

The pivotal trials were all international, multi-centre, randomised and double-blind with similar inclusion and exclusion criteria and patient populations [251, 253, 255, 256]. Sample sizes in the THR pivotal trials (i.e. RECORD 2 and RE-NOVATE) were similar. In the TKR trials however, sample size (and hence the power of the study) was reduced in RE-MODEL [256] as compared to RECORD 3 [251].

All trials were designed to assess the same pre-specified composite primary outcome and used pre-specified definitions to capture haemorrhagic events. The methods of ascertaining VTE outcomes were similar amongst all trials; although it is possible that different adjudication panels may have introduced some degree of heterogeneity. In spite of this, all trials were double-blinded and therefore we can expect a reasonably unbiased estimate of the relative treatment effect of dabigatran etexilate vs. enoxaparin sodium and rivaroxaban vs. enoxaparin sodium. Of concern however is the differing definition of major bleeding between trials; this may have biased the results towards demonstrating a lower bleeding risk with rivaroxaban. Indeed, Table

11 and Table 12 indicate that the risks of having a major bleed in the rivaroxaban pivotal trials was lower than the risk in the dabigatran etexilate pivotal trials.
The major concern when assessing similarity is the unequal duration of enoxaparin sodium in the THR trials (RECORD 2 and RE-NOVATE) [253, 255]. The resulting treatment-effect modification might bias the results of an indirect comparison towards demonstrating superior efficacy with rivaroxaban. Indeed, a published meta-analysis has previously highlighted that extended duration thromboprophylaxis with LMWH is associated with significant reductions, compared with standard duration, in the likelihood of developing symptomatic VTE after MOS [259]. It is reassuring, however, to note that the risks of developing a distal DVT, proximal DVT or a symptomatic PE whilst on enoxaparin sodium were only moderately lower in RE-NOVATE [255] than in RECORD 2 [253] (Table 11).

Although the between trial difference in the duration of prophylaxis was smaller between the TKR trials (RE-MODEL and RECORD 3), the risks of developing a VTE when on enoxaparin sodium were higher in RE-MODEL (six to ten days of anticoagulation) than in RECORD 3 (ten to 14 days of anticoagulation) (Table 12). Again, this raises the concern about the appropriateness of performing an indirect comparison between these trials.

The principle assumption underlying the indirect comparison methodology is similarity of treatment effects [238]. It would appear that, although the pivotal trials are similar, the similarity assumption does not fully hold. The true validity of this indirect comparison is therefore uncertain.

Since this work was completed, Trkulja *et al* published an indirect comparison of rivaroxaban and dabigatran etexilate [260]. The authors used separate meta-analyses of two sets of trials (RECORDs 1- 4 for rivaroxaban) and (RE-NOVATE, REMOBILIZE and RE-MODEL for dabigatran etexilate) to indirectly estimate risk differences (RDs). The RD (rivaroxaban vs. dabigatran etexilate) for symptomatic VTE was -0.3% (95% CI, -1.3 to 0.7; p = 0.275) and for major/clinically relevant bleeding was 0.97% (95% CI, -0.43 to 2.37; p = 0.085). It is difficult to compare this published study to the analysis undertaken here; unlike this analysis, Trkulja *et al* combined the THR and TKR disease states and included all seven pivotal trials.

The indirect comparison presented here indicates that, after THR, rivaroxaban offers better efficacy with less accompanying major haemorrhage compared to dabigatran etexilate. After TKR, rivaroxaban is associated with better efficacy and a small increased risk of major bleeding. At the time of this analysis, both drugs were comparably priced [261]. Any recommendations (arising from this indirect comparison) on a price review of these drugs, based on their relative efficacy and safety, will be reserved until the economic evaluations (in the subsequent chapters of this thesis) have been completed.

3.4.6 Conclusion

Based on the indirect comparisons, when compared to dabigatran etexilate after THR, rivaroxaban is associated with a significant reduction in the risks of developing distal DVT and proximal DVT and with a non-significant decrease in the risk of symptomatic PE. Rivaroxaban is also associated with a non-significantly reduced risk of major haemorrhage after THR.

After TKR, rivaroxaban is associated with a significant decrease in the risk of distal DVT and a non-significant decrease in the risk of proximal DVT. Rivaroxaban is also associated with a non-significantly increased risk of major haemorrhage.

There is some uncertainty associated with the strength of this indirect comparison.

The results of this indirect comparison will be used to inform the efficacy and bleeding risk parameters in the economic evaluations in subsequent chapters of this thesis.

The major limitations of this indirect comparison have been noted.

The skills which I have gained in performing this Bucher *et al* [234] indirect comparison will be of benefit in the future when performing such comparisons in different therapeutic areas.

Chapter 4

A Cost-Effectiveness Model Comparing Rivaroxaban, Dabigatran etexilate and Enoxaparin sodium as Thromboprophylaxis after Total Hip- and Total Knee- Replacement

4 A COST-EFFECTIVENESS MODEL COMPARING RIVAROXABAN, DABIGATRAN ETEXILATE AND ENOXAPARIN SODIUM AS THROMBOPROPHYLAXIS AFTER TOTAL HIP- AND TOTAL KNEE- REPLACEMENT 103

4 A Cost-Effectiveness Model Comparing Rivaroxaban, Dabigatran etexilate and Enoxaparin sodium as Thromboprophylaxis after Total Hip- and Total Knee-Replacement

4.1 Introduction

In 2008, two oral anticoagulants, dabigatran etexilate (Pradaxa®; Boehringer Ingelheim Ltd) and rivaroxaban (Xarelto®; Bayer Ltd), became licensed in Ireland for the prevention of VTE in adult patients (over 18 years) undergoing elective THR or TKR [73, 74]. Treatment with rivaroxaban should be continued for five weeks after THR and for two weeks after TKR [73]. Treatment with dabigatran etexilate should be continued for 28-35 days after THR and for ten days after TKR [74].

The cost of these new agents will be a potential obstacle on their usage and therefore it is essential to consider their cost-effectiveness.

4.2 Standard Irish Practice

Data on the relative use of various licensed thromboprophylaxis regimens in the hospital setting in Ireland is not available. Clinical guidelines relating to VTE prophylaxis after THR and TKR recommend the use of LMWH or fondaparinux [134, 157, 262]. Fondaparinux is not available in Ireland; LMWH was therefore chosen as the comparator in this analysis. A number of LMWHs are available in Ireland [160]. Studies which have directly compared different LMWHs and have shown them to be comparable in efficacy in the treatment and prevention of thromboembolism [263]. Enoxaparin sodium was selected as the LMWH in this economic evaluation to accommodate the phase III pivotal clinical trials (pertaining to both dabigatran etexilate and rivaroxaban). Enoxaparin sodium was the comparator in all such trials [251, 253, 255, 256].

4.3 Objective

The objective of this study was to evaluate the cost-effectiveness of rivaroxaban, dabigatran etexilate and enoxaparin sodium as VTE prophylaxis in patients undergoing elective THR and TKR in the Irish healthcare setting.

4.4 Methods

The evaluation was conducted from the Irish HSE perspective.

The timeframe was 180 days post surgery to accommodate the 90 day risk period for development of a primary VTE event after THR or TKR [133] and the measurement of acute costs associated with VTE development. Anticoagulant treatment duration for a symptomatic distal DVT of up to 90 days and for a symptomatic proximal DVT and PE of up to 180 days has been described [180]. In contrast to the extensive documentation available on the short-term outcome of patients with acute DVT, less information is available on the long-term clinical course of the disease [85]. From a decision maker's perspective it was considered pragmatic to include the well documented acute events only.

The outcomes are VTE events and thromboprophylaxis related major bleed events, stroke and death. Such events impact on the quantity and QoL. As such, the primary outcome measure was QALYs and the secondary outcome was LYGs.

While consideration of the cost-effectiveness of a pharmaceutical is necessary, it is not the sole basis for decision making; other factors such as the total budget impact and the innovative nature of the product are important. Currently in Ireland there is no set cost-effectiveness threshold; however, the majority of pharmaceuticals which had been reimbursed, up to the time of this analysis (2008), had had an ICER of €45,000 per QALY or less [4]. This threshold was considered in this analysis. It should be noted here that in recent more economically constrained times, pharmaceuticals with an ICER of greater than €20,000 per QALY are less likely to be reimbursed [37].

4.4.1 The Model

A static decision tree model was developed using TreeAge Pro 2008® (TreeAge Software Inc, Williamstown, MA, USA).

The structure of the thromboprophylaxis model is shown in Figure 8. Published model based economic evaluations of thromboprophylaxis after THR and TKR [199, 201, 203, 206, 208, 217, 219, 264, 265] were used to inform the unique stucture of this model.

The beginning of the tree shows the choice of prophylaxis given after surgery. Similar to Gordois *et al* [264] there is a probability of developing a prophylaxis-related major bleed on receiving prophylaxis. This may result in death, a stroke or in no sequelae (comparable to Wolowacz *et al* [206] and Marchetti *et al* [203]).

All patients are at risk of developing a surgery related distal DVT, a proximal DVT or a PE. Similar to Oster *et al* [265] a DVT may be symptomatic or asymptomatic. As described by Gordois et al [264] a VTE may become symptomatic before or after discharge. The model assumes that, where the primary VTE is a PE, it is symptomatic, to reflect phase III clinical trial data, which did not report the incidence of asymptomatic PEs [251, 253, 255, 256]. Akin to a number of published models [199, 201, 203, 206, 208, 217, 219], different branches exist for distal and proximal DVTs, since distal DVTs can propagate to the proximal veins [78] and proximal DVTs present a higher risk of propagation to PE [217]. The model assumes that symptomatic VTEs are detected and treated and that asymptomatic VTEs remain untreated (as illustrated by Wolowacz *et al* [206]).

Symptomatic DVTs will be diagnosed and treated and there will be associated probabilities of death or survival. An asymptomatic DVT will not be investigated or treated and there will be associated probabilities of death and survival (similar to Gordois *et al* [264]). Asymptomatic and untreated distal DVTs either resolve or propagate to the proximal veins. Asymptomatic and untreated proximal DVTs either resolve or propagate to a PE. A PE may be immediately fatal. Where a PE is not immediately fatal, it may be symptomatic and treated and there will be associated probabilities of death or survival. Where a PE is asymptomatic, it will remain untreated and there will be associated probabilities of death or survival. As described by Wolowacz *et al* [206] pre-discharge events result in a prolonged hospitalisation followed by outpatient anticoagulant visits; post-discharge events require re-admission followed by outpatient anticoagulant visits.

Separate models were run for both THR and TKR to reflect the different VTE risks after either surgery [134].

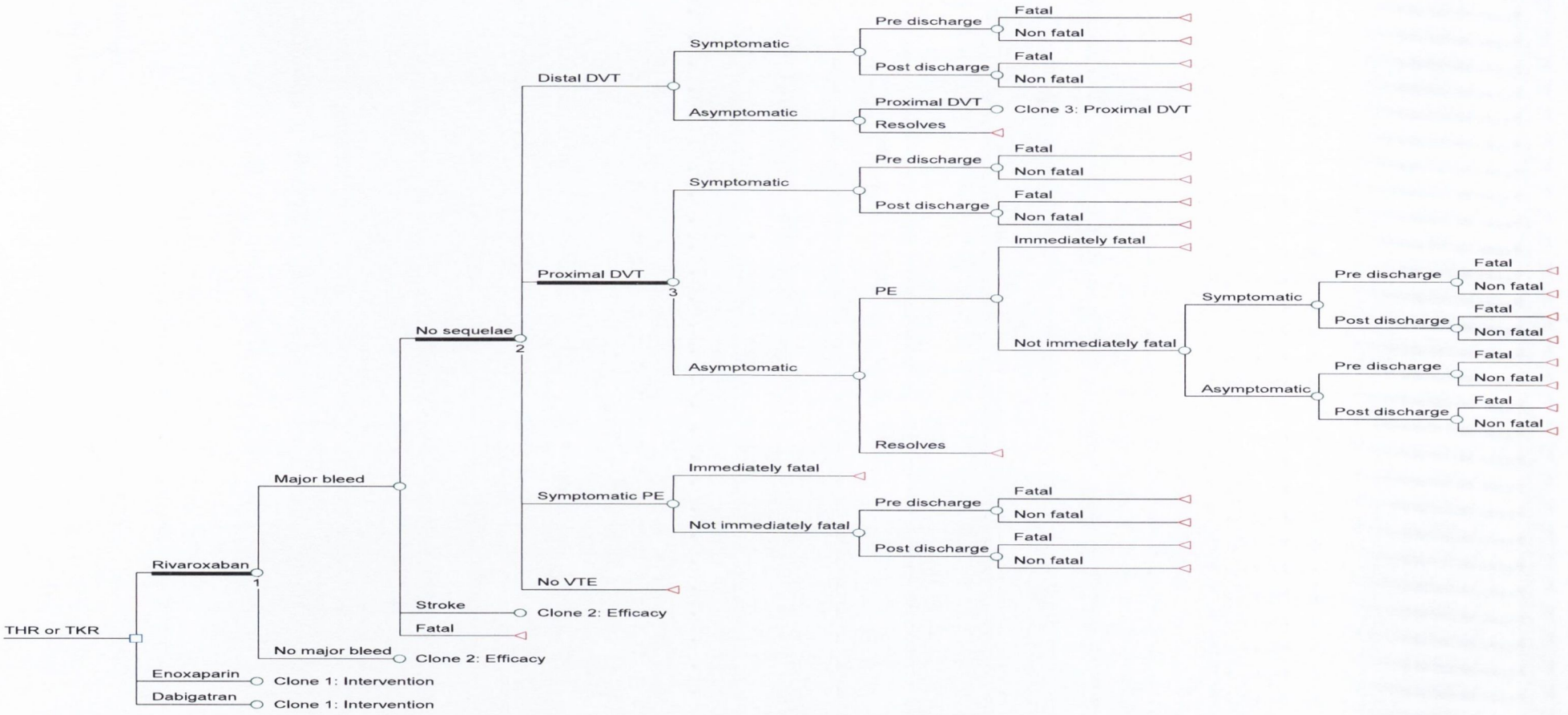


Figure 8: 180 day Thromboprophylaxis model

THR=total hip replacement; **TKR**=total knee replacement; **DVT**=deep venous thrombosis; **PE**=pulmonary thrombosis; **VTE**=venous thromboembolism.

4.4.2 Clinical Inputs

4.4.2.1 Treatment Efficacy and Major Bleeding Probabilities

The probabilities of treatment efficacy (VTE events) and major bleeding were derived from pivotal clinical trials for rivaroxaban and dabigatran etexilate (which reported venographically confirmed VTE events) [251, 253, 255, 256].

For the THR model, efficacy and bleeding rate point estimates pertaining to rivaroxaban and enoxaparin sodium were obtained from RECORD 2 [253]. The Bucher *et al* [234] method of adjusted indirect comparison was used to determine point estimates pertaining to dabigatran etexilate under the assumption that the treatment effect seen in RE-NOVATE [255] would be the treatment effect seen in RECORD 2 had a dabigatran etexilate arm been included (Table 11).

For the TKR model, efficacy and bleeding rate point estimates pertaining to dabigatran etexilate and enoxaparin sodium were derived from RE-MODEL [256]. Those pertaining to rivaroxaban were derived from an adjusted indirect comparison under the assumption that the treatment effect seen in RECORD 3 [251] would be the treatment effect seen in RE-MODEL had a rivaroxaban arm been included (Table 12).

There are two licensed doses of dabigatran etexilate; 220mg OD and 150mg OD. In neither RE-NOVATE nor RE-MODEL was there a subgroup analysis to determine the efficacy and safety in these populations [255, 256]. Therefore, an economic evaluation was performed for the 220 mg dose only.

The probabilities of treatment efficacy (VTE events) and major bleeding derived from the pivotal clinical trials were supplemented by thromboprophylaxis independent probabilities, which were identified via a systematic literature search.

4.4.2.2 Thromboprophylaxis Independent Probabilities

These were derived from a systematic search of literature published in the English language since 1980, pertaining to humans. Additional references were identified

from the reference lists of published articles. Combinations of the following search terms were used:

For PubMed MeSH: arthroplasty, replacement, knee; arthroplasty, replacement, hip; venous thrombosis; pulmonary embolism; thromboembolism; phlebography; economics; costs and cost analysis; intracranial hemorrhages; hemorrhage.

For Embase Thesaurus: hip arthroplasty; knee arthroplasty; deep vein thrombosis; venous thromboembolism; leg thrombosis; lung embolism; phlebography; leg phlebography; pharmacoeconomics; bleeding; brain haemorrhage.

CRD: databases including DARE, NHS EED and HTA were searched for relevant references on anticoagulant prophylaxis relating to TKR and THR.

For NICE: completed HTAs were searched; all appraisals of anticoagulant prophylaxis relating to TKR and THR were retrieved.

4.4.2.2.1 Deep Vein Thrombosis

Only 5% of thrombi restricted to the distal veins become clinically apparent [266], this rises to 40% where there is proximal vein involvement [266, 267]. In this analysis it was therefore assumed that 5% and 40% of distal and proximal DVTs respectively would be symptomatic.

Only one prospective study was located which examined the risk of a venography confirmed/untreated distal DVT propagating to a proximal DVT. Fifty-one patients (aged mean 62 years, 57% male), admitted with distal DVT, propagation to the proximal vein segments occurred in 18% of limbs [268]. In this analysis it was therefore assumed that 18% of distal DVTs would propagate to the proximal veins.

Just one prospective study was located which examined the risk of a venography confirmed/untreated proximal DVT propagating to a PE. Moser *et al* [269] examined 68 patients with clinically suspected or a high risk of DVT. Venography confirmed DVT in 36 cases, with proximal involvement in 15 of these. In these 15, V/Q scanning indicated a V/Q pattern characteristic of PE in 8 cases (53%) [269]. In this

economic analysis it was therefore assumed that 53% of undetected and untreated proximal thrombus would propagate to a PE.

One meta-analysis [270] and 11 prospective studies [176, 177, 271-279] were located which described the mortality risk associated with treated DVT; all concluded that this risk is small. For this analysis, the prospective studies were all considered too small to provide reliable estimates; these were excluded. In the meta-analysis by Douketis *et al* [270] it was estimated that patients undergoing treatment for a DVT experience a mortality rate of 0.4%.

4.4.2.2.2 Pulmonary Embolism

Two studies were located which investigated the probability that a PE will be symptomatic [280, 281]. Karwinski *et al* [280] retrospectively reviewed data pertaining to 21,529 autopsies carried out between 1960 and 1984 in a Norwegian hospital. A total of 48 of 484 (16.3%) patients with PE had the diagnoses suspected before death (excluding immediately fatal PEs). Likewise, Rubinstein *et al* [281] reviewed 1276 autopsy reports at a Toronto Hospital from 1980 to 1984. Of 44 patients identified with major PE, 14 (32%) had the diagnosis suspected before death [281]. It is possible that the more recent smaller study may convey data that is more reflective of the current population and methods of diagnosis. In this economic analysis, it was therefore assumed that 32% of PEs are symptomatic (excluding immediately fatal).

The prevalence of acute PE among 51,645 patients hospitalised over a 21-month period was assessed as part of the collaborative PIOPED study. PE was observed at autopsy in 59 patients; death had occurred within 2.5 hours in 13 cases (22%). In the same study, PE at autopsy was unsuspected antemortem in 52 patients and PE that caused death was unsuspected antemortem in 14 cases (27%) [282]. In this analysis it was therefore assumed that 22% of PE are immediately fatal and that asymptomatic PE is fatal in 27% of cases.

One meta-analysis [270] and five prospective studies [279, 283-286] were located which described the mortality risk associated with treated PE. All concluded that this risk was small. In order to obtain reliable estimates the larger sample size afforded by the meta-analysis was chosen for this evaluation. The meta-analysis by Douketis *et al*

[270] revealed that among patients presenting with PE, the rate of fatal PE during anticoagulation therapy was 1.5%.

4.4.2.2.3 Timing of Venous Thromboembolism Diagnosis

Monreal *et al* [287] describe a prospective cohort study in 1,033 consecutive patients who had undergone MOS. VTE was confirmed in 51 patients (4.9%); this diagnosis was made after discharge in 27 (53%) [287]. In a retrospective study, White *et al* [133] used a hospital discharge database to identify cases of VTE (DVT and/or PE) after THR (n=19,580) and TKR (n=24,059). VTE occurred in 2.8% of the THR cohort and in 2.1% of the TKR cohort. The diagnosis of VTE was made after discharge in 76% and 47% of the THR and TKR cohorts respectively [133]. The later study was preferable for this economic analysis as data pertaining to both THR and TKR cohorts is presented.

4.4.2.2.4 Major Bleed

In 2010, the UK National Clinical Guideline Centre - Acute and Chronic Conditions estimated that about 3% of major bleeds would results in a stroke. This was based on data from a systematic review of bleeding associated with VTE prophylaxis [157]. Following this guideline, 3% of major bleeds will result in a stroke in the decision tree presented here.

Several clinical studies have evaluated the effectiveness and safety of thromboprophylatic agents, however clinically significant bleeding is uncommon [157]. In order to obtain reliable estimates the larger sample size afforded by a meta-analysis was chosen for this evaluation. One meta-analysis was located. Muntz *et al* [288] performed a systematic review of RCTs pertaining to thromboprophylaxis after MOS. Out of a total of 632 episodes of major bleeding, 5 (0.8%) cases of fatal bleeding were identified.

The economic model probabilities are summarised in Table 13.

Table 13. Probabilities used in the economic evaluations of the 180 day model

	Parameter	Probability
THR		
Rivaroxaban [253]	Distal DVT	0.010
	Proximal DVT	0.006
	Symptomatic PE [a]	0.0012
	Major Bleed	0.0008
Dabigatran etexilate [253, 255]	Distal DVT	0.029 [b]
	Proximal DVT	0.036 [b]
	Symptomatic PE [a]	0.008 [b]
	Major Bleed	0.001 [b]
Enoxaparin sodium [253]	Distal DVT	0.031
	Proximal DVT	0.051
	Symptomatic PE [a]	0.005
	Major Bleed	0.0008
TKR		
Rivaroxaban [251, 256]	Distal DVT	0.175 [c]
	Proximal DVT	0.023 [c]
	Symptomatic PE [a]	0.00 [c]
	Major bleed	0.015 [c]
Dabigatran etexilate [256]	Distal DVT	0.334
	Proximal DVT	0.028
	Symptomatic PE [a]	0.00
	Major bleed	0.015
Enoxaparin sodium [256]	Distal DVT	0.329
	Proximal DVT	0.047
	Symptomatic PE [a]	0.001
	Major bleed	0.013
Thromboprophylaxis-independent probabilities		
Proximal DVT is symptomatic [266, 267]		0.40
Distal DVT is symptomatic [266]		0.05
PE is symptomatic (excluding immediately fatal) [281]		0.32
DVT (proximal or distal) fatal during treatment [270]		0.004
PE fatal during treatment [270]		0.015
PE fatal if asymptomatic [282]		0.27
PE immediately fatal [282]		0.22
Distal DVT propagates to the proximal vein [268]		0.18
Proximal DVT propagates to PE [269]		0.53
VTE detected pre-discharge (THR) [133]		0.24
VTE detected pre-discharge (TKR) [133]		0.53
Major bleed results in stroke [157]		0.03
Major bleed results in death [288]		0.008

a. Where a primary VTE is a PE, the model assumes it is symptomatic to reflect the pivotal trials.

b. Derived using the Bucher [234] method of indirect comparison, assuming that the RR_{DE} seen in RE-NOVATE [255] would be that same in RECORD 2 [253] had a dabigatran arm been included.

c. Derived by indirect comparison, assuming that the RR_{RE} seen in RECORD 3 [251] would be the same as in RE-MODEL [256] had a rivaroxaban arm been included.

DVT=deep vein thrombosis; **PE**=pulmonary embolism; **THR**=total hip replacement; **TKR**=total knee replacement; **VTE**=venous thromboembolism.

4.4.3 Preference Values

These were derived from a systematic search of published literature. Additional references were identified from the reference lists of published articles. Combinations of the following search terms were used:

For Pubmed MeSH: venous thrombosis; pulmonary embolism; thromboembolism; intracranial hemorrhages; hemorrhage; economics; costs and cost analysis; patient preference.
Free text terms: standard gamble; time trade off; SG; TTO; EuroQol; EQ5D; EQ-5D; quality of well being; health utility index; health utilities index; QALY; quality adjusted life year.

For Embase Thesaurus: deep vein thrombosis; venous thromboembolism; leg thrombosis; thromboembolism; lung embolism; bleeding; brain haemorrhage; cost utility analysis; pharmacoeconomics.
Free text terms: standard gamble; time trade off; SG; TTO; EuroQol; EQ5D; EQ-5D; quality of well being; health utility index; health utilities index; QALY; quality adjusted life year

For NICE: completed HTAs were searched; all appraisals of anti-coagulant prophylaxis were retrieved.

4.4.3.1 Venous Thromoboembolic Events

The literature search highlighted a lack of good quality preference value data for this population. Beyth *et al* [84] report SF-36 measures for patients with DVT; however the results are not presented in a manner that can be transformed into a preference value; thus this study was excluded from this analysis. Hedner *et al* [289] determined preference scores in DVT patients undergoing warfarin treatment. The authors did not determine values for PE and so this study was excluded from this analysis. Brothers *et al* [290] report on preference values for PE and DVT. The scores were derived by the consensus of three vascular surgeon authors; this study was excluded because of this method of elicitation used [290]. Cykert *et al* [291] reported QoL estimates for various outcomes including DVT and PE. A stratified sample of 106

female healthy volunteers, aged at least 50 years, from urban areas of central North Carolina and south Florida were interviewed using the standard gamble methodology. For this economic analysis, the QoL estimate reported by Cykert *et al* [291] was applied for the anticoagulant treatment duration of 90 days for symptomatic distal DVT and 180 days for symptomatic proximal DVT and PE [114, 180].

4.4.3.2 Major Bleed

Good quality empirical values pertaining to major bleed were not located. To estimate loss of QoL for this acute event, the approach taken previously by the National Collaborating Centre for Acute Care (NCC-AC) was followed. Here the QoL lost is assumed to be equivalent to a complete loss of QoL during the hospital stay [131]. In this analysis, it was assumed that a major bleed would manifest as a GI haemorrhage. The duration of in-patient stay for a GI haemorrhage was calculated as five days, based on the weighted average length of stay for GI haemorrhage (DRG codes G61A & G61B), recorded by the National Casemix Unit of the HSE [292].

4.4.3.3 Stroke

Robinson *et al* [293] and Gage *et al* [294] both assessed stroke preference values in patients with atrial fibrillation. These studies were excluded since the populations studied do not reflect the population in this economic evaluation. Likewise a study by O'Reilly *et al* [295] was excluded because the population studied had type II diabetes. A number of further studies were excluded as they had determined scores for severe, moderate and minor stroke [296-299]; our economic model does not model such a range of stroke health states. Lenert and Soetikno [300] estimated the preference value of stroke, elicited from 30 healthy volunteers and 30 physicians using standard gamble methods; this study was chosen to inform the economic evaluation.

4.4.3.4 Quality of life of the General Population

In the absence of Irish-specific values, preference weights for the general population were taken from self reported time-trade-off QoL values in a US adult population [301]. In this source, individuals were classified by the number of self-reported chronic health conditions affecting them. The mean of the scores recorded for the '0' and '1-3' health conditions subgroups was used in this analysis.

Kind *et al* [302] conducted a UK nationally representative interview survey of 3395 men and women (≥ 18 years). The survey collected information on health status using the EQ-5D descriptive system. This study was not used in this economic evaluation because it was considered difficult to reconcile the lower age specific population value in Kind *et al* (0.8) [302] with the higher values associated with the DVT and PE health states obtained from Cykert *et al* [291].

In this analysis, multiplicative approach for preference values was taken in the economic model pathways e.g. the preference value for the pathway: major bleed with stroke and symptomatic distal DVT, was calculated by multiplying the individual preference values for each event together.

The preference values used in the cost utility analyses are summarised in Table 14.

Table 14. Preference values used in the economic evaluations of the 180 day model

Parameter	Reported preference	Value used in Model	Source
No Symptomatic VTE		1	Assumption
Symptomatic Distal DVT	0.86	0.93 i.e. ([0.86x90]+[1x90])/180	Cykert [291] reported symptomatic DVT preference value of 0.86; applied for 3 months
Symptomatic Proximal DVT	0.86	0.86	Cykert [291] reported symptomatic DVT preference value of 0.86; applied for 6 months
Symptomatic PE	0.81	0.81	Cykert [291] reported symptomatic PE preference value of 0.81; applied for 6 months
Major Bleed	0	0.97 i.e. ([0x5] + [1x175])/180	Assumed preference value of 0 during extended hospital stay for major bleeding; applied for 5 days [131]
Stroke	0.6	0.6	Lenert and Soetikno [300]
General Population Weight	0.973 (with 0 health conditions) 0.909 (with 1-3 health conditions)	0.941 i.e. (0.973+0.909)/2	Fryback and Lawrence [301]
Death		0	Assumption

Multiplicative preference values were applied in the model e.g. for the model pathway: major bleed with a stroke and a symptomatic distal DVT, the preference value applied was 0.509 (i.e.0.97 x 0.6 x 0.93 x 0.941)
DVT=deep vein thrombosis; **PE**=pulmonary embolism; **VTE**=venous thromboembolism.

4.4.4 Direct Medical Costs

4.4.4.1 Costs of Prophylaxis of Venous Thromboembolism

The daily dose costs of the thromboprophylaxis used in the models are as follows:

- rivaroxaban: €5.15 (10mg); Proposed HSE Price (05/2008)
- dabigatran etexilate: €5.18 (220mg); Proposed HSE Price (07/2008)
- enoxaparin sodium: €5.10; Monthly Index of Medical Specialities (MIMS) Ireland (10/2008) [303]

4.4.4.2 Administration Costs

The cost of nursing time for drug administration and blood monitoring for all drugs were assumed to be the same. It was assumed that compliance was 100% with all drugs. Administration costs are summarised in Table 15.

Table 15: Drug administration and blood monitoring costs

Resource	Applied to	Units	Unit cost	Total cost
Nurse time per inpatient; oral or injection administration	All patients	3 mins[a]	0.51[b]	1.53
Nurse time for blood tests	All patients	4[c] x 3 mins[a]	0.51[b]	6.12
Blood tests	All patients	4 tests[c]	15.00[d]	60.00

All costs are in €, year 2008 values

a. Nurse time was assumed.
b. Unit cost (per minute) of a staff nurse sourced from the Irish HSE consolidated salary scales. [292]
c. Patients have an average of four full blood counts after surgery. [160]
d. Inhouse database of costs provided by university teaching hospital (average costs used), Dublin (2008 Aug).

4.4.4.3 Length of Stay and Cost of Primary Hospitalisation

The weighted average lengths of hospital stay were calculated from the Irish HSE DRGs as 14 days for THR and 12 days for TKR [292]. The weighted average costs of elective THR (€13,048, DRG codes I03B & I03C), elective TKR (€12,870, DRG code I04Z), GI haemorrhage (€2555, DRG codes G61A &G61B)) and acute care for stroke (€14,961, DRG codes B70A, B70B, B70C) were calculated from the Irish HSE DRGs price year 2005 [292]. All costs were inflated to current price year (2008) using the consumer price index for health [193].

4.4.4.4 Costs of Diagnosis of Venous Thromboembolism

It was assumed that patients suspected of having a DVT would have a d-dimer blood test and a Doppler ultrasound. It was assumed that patients suspected of having a PE would have a chest X-ray, an E.C.G and a CTPA.

4.4.4.5 Costs of Treatment of Venous Thromboembolism

The standard treatment for a VTE event is warfarin [114]. In acute thrombosis, the initial period of treatment with warfarin may be associated with a procoagulant state; therefore, LMWH treatment should be started and continued for at least five days after initiation of warfarin and until the INR is greater than 2 for at least two consecutive days [160]. In this analysis, it was assumed that patients would receive enoxaparin sodium for seven days.

4.4.4.6 Cost of Treatment of a Pre-Discharge Venous Thromboembolism

Nerurkar *et al* [217] reviewed patient hospitalisation data from over 900 US hospitals. They estimated that the incremental LOS for patients who developed a distal DVT,

proximal DVT or PE after TKR surgery was 3.27 days, 5.05 days and 7.9 days respectively. In this analysis, it was assumed that the incremental LOS associated with a VTE after THR surgery was the same as that after TKR. An immediately fatal PE was assumed to be untreated and incur no direct costs. The cost per additional bed day was sourced from a university teaching hospital in Dublin.

4.4.4.7 Cost of Treatment of a Post-Discharge Venous Thromboembolism

It was assumed that patients presenting with a VTE after discharge would incur an ED visit and be re-admitted. The cost and length of hospitalisation was estimated using weighted averages from the Irish HSE DRGs [292]. The LOS was calculated as 7 days and 11.84 days for a DVT and a PE respectively. The costs associated with treatment of a VTE pre- and post-discharge are summarised in Table 16 and Table 17.

Table 16. Cost of deep vein thrombosis detected pre- and post-discharge

Resource	Applied to patients	Distal DVT-survives (units)	Distal DVT-fatal[a] (units)	Proximal DVT-survives (units)	Proximal DVT-fatal[a] (units)	Unit cost (€)
Diagnosis						
ED visit	Post-discharge only	1	1	1	1	200.00[b]
D-dimer	All	1	1	1	1	15.00[b]
Doppler ultrasound	All	1	1	1	1	130.00[b]
Treatment						
Additional hospital days	Pre-discharge only	3.3[217]	3.3[217]	5.0[217]	5.0[217]	500.00[b]
Hospital re-admission for DVT	Post-discharge only	1	1	1	1	3470.00[c]
Inpatient enoxaparin sodium (days)	All	7	7	7	7	5.10 [303]
Warfarin (days)[d]	All	3x28 [114]	3(THR pre-) 1(TKR pre-) 0 (post-)	6x28 [114]	5(THR pre-) 3(TKR pre-) 0 (post-)	0.11 per day [303]
Graduated compression stockings (pairs)	All	6	1	6[e]	1	15.00[b]
Anticoagulant clinic visits	All	5[e]	0	7[e]	0	60.00[e]
Total cost pre-discharge DVT		2229.94	1846.03(THR) 1845.81(TKR)	3209.18	2696.25(THR) 2696.03(TKR)	
Total cost post-discharge DVT		4249.94	3865.70	4379.18	3865.70	

All costs are in €, year 2008 values

a. Where a DVT was fatal, it was assumed that death occurred at discharge.
b. In-house database of costs provided by university teaching hospitals (average costs used), Dublin (2008 Aug)
c. Casemix, Irish Health Service Executive [292]. Costs inflated to 2008 [193]
d. Where a VTE occurred pre-discharge, it was assumed that this would occur on day 7 post-surgery.
e. Expert opinion. Clinical Pharmacology Department, St James's University Teaching Hospital, Dublin.

ED=Emergency department; **DVT**=deep vein thrombosis; **THR**=total hip replacement; **TKR**=total knee replacement; **Pre**=pre-discharge; **Post**=post-discharge.

Table 17: Cost of pulmonary embolism detected pre- and post-discharge

Resource	Applied to patients	PE-survives (units)	PE-fatal[a] (units)	Unit cost (€)
Diagnosis				
ED Visit	Post-discharge only	1	1	200.00[b]
CTPA	All	1	1	113.00[b]
Chest x-ray	All	1	1	47.00[b]
ECG	All	1	1	50.00[b]
Treatment				
Additional hospital days	Pre-discharge only	8 [217]	8 [217]	500.00[b]
Hospital re-admission for PE	Post-discharge only	1	1	5790.00[c]
Inpatient enoxaparin sodium (days)	All	7	7	5.10 [303]
Warfarin (days)[e]	All	6x28 [114]	8(THR pre-) 6(TKR pre-) 5 (post-)	0.11per day[3
Graduated compression stockings (pairs)	All	6[d]	1	15.00[b]
Anticoagulant clinic visits	All	7[d]	0	60.00[d]
Total cost pre-discharge PE		4774.18	4261.58(THR) 4261.36(TKR)	
Total cost post-discharge PE		6764.18	6251.25	

All costs are in €, year 2008 values

a. Where a PE was fatal it was assumed that death occurred at discharge (excludes immediately fatal).
b. In-house database of costs provided by university teaching hospitals (average costs used), Dublin (2008 Aug)
c. Casemix, Irish Health Service Executive [292]. Costs inflated to 2008 [193]
d. Expert opinion. Clinical Pharmacology Department, St James's University Teaching Hospital, Dublin.
e. Where a VTE occurred pre-discharge, it was assumed that this would occur on day 7 post-surgery.

ED=Emergency department; **CTPA**= Computed tomography pulmonary angiogram; **ECG** = electrocardiogram; **THR**=total hip replacement; **TKR**=total knee replacement; **PE**=pulmonary embolism; **Pre**=pre-discharge; **Post**=post-discharge

4.4.5 Discounting

Most analysts agree that costs should be discounted in any study having a time horizon longer than one year [23]. This analysis was therefore not subjected to discounting.

4.4.6 Validation

A colleague also built and ran the model in Microsoft Office Excel 2003. A hospital clinical team validated the structure of the model and the care pathways and also confirmed that the parameter values were reasonable.

4.4.7 Basecase Analysis

The basecase cost-effectiveness of rivaroxaban versus enoxaparin sodium and dabigatran etexilate versus enoxaparin sodium were compared by ICERs according to standard decision rules [304].

4.4.8 Sensitivity Analysis

A one-way SA of all the parameters in the model was performed to determine the specific variables the intervention was sensitive to. The upper and lower bounds of the 95% CI were used where these were available for point estimates; otherwise point estimates were varied ± 50%. The total costs were varied ± 20%, whilst multiplicative preference values were varied ±10%.

In the absence of data regarding the relative use of the various LMWHs in the hospital setting in Ireland, enoxaparin sodium was chosen as the comparator in the basecase. SC tinzaparin (4500 units OD; daily dose cost = €4.88 [305]) is also used in Ireland for VTE prophylaxis in MOS [160]. In the SA the impact of using a weighted average cost (assuming a 50:50 notional market share for enoxaparin sodium and tinzaparin) on the ICER was investigated. It is noted that the different LMWHs have been shown to be comparable in efficacy in the treatment and prevention of thromboembolism [263]

A PSA using second order Monte Carlo simulation was performed, in which input parameters were varied according to estimated probability distributions. Parameters were sampled from appropriate statistical distributions for each parameter type. Probability parameters are constrained on the 0-1 interval and distribution forms that are consistent with this restriction should be chosen [51]. The Beta distribution was chosen for the probability parameters because of its special relationship with binomial data [306]. Binomial data (the number of events of interest, n, observed from a given sample size, N) was available for all but two probability inputs. Where binomial data was unavailable, Beta distributions were fitted to plausible ranges for the parameters. The Dirichlet distribution, which is the multivariate generalization of the Beta distribution, was adopted for all multibranch nodes of the model. These were populated using the methodology described by Briggs *et al* [307].

The direct medical costs were specified as log-Normal distributions as they are constrained to be positive, they are fully continuous and costs are invariably highly skewed. The log-Normal distribution will explicitly accommodate skewness [308]. In order to quantify the uncertainty associated with the direct medical costs, an elicitation exercise was performed [309]. A Departmental Statistician constructed the predictive probability distributions for the costs by varying the values of the coefficient of variation (CoV). The author/analyst who had obtained the initial costs then selected the distribution that most closely matched the uncertainty associated with these at the time that they had been obtained. The associated value of the CoV (0.2) was then fixed to the log-Normal distribution applied to the costs, within the model.

Since preference values are bounded on the 0-1 interval, these parameters were assumed to have a Beta distribution. Beta distributions were fitted to ranges for the parameters. In the absence of other information, the standard deviation (SD) for the Beta distribution was fixed at 0.2 during the fitting process. Again, the value of the CoV was determined during an elicitation exercise.

The PSA parameters are summarised in Table 18.

The Monte Carlo simulation entails making random draws of the uncertain parameters from their probability distribution, running the model for each simulated set of parameters and collecting the outputs from each run [310]. The expected costs and QALYs of all three strategies, for each PSA simulation were recorded and were combined to form a measure of the expected NMBs for each intervention. The NMB is calculated as the total number of QALYs multiplied by the cost-effectiveness threshold, minus the total costs for each intervention [56, 57].

In the PSA the values of NMB were then used to identify the probability of each option being cost-effective over the threshold range of €0 - €100,000 in order to produce the CEAC [56]. The option which is optimal (has the highest expected NMB) at the different threshold values was also identified in order to produce the CEAF [58].

Monte Carlo sampling estimates are subject to potential error [66]. The process of re-sampling from each of the distributions and recalculating the cost-effectiveness from the model was repeated 30,000 times. This number of PSA iterations was chosen as it could be demonstrated that the PSA results did not change appreciably in three successive runs. The standard error of a Monte Carlo analysis was also calculated by dividing the standard deviation of the PSA results (the potential opportunity loss) by the square root of the number of iterations [311]. The standard approach to ensuring that a Monte Carlo exception is estimated with sufficient accuracy is to increase the number of PSA iterations until the standard error is less than some defined acceptable level [66].

The Monte Carlo (MC) error was calculated where: [311]

$$\text{Monte Carlo error} = \sigma/\sqrt{n}$$

Where: σ =standard deviation of NMB gained with Perfect Information (opportunity loss)
n= number of iterations

The running time for the PSA was approximately 15 seconds.

Table 18. Summary of distributions used in the probabilistic analysis of the 180 day model

Parameter	Distribution[a]	Source
THR		
Distal DVT, proximal DVT, no VTE, PE occur on rivaroxaban	Dirichlet (10; 6; 850; 2)	[253]
Distal DVT, proximal DVT, no VTE, PE occur on enoxaparin	Dirichlet (28; 45; 795; 5)	[253]
Distal DVT, proximal DVT, no VTE, PE occur on dabigatran	Dirichlet[b] (26.5; 32.2; 811.7; 7.7)	[253, 255]
Major bleed occurs on rivaroxaban	Beta (2,1228)	[253]
Major bleed occurs on enoxaparin	Beta (2,1229)	[253]
Major bleed occurs on dabigatran	Beta (2.2,1145.8)	[253, 255]
TKR		
Distal DVT, proximal DVT, no VTE, PE occur on rivaroxaban	Dirichlet[b] (145.3; 19.6; 662.1; 1)	[251, 256]
Distal DVT, proximal DVT, no VTE, PE occur on enoxaparin	Dirichlet[b] (168.7; 25; 318.6; 1.74)	[256]
Distal DVT, proximal DVT, no VTE, PE occur on dabigatran	Dirichlet[b] (169; 14.9; 322; 1)	[256]
Major bleed occurs on rivaroxaban	Beta (19.75,1202.25)	[251, 256]
Major bleed occurs on enoxaparin	Beta (10,686)	[256]
Major bleed occurs on dabigatran	Beta (11,670)	[256]
Thromboprophylaxis Independent Parameters		
Major bleed results in death, stroke, no sequalae	Dirichlet[b] (3.99; 14; 363.01)	[131, 288]
Proximal DVT is symptomatic	Beta[c] (2.099,3.149)	[266, 267]
Distal DVT is symptomatic	Beta[c] (0.262,4.985)	[266]
PE is symptomatic (excludes immediately fatal)	Beta (15,31)	[281]
DVT (proximal or distal) fatal during treatment	Beta (18,4205)	[270]
PE fatal during treatment	Beta (20,1284)	[270]
PE fatal if asymptomatic	Beta (15,39)	[282]
PE immediately fatal	Beta (14, 47)	[282]
Distal DVT propagates to the proximal vein	Beta (6,24)	[268]
Proximal DVT propagates to PE	Beta (9, 8)	[269]
VTE detected pre-discharge (THR)	Beta (134,424)	[133]
VTE detected pre-discharge (TKR)	Beta (269,241)	[133]
Total costs	Lognormal, SD=0.2	
Preference Values		
Model Pathway Events (Multiplicative values)		
Major bleed & stroke & distal DVT (0.509)	Beta[c] (2.671,2.576)	[131, 291, 292, 300, 301]
Major bleed & stroke & proximal DVT (0.471)	Beta[c] (2.472,2.776)	
Major bleed & stroke & no VTE (0.548)	Beta[c] (2.876,2.372)	
Major bleed & stroke & PE (0.444)	Beta[c] (2.33,2.918)	
Major bleed & distal DVT (0.849)	Beta[c] (4.455,0.792)	
Major bleed & proximal DVT (0.785)	Beta[c] (4.12,1.128)	
Major bleed & no VTE (0.913)	Beta[c] (4.791,0.457)	
Major bleed & PE (0.739)	Beta[c] (3.878,1.37)	
Distal DVT (0.875)	Beta[c] (4.592,0.656)	
Proximal DVT (0.809)	Beta[c] (4.246,1)	
No VTE (0.941)	Beta[c] (4.938,0.31)	
PE (0.762)	Beta[c] (3.999,1.249)	

a. The ordering of the parameters of the Dirichlet distribution, as shown in the parenthesis, refers to the same ordering of the parameters described in the first column. The alpha and beta parameters of the Beta distribution are described in parentheses.

b. Where the sample size for each event is different the Dirichlet distribution was calculated based on a common denominator.

c. In the absence of other information, standard deviation for the Beta distribution was fixed at 0.2 during the fitting process.

DVT=deep vein thrombosis; **VTE**=venous thromboembolism; **PE**=pulmonary embolism; **THR**=total hip replacement; **TKR**=total knee replacement; **SD**=standard deviation.

4.5 Results

4.5.1 Basecase Analysis

4.5.1.1 Total Hip Replacement

The basecase CEA and CUA indicate that the 35 day rivaroxaban strategy dominates both 35 days of dabigatran etexilate and 14 days of enoxaparin sodium. The ICERs for dabigatran etexilate relative to enoxaparin sodium were €50,625 per LYG and €33,750 per QALY.

4.5.1.2 Total Knee Replacement

The basecase CEA and CUA indicate that the 14 day rivaroxaban strategy dominates both 10 days of dabigatran etexilate and 14 days of enoxaparin sodium. Dabigatran etexilate also dominates enoxaparin sodium.

The basecase results are summarised in Table 19.

Table 19. Results of the basecase analyses of the 180 day model

	Cost (€)	Incremental Cost (€)	Effect (QALY)	Incremental Effect (QALY)	ICER (QALY)	Effect (LYG)	Incremental Effect (LYG)	ICER (LYG)
THR								
Rivaroxaban	13342		0.9391			0.9988		
Enoxaparin	13360	17	0.9291	-0.0101	Dominated by rivaroxaban	0.9922	-0.0066	Dominated by rivaroxaban
Dabigatran	13441	99	0.9315	-0.0076	Dominated by rivaroxaban	0.9938	-0.005	Dominated by rivaroxaban
TKR								
Rivaroxaban	13192		0.9317			0.9945		
Dabigatran	13264	72	0.9244	-0.0073	Dominated by rivaroxaban	0.9900	-0.0045	Dominated by rivaroxaban
Enoxaparin	13269	77	0.9234	-0.0083	Dominated by rivaroxaban	0.9893	-0.0052	Dominated by rivaroxaban

All costs are in €, year 2008 values

QALY=quality adjusted life year; **ICER**=incremental cost-effectiveness ratio; **LYG**=life years gained; **THR**=total hip replacement; **TKR**= total knee replacement.

4.5.2 One-Way Sensitivity Analysis

All model parameters were varied in a one-way SA.

4.5.2.1 Total Hip Replacement

Rivaroxaban versus both comparators

Rivaroxaban continued to dominate both comparators in all but four instances of parameter variation. All such instances pertained to thromboprophylatic dependent probabilities:

When the probabilities that a proximal DVT or a PE will occur on enoxaparin sodium were individually decreased to the 95% CI lower limit, the ICERs of rivaroxaban relative to enoxaparin sodium were €1,642/QALY and €248/QALY respectively.

When the probability that a PE will occur on rivaroxaban was increased to the 95% CI upper limit the ICER (rivaroxaban vs. enoxaparin) was €699/QALY.

When the probability of a proximal DVT being symptomatic was decreased by 50%, the ICER (rivaroxaban vs. enoxaparin) was €1,335/QALY.

Of note, in theses four instances, rivaroxaban continued to dominate dabigatran etexilate.

Dabigatran etexilate versus enoxaparin sodium

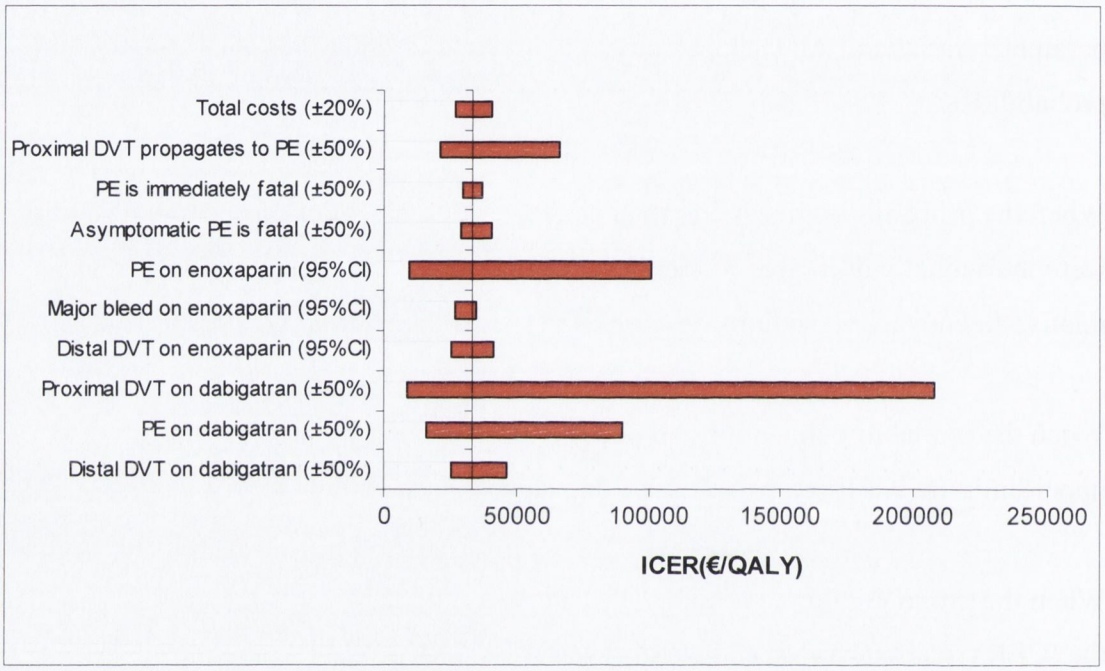
The basecase ICER for dabigatran etexilate versus enoxaparin sodium was €33,750/QALY.

Enoxaparin sodium dominated when the probability that a proximal DVT would occur on enoxaparin sodium was decreased to the 95% CI lower limit.

The ICER was sensitive to a number of other parameter changes, the most significant of which are illustrated in Figure 9. The €45,000/QALY threshold was reached in five instances; when the probability of a PE occurring on enoxaparin sodium was decreased to the 95%CI lower limit (€101,000/QALY), when the probabilities of a

distal DVT (€46,842/QALY), proximal DVT (€208,000/QALY) or a PE (€66,154/QALY) occurring on dabigatran etexilate were individually increased by 50% and when the probability that a proximal DVT will progress to a PE (€66,154/QALY) was decreased by 50%.

Figure 9: Total hip replacement 180 day model: Tornado diagram for the one-way sensitivity analysis. Showing the variation around the ICER (€33,750/QALY) for the basecase of dabigatran vs. enoxaparin after THR (€, year 2008 values)



ICER=Incremental cost effectiveness ratio; **THR**=total hip replacement; **DVT**=deep vein thrombosis; **PE**=pulmonary embolism.

4.5.2.2 Total Knee Replacement

Rivaroxaban versus both comparators
Rivaroxaban continued to dominate both comparators in all but two instances, both of which pertained to thromboprophylatic dependent probabilities:

When the probability that a distal DVT will occur on dabigatran etexilate was decreased by 50%, the ICER (rivaroxaban vs. dabigatran etexilate) was €6,255/QALY and enoxaparin sodium was dominated by both comparators.

When the probability that a distal DVT will occur on enoxaparin sodium was decreased by 50%, the ICER (rivaroxaban vs. enoxaparin sodium) was €1,521/QALY and dabigatran etexilate was dominated by both comparators.

Dabigatran etexilate versus enoxaparin sodium
In the basecase analysis, dabigatran etexilate dominated enoxaparin sodium. This was sensitive to a number of parameter changes:

Enoxaparin sodium dominated dabigatran etexilate on five occasions; when the probabilities that a distal DVT, a proximal DVT or a PE occurring on dabigatran etexilate were individually increased by 50% and when the probabilities that a distal DVT and a proximal DVT occurring on enoxaparin sodium were individually decreased by 50%.

The model was sensitive to a number of further parameter changes. When the probability that a major bleed will occur on dabigatran etexilate was increased to the 95% CI upper limit, the ICER (dabigatran etexilate vs. enoxaparin sodium) was €31,000/QALY. When the probability that a major bleed will occur on enoxaparin sodium was decreased to the 95% CI lower limit, this ICER was €22,857/QALY. When the total costs were increased by 20%, this ICER was €29,763/QALY.

4.5.3 Probabilistic Analysis

4.5.3.1 Total Hip Replacement

In order to validate the PSA model, the mean expected costs and QALYs for the PSA were compared to the results of the deterministic analysis. As a further validation of the PSA model, it was demonstrated that the results did not appreciably change on three successive runs of the PSA, as illustrated in Table 20.

Table 20. Total hip replacement 180 day: ICERs for the deterministic and probabilistic (30,000 simulations) analyses

	Cost (€)	Effect (QALY)	ICER (€/QALY)
Basecase results			
Rivaroxaban	13342	0.9391	Rivaroxaban dominates enoxaparin Rivaroxaban dominates dabigatran
Enoxaparin sodium	13360	0.9291	
Dabigatran etexilate	13441	0.9315	Dabigatran vs. enoxaparin = 33750
PSA mean results			
Rivaroxaban	13628	0.9391	Rivaroxaban dominates enoxaparin Rivaroxaban dominates dabigatran
Enoxaparin sodium	13644	0.9290	
Dabigatran etexilate	13721	0.9313	Dabigatran vs. enoxaparin =33478
PSA run 2 mean results			
Rivaroxaban	13617	0.9379	Rivaroxaban dominates enoxaparin Rivaroxaban dominates dabigatran
Enoxaparin sodium	13641	0.9278	
Dabigatran etexilate	13720	0.9301	Dabigatran vs. enoxaparin = 34348
PSA run 3 mean results			
Rivaroxaban	13619	0.9387	Rivaroxaban dominates enoxaparin Rivaroxaban dominates dabigatran
Enoxaparin sodium	13652	0.9286	
Dabigatran etexilate	13730	0.9309	Dabigatran vs. enoxaparin =33913

All costs are in €, year 2008 values

ICER=incremental cost effectiveness ratio; **PSA**=probabilistic analysis; **QALY**=quality adjusted life year.

Monte Carlo Error: With 30,000 PSA simulations, the MC error was 0.74 (when expressed as a percentage of the mean opportunity loss) at a threshold of €45,000 per QALY. An illustration of the calculation of the MC Error is shown in Table 21.

Table 21. Total hip replacement: Calculation of the Monte Carlo Error at €45,000/QALY (30,000 simulations).

Iteration	NMB (where λ=€45,000/Qaly)				Max NMB - Rivaroxaban NMB[c]
	Rivaroxaban	Enoxaparin	Dabigatran	Max NMB[b]	
1	26778	27448	22069	27448	669
2	34472	30270	34310	34472	0
3	30169	29866	31386	31386	1217
4	34031	31433	26449	34031	0
5	27342	34426	25004	34426	7084
6	31327	31143	34160	34160	2832
n=30,000					
Mean	28609[a]	28148	28187		1852[d]
					MC Error = 13.74[e] (0.74% of the mean opportunity loss)[f]

All values in the table are rounded to the nearest full unit.

a. Rivaroxaban is the optimal strategy with current information (has highest expected mean NMB)
b. The maximum expected NMB across each PSA iteration is shown
c. Max NMB - Rivaroxaban NMB is the potential opportunity loss when rivaroxaban is chosen as the strategy of choice
d. The mean opportunity loss is shown
e. The MC Error is calculated as:

$$\text{MC Error} = (\sigma\,(\Sigma_{i=1}^{30000}(\text{Max NMB-Rivaroxaban NMB}))/\sqrt{30000}$$

f. The MC Error can be expressed as a percentage of the mean opportunity loss

THR=total hip replacement; **NMB** = net monetary benefit; **λ** = cost-effectiveness threshold; **n**=number of PSA iterations; **MC** =Monte Carlo.

The cost-effectiveness plane for THR, illustrating the individual scatterplots for rivaroxaban compared with enoxaparin sodium and dabigatran etexilate compared with enoxaparin sodium is shown in Figure 10a.

Figure 11a illustrates the CEAC for the comparison between the three strategies. Rivaroxaban has the highest probability of being the most cost-effective strategy over the threshold range of €0 - €100,000 per QALY. At a threshold of €45,000 per QALY, the probability that rivaroxaban is the most cost-effective strategy was 39%, followed by dabigatran etexilate at 31% and enoxaparin sodium at 30%.

Over the threshold range €0 - €100,000 per QALY, the CEAF (also depicted in Figure 11a) for the decision between the three strategies traces the CEAC for rivaroxaban.

4.5.3.2 Total Knee Replacement

The mean PSA outcomes were compared to the results of the deterministic analysis and are shown in Table 22. It is also demonstrated that the PSA results did not change appreciably over three successive runs.

Table 22. Total knee replacement 180 day: ICERs for the deterministic and probabilistic (30,000 simulations) analyses

	Cost (€)	Effect (QALY)	ICER (€/QALY)
Basecase results			
Rivaroxaban	13192	0.9317	Rivaroxaban dominates enoxaparin Rivaroxaban dominates dabigatran
Dabigatran etexilate	13264	0.9244	Dabigatran dominates enoxaparin
Enoxaparin sodium	13269	0.9234	
PSA mean results			
Rivaroxaban	13489	0.9297	Rivaroxaban dominates enoxaparin Rivaroxaban dominates dabigatran
Dabigatran etexilate	13559	0.9214	Dabigatran dominates enoxaparin
Enoxaparin sodium	13564	0.9202	
PSA run 2 mean results			
Rivaroxaban	13479	0.9293	Rivaroxaban dominates enoxaparin Rivaroxaban dominates dabigatran
Dabigatran etexilate	13564	0.9211	Dabigatran dominates enoxaparin
Enoxaparin sodium	13576	0.9198	
PSA run 3 mean results			
Rivaroxaban	13456	0.9309	Rivaroxaban dominates enoxaparin Rivaroxaban dominates dabigatran
Dabigatran etexilate	13534	0.9226	Dabigatran dominates enoxaparin
Enoxaparin sodium	13547	0.9213	

All costs are in €, year 2008 values
ICER=incremental cost effectiveness ratio; **PSA**=probabilistic analysis; **QALY**=quality adjusted life year.

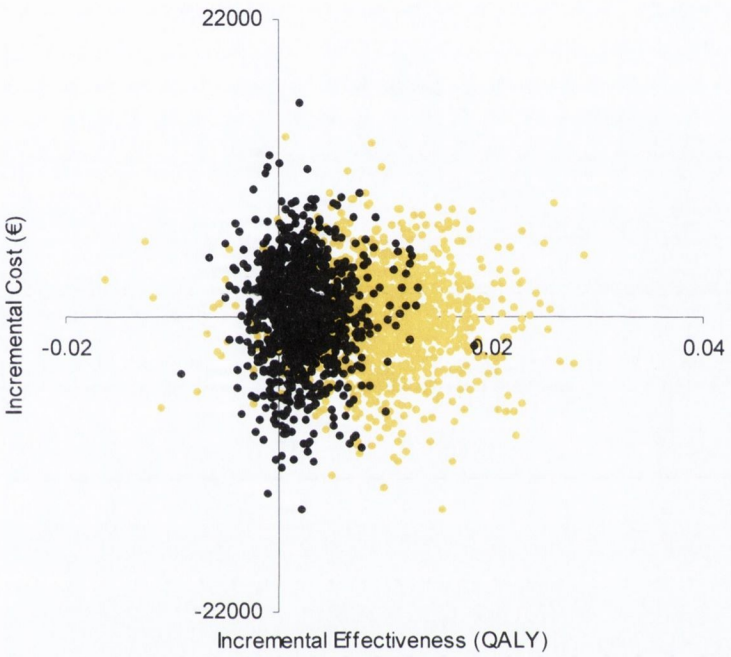
With 30,000 iterations the MC error (at €45,000 per QALY) was 0.71% of the mean opportunity loss.

The cost-effectiveness plane for TKR is shown in Figure 10b. The results of the PSA are presented on the CEAC in Figure 11b; rivaroxaban has the highest probability of being the most cost-effective strategy over the threshold range of €0- €100,000 per QALY. At a threshold of €45,000 per QALY, the probability that rivaroxaban is the most cost-effective strategy was 42%, followed by dabigatran etexilate at 32% and enoxaparin sodium at 26%.

Figure 11b also indicates that, over the threshold range €0- €100,000 per QALY, the CEAF for the decision between the three strategies traces the CEAC for rivaroxaban.

Figure 10: Cost-effectiveness plane for the 180 day model.
Rivaroxaban and dabigatran etexilate compared with enoxaparin sodium after (**a**) total hip replacement and (**b**) total knee replacement; showing 1000 points drawn from 30,000 for each drug. Costs are in €, year 2008 values.

(a) Total Hip Replacement



(b) Total Knee Replacement

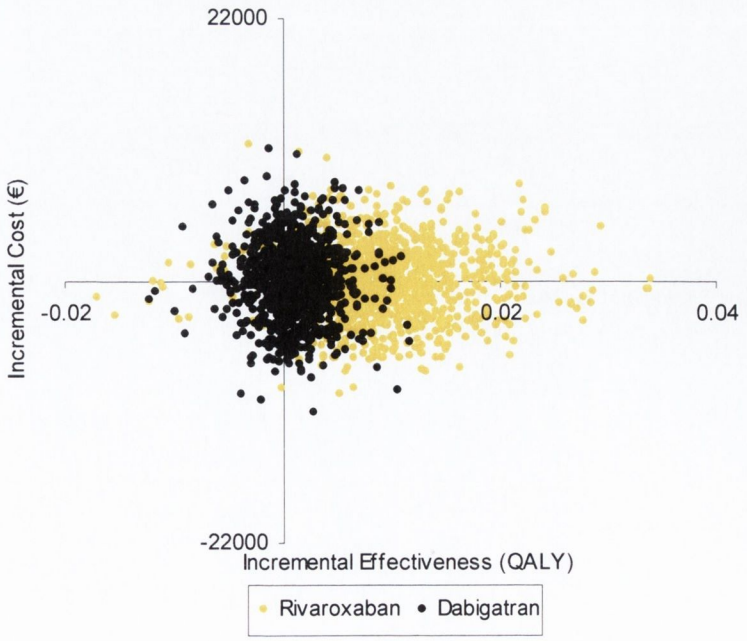
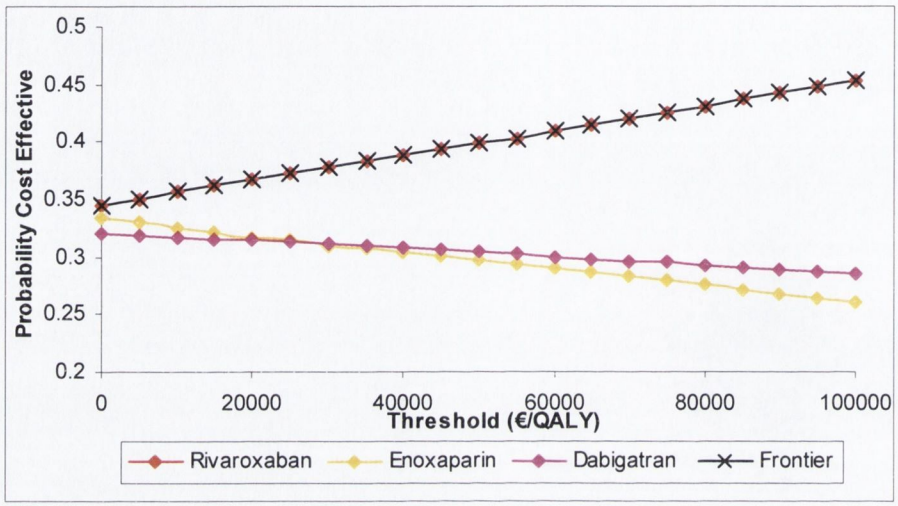
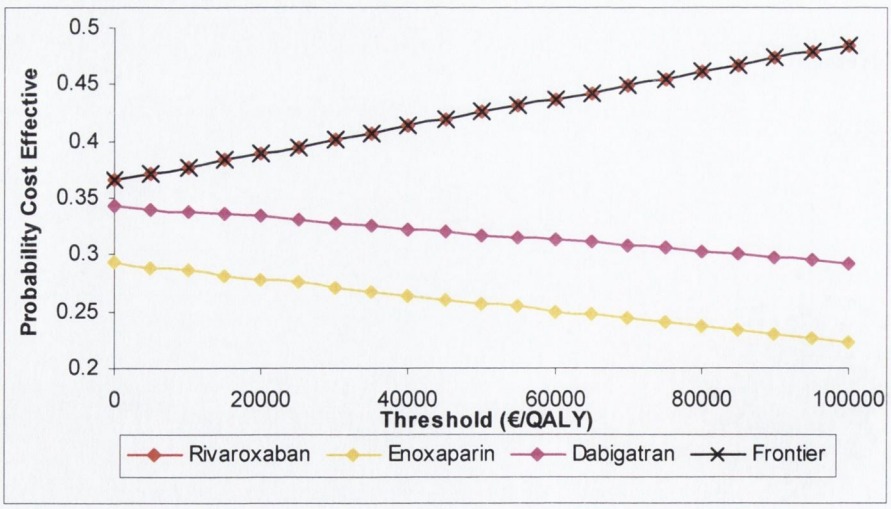


Figure 11. Cost-effectiveness acceptability curve for the 180 day model.
(**a**) total hip replacement and (**b**) total knee replacement. The cost-effectiveness acceptability frontier shows the optimal strategy over the range of threshold values. Costs are in €, year 2008 values.

(a) Total Hip Replacement



(b) Total Knee Replacement



4.6 Discussion

This is the first published CEA that simultaneously evaluates the cost-effectiveness of dabigatran etexilate, rivaroxaban and enoxaparin sodium as VTE prophylaxis after THR and TKR.

Total Hip Replacement: Deterministic analyses indicate that when all three strategies are considered, rivaroxaban dominates. All model parameters were varied in a one way SA. This result was sensitive to four parameter variations; however, the €45,000 per QALY (and the €20,000 per QALY) thresholds for rivaroxaban versus enoxaparin sodium were not reached in these instances.

Although the deterministic analyses indicate that rivaroxaban is the strategy of choice, the payer is also likely to be interested in how dabigatran etexilate compares to enoxaparin sodium. The basecase ICERs for dabigatran etexilate compared to enoxaparin sodium were €50,625 per LYG and €33,750 per QALY. Crucially, this ICER (€33,750 per QALY) was considered cost-effective at the time of the analysis (in 2008 the payer threshold was €45,000 per QALY). In recent times this threshold has dropped to €20,000 per QALY and the drug would no longer be considered cost-effective for this indication. This ICER is sensitive to a number of parameter variations. Enoxaparin sodium dominated in one instance (when the risk of a proximal DVT occurring on enoxaparin sodium was decreased). The model was sensitive to a number of other parameter changes. The €45,000 per QALY threshold was reached in five instances; those pertaining to the risks of proximal DVT, distal DVT or a PE occurring on dabigatran etexilate, the risk of a PE occurring on enoxaparin sodium and the risk that a proximal DVT would progress to a PE.

The PSA indicates that, at a threshold of €45,000 per QALY, rivaroxaban has the highest probability (39%) of being the most cost-effective strategy. Indeed, as depicted in Figure 11a, rivaroxaban has the highest probability of being the most cost-effective strategy (as indicated by the CEAC) and is the optimal choice (as indicated by the CEAF) over the threshold range €0 - €100,000 per QALY.

The results of the PSA are also illustrated on the cost-effectiveness plane (Figure 10a). When the two interventions are compared to enoxaparin sodium, the

incremental costs for dabigatran etexilate and rivaroxaban are comparable, but the incremental effect of rivaroxaban is greater than that of dabigatran etexilate. The overlap in the scatterplot indicates that there is uncertainty that rivaroxaban is more cost effective than dabigatran etexilate.

Total Knee Replacement: Deterministic analyses indicate that rivaroxaban is the less costly and more effective option. This result was robust to all but two parameter changes, the payer thresholds (€20,000 per QALY and €45,000 per QALY) were not reached on these occasions.

In the basecase, dabigatran etexilate dominated enoxaparin sodium. In five instances of parameter variation (all pertaining to thromboprophylatic dependent probabilities), enoxaparin sodium dominated dabigatran etexilate. The model was further sensitive to the probability of a major bleed occurring on either drug and to the total direct medical costs. The €20,000 per QALY threshold (but not the €45,000 per QALY threshold) was surpassed on each of these three instances.

At a threshold of €45,000 per QALY, rivaroxaban has the highest probability of being the most cost-effective option, at 42%. Again, over the entire threshold range, rivaroxaban has the highest probability of being the most cost-effective option and is the optimal strategy as depicted in Figure 11b.

The results of the PSA were also illustrated on the cost-effectiveness plane (Figure 10 b). Similar to the THR model, when the two interventions are compared to enoxaparin sodium, the incremental costs for dabigatran etexilate and rivaroxaban are comparable, but the incremental effect of rivaroxaban is greater. Again, overlap in the scatterplots indicates that there is uncertainty that rivaroxaban is more cost-effective than dabigatran etexilate.

Monte Carlo sampling estimates in the PSA are subject to a potential error [66]. The approach taken here to ensuring that the Monte Carlo exception was estimated with sufficient accuracy was to increase the number of iterations until the PSA results did not change appreciably on repeated runs. As a further measure, the standard error of a Monte Carlo analysis can also be calculated to ensure that it is less than some

acceptable level [66]. A systematic literature search indicates that this defined acceptable level has not been described in the literature. In this analysis, a small error level of about 0.7% of the mean opportunity loss was considered acceptable. The running time for 30,000 iterations was about 15 seconds.

The probabilities of treatment efficacy (VTE events) and major bleeding for the three strategies were derived from pivotal clinical trials [251, 253, 255, 256] and the Bucher *et al* [234] method of adjusted indirect comparison was used to determine point estimates.

The adjusted indirect comparison (Table 11) indicates that, after THR, rivaroxaban offers better efficacy with less accompanying haemorrhage as compared to dabigatran etexilate. It is not unexpected therefore, that rivaroxaban is likely to be the more cost-effective option, given comparable pricing for both drugs.

The adjusted indirect comparison for the TKR model (Table 12) indicates that (as compared to dabigatran etexilate), rivaroxaban is more effective in preventing total VTE events; however it is associated with a very small increased risk of haemorrhage. The ongoing costs and preference levels commensurate with stroke in the proportion of patients who had developed a stroke secondary to a prophylaxis related major bleed are not captured in this short time horizon model. It is not surprising therefore, that when the 180 day pharmacoeconomic model is used rivaroxaban is again identified as more cost-effective than dabigatran etexilate.

In other jurisdictions, there will be differences in the availability of healthcare resources, clinical practice patterns and relative prices. In this study, resource use and unit cost data are presented separately to facilitate adaption of the model to other settings. This economic model has subsequently been adapted to other jurisdictions [312, 313].

The decision analytic modelling skills that I have developed in this study will be of benefit in future analyses within other therapeutic areas. The decision tree is widely used in evaluations in disease states with distinct events that occur, with a given probability, within a relatively limited time horizon [41]. The decision tree, however, has important limitations. Within the tree, events are implicitly taken as occurring

over an instantaneous discrete period. As there is no explicit time variable in a decision tree, those elements of an economic evaluation that are time dependent can be difficult to implement. Also a tree can become very complex when used to model complicated long-term prognoses, particularly relating to chronic diseases [17]. For diseases with an ongoing risk (particularly where this risk is continuously changing), over a long time frame, Markov models are more appropriate. An objective of the next chapter of this thesis will be the development of Markov modelling skills.

There are a number of limitations to this study.

There are no clinical trials that directly compare rivaroxaban and dabigatran etexilate. The limitations to the indirect comparison performed have been discussed (section 3.4.5). Of most concern is the difference in the duration of enoxaparin sodium between the trials (most notably the THR trials) and the differing definition of major bleeding between trials [251, 253, 255, 256]. In the RE-NOVATE and RE-MODEL studies, surgical site bleeding that fulfilled the criteria of a major bleeding event was categorised as a major bleed [255, 256]. By contrast, surgical site bleeding was not included in the major bleeding category in RECORD 2 and RECORD 3 unless they required re-operation or were fatal [251, 253]. It has been acknowledged that this may have been responsible for the relatively low overall bleeding rates observed with rivaroxaban [253]. Also the pivotal trial used different independent venogram adjudication committees to interpret venograms [251, 253, 255, 256]. The reported frequency of asymptomatic DVT in clinical trials is significantly influenced by the centre in which the venograms are adjudicated thus introducing different event rates and therefore heterogeneity [314].

In acknowledgement of concerns regarding the indirect comparison, both models were subjected to an extensive SA. Table 11 and Table 12 illustrate the RR (efficacy and safety) of dabigatran etexilate versus rivaroxaban after THR and TKR. The wide CI indicates a large degree of uncertainty surrounding these RR values (particularly in the THR model). The knowledge of how to calculate these CIs was only gained after completion of the SA. It is a limitation that this particularly high degree of uncertainty is not captured in the SA.

There is a lack of Irish cost and preference data. As such, values from disparate sources from a range of jurisdictions have been used. However, the elicitation exercises performed in determining the distributions applied to these input data acknowledged their inherent uncertainty.

PSA allows the uncertainty in individual parameters to be fully characterised; [315] however, probabilistic models still employ the analysts' judgements about the range of variation in key parameters and their distributional form; hence, the importance of transparency [316]. There are no guidelines currently in Ireland as to the handling of ranges fitted to PSA distributions. The distributional assumptions chosen in this analysis have been justified (see section 4.4.8). Binomial data were available for the majority of the probability parameters; the Beta distribution was a pragmatic choice. If this economic model had instead included RRs as parameters; the CIs for the RR would have been an appropriate distributional choice [317]. The distribution of cost data is typically truncated and positively skewed. Gamma or log-Normal distributions can accommodate this skewness [318]. In their review of technology assessment reports prepared for NICE, Andronis *et al* concluded that the log-Normal distribution was most commonly chosen for cost-related parameters [319]. To reflect this, the log-Normal distribution was chosen here, however the Gamma distribution might have been considered instead [319]. In this analysis, the preference values are all bounded on the 0-1 interval; the pragmatic approach to fit a Beta distribution was taken. However, this distribution would not be the appropriate choice should any health states be ranked worse than death [320, 321]. In such instances, either a log-Normal or Gamma distribution could be fitted [320]. It has been highlighted elsewhere that economic evaluations are sensitive to choice of distribution [318]; it is a limitation that this structural uncertainty (particularly relating to the choice of distribution fitted to the costs) was not investigated here.

Preference value catalogues for single health states have been developed at a population level. Conversely, off-the-shelf values for joint health states are lacking. In practice, estimation of the joint health-states preference values relies on several predictive models based on the single health-state values (including the multiplicative, disutility and additive models) [322]. In this economic evaluation, the multiplicative approach was taken. For example, the values for major bleed and stroke are 0.97 and

0.6 respectively; the joint health-states value for both a major bleed and a stroke is 0.582 (i.e. 0.97 × 0.6). This approach is probably the most commonly used one in clinical decision analysis [322]. Its use has also been supported in the literature [323]. Recent research however has revealed that the multiplicative model results in a numerically large and statistically significant difference from the preference value of subjects with both conditions. It concluded that the multiplicative approach may result in double-counting [322]. Since no existing models can accurately predict joint health-states preference values based on single health-state preference values, research to identify better models has been recommended elsewhere [322]. Certainly further work on our economic model might involve investigating the impact of using different predictive models on the ICER.

A further source of structural uncertainty inherent in our model surrounds the choice of thromboprophylaxis independent probabilities and preference values. These parameters were obtained through a systematic literature search. The reasons for excluding other located values have been made explicit; however a structural uncertainty analysis could have investigated the impact of these values on the ICER. In particular, the UK General Population Health State preference value [302] was excluded as it was lower than the values associated with the DVT and PE from Cykert *et al* [291]. An additional structural uncertainty analysis here might have used this UK Population value and applied a disutility for all subsequent events.

The pivotal trials detected DVTs venographically. The model uses an alternative source to estimate the probability of an asymptomatic VTE event becoming symptomatic. Venography is the most sensitive diagnostic tool for identifying proximal and distal thrombi and has been used widely in clinical trials. However, its use in clinical trials is controversial [124]. In such trials, patients with detected asymptomatic DVT typically receive anticoagulant therapy, which alters the natural history of the disease and undoubtedly lowers the rate of symptomatic events [125].

Enoxaparin sodium was used as the comparator LMWH to accommodate the pivotal clinical trials. Other LMWHs are also available for use in Ireland. Reassuringly however, it has been reported that studies which have directly compared different LMWHs have shown them to be comparable in efficacy in the treatment and

prevention of thromboembolism [263]. The impact of using a weighted average cost (assuming a 50:50 notional market share for enoxaparin sodium and tinzaparin) on the ICER was investigated. Both the THR and TKR models were robust to this change; rivaroxaban continued to dominate both comparators.

As yet, there is no generic enoxaparin product available in Ireland. LMWHs are complex biological drug products derived from animal tissue [324]. Generic biologics are referred to as biosimilars [325]. The IPHA/HSE Agreement does not indicate how biosimilar medicines will be priced relative to the biological reference medicine [15]. Therefore, the impact of using a 'generic' price for enoxaparin has not been investigated in this analysis.

The recommended duration of anticoagulation treatment remains controversial [326]. In this analysis, the treatment duration was assumed to be 90 days for symptomatic distal DVT and 180 days for symptomatic proximal DVT or PE [180]. Indeed, contrary to this, the British Society for Haematology recommends at least three months treatment for proximal DVT or PE and only six weeks treatment for a confirmed distal DVT [179]. However, in the SA, the direct medical costs and preference values were awarded wide distributions in acknowledgement of any intrinsic uncertainties.

Patients undergoing MOS are at a particularly high risk for VTE [78, 129-133]. Other risk factors exist including a number which were not exclusion criteria in the pivotal clinical trials (increasing age, congestive heart failure, sepsis, trauma, vasculitis [80] and ethnicity [127]). In RE-MODEL and RE-NOVATE the primary efficacy results were consistent in the predefined subgroup analyses by age, sex, body-mass index, time to first oral dose, and duration of treatment [255, 256]. The RECORD trials make no mention of sub-group analyses [251-253]. It was therefore not possible to explore sub-groups based on baseline VTE risk (additional to MOS) in this economic analysis.

Rivaroxaban and dabigatran etexilate are comparably priced. In this analysis, rivaroxaban dominates enoxaparin sodium after both THR and TKR. The results of this analysis could be used to prompt a price review of dabigatran etexilate. One pragmatic way to achieve this might involve a one way SA to investigate the impact of changing the price of dabigatran etexilate on the ICER (dabigatran etexilate vs.

enoxaparin sodium). The price at which dabigatran etexilate dominates enoxaparin sodium would then be chosen as the recommended reimbursement price.

4.7 Conclusions

Basecase analysis indicates that when both rivaroxaban and dabigatran etexilate are compared with enoxaparin sodium, rivaroxaban is the less costly and more effective option following THR and TKR. One-way SA indicates that the results are sensitive to a number of parameter variations. In both disease states, PSA indicates that rivaroxaban is the most cost-effective strategy at a payer threshold of €45,000 per QALY. However, overlap in the respective scatterplots indicates that there is uncertainty regarding this strategy being more cost-effective than dabigatran etexilate when both are compared with enoxaparin sodium.

Chapter 5

A Lifetime Cost-Effectiveness Model Comparing Rivaroxaban, Dabigatran etexilate and Enoxaparin sodium as Thromboprophylaxis after Total Hip- and Total Knee- Replacement

5 A LIFETIME COST-EFFECTIVENESS MODEL COMPARING RIVAROXABAN, DABIGATRAN ETEXILATE AND ENOXAPARIN SODIUM AS THROMBOPROPHYLAXIS AFTER TOTAL HIP- AND TOTAL KNEE- REPLACEMENT 145

5 A Lifetime Cost-Effectiveness Model Comparing Rivaroxaban, Dabigatran etexilate and Enoxaparin sodium as Thromboprophylaxis After Total Hip- and Total Knee- Replacement

5.1 Introduction

In contrast to the extensive documentation available on the short-term outcome of patients with acute DVT, less information is available on the long-term clinical course of the disease [85]. Recent studies however indicate that VTE is a disease with long-term consequences, including the risk of VTE recurrences and the development of PTS [82-89]. Indeed it has been recommended that thromboprophylaxis models should adopt two different time horizons (a short-term and a long-term horizon), since the prognosis of patients after an episode of VTE is impacted both by the acute events and by recurrence of VTE and PTS [124]. It would also be appropriate to consider ongoing costs and preference levels commensurate with stroke, in the proportion of patients who had developed a stroke, secondary to a prophylaxis related major bleed.

It is hypothesised that strategies that reduce VTE would lead to a similar reduction in the incidence of recurrence and PTS. There are no direct RCTs that investigate these long-term outcomes in the three strategies under investigation. As such a long-term time horizon model will rely upon literature based extrapolation.

A systematic literature search has previously identified a number of model based economic evaluations of thromboprophylaxis strategies after THR and TKR. Five such models were located which combined a decision tree with a Markov process [200, 202, 206, 207, 223]. All had a lifetime time horizon (see Table 9).

5.2 Objective

The objective of this study was to evaluate the cost-effectiveness of rivaroxaban, dabigatran etexilate and enoxaparin sodium for the prophylaxis of VTE and associated long-term complications after THR and TKR in the Irish healthcare setting. The time horizon chosen was the full life of the patient, in accordance with previous economic evaluations which have combined a decision tree with a Markov process [200, 202, 206, 207].

5.3 Method

The impact of taking into account the long-term events associated with VTE (recurrent VTE and PTS) and stroke was investigated by extending the time horizon of the thromboprophylaxis economic evaluation from 180 days to lifetime. The incremental cost per QALY and incremental cost per LYG were computed to formally compare treatment strategies.

At the time of this analysis (2008), the majority of pharmaceuticals which had been reimbursed had a cost-effectiveness threshold of €45,000 per QALY or less [4]. In the main, this threshold was used in this analysis.

5.3.1 The Model

Figure 12 (a, b and c) illustrates the thromboprophylaxis model, which was developed using TreeAge Pro 2008® (TreeAge Software Inc, Williamstown, MA, USA). The model combines a 180 day decision tree module (Figure 12a) and a lifetime Markov process module (Figure 12b). It evaluated the cost-effectiveness of rivaroxaban, dabigatran etexilate and enoxaparin sodium for the prophylaxis of VTE after THR and TKR. The TreeAge Pro 2008® model, in its entirety, is presented in appendix 1.

The structure of the decision tree component (Figure 12a) of the model has previously been described (section 4.4.1). Briefly, on receiving thromboprophylaxis, there is a probability of developing a prophylaxis-related major bleed, which may result in death, a stroke or in no sequelae. All patients are at risk of developing a surgery related distal DVT, a proximal DVT or a PE. Entry into the Markov process is based on the final state of the decision tree. In particular, the probability of future events is conditionally independent of treatment.

The Markov process (Figure 12b) branches off from each terminal node of the decision tree. Patients surviving the decision tree module enter the Markov process in one of five health states: 'Stroke'; 'Treated VTE'; 'Untreated VTE'; 'No VTE' and 'Death' (absorbing state). All patients in the 'Stroke', 'Treated VTE', 'Untreated VTE', 'No VTE' states and the subsequent 'PTS' states are at risk of all cause mortality. Patients who develop a stroke in the decision tree remain permanently

disabled and enter the Markov process in the 'Stroke' state, where they remain until death or the end of the simulation. Patients who survived a symptomatic, treated VTE in the decision tree enter the 'Treated VTE' state. Patients who survived an asymptomatic, untreated VTE enter the 'Untreated VTE' state. Patients who had no VTE event and those who had recovered with no sequelae from a bleed enter the 'No VTE' state. Patients who had a fatal VTE or bleed enter the Markov process in the 'Death' state. In the Markov process, VTE events were modelled as transitory events (as depicted in Figure 12c), rather than health states.

In each one-year cycle, patients could develop symptoms of VTE or PTS or could die from other causes. Patients in the 'Treated VTE' or the 'Untreated VTE' states could remain in that state or develop a recurrent VTE or develop PTS or die. Patients in the 'No VTE' state could remain in that health state, or develop an idiopathic VTE or idiopathic PTS or die. A VTE may be symptomatic or asymptomatic. It is assumed that a symptomatic VTE is detected and treated and patients may survive or die. It is assumed that an asymptomatic VTE will remain untreated and patients may survive or die.

A distinction was established between the first and subsequent years of PTS to allow for differences in diagnostic and treatment patterns and associated costs [197]. Once patients enter the 'PTS Year 1' state, they will either die or enter the 'PTS Maintenance' state. Once in the 'PTS Maintenance' state, they remain in this state until death or the end of the simulation. For model simplification purposes, it was assumed that once patients entered the PTS health states, they were no longer at risk of recurrent VTE events.

The same background mortality risk is assumed for all individuals regardless of health state.

The Markov structure was patterned onWolowacz *et al* [206]. In the Wolowacz *et al* model however, separate states exist for mild-moderate and severe PTS and patients in a PTS state remain at risk of recurrent VTE [206].

Figure 12: Lifetime thromboprophylaxis model – incorporating a decision tree (Figure 12a) and a Markov module (Figure 12b) with a Transition Sub-tree (Figure 12c)
Figure 12a: Decision tree (180 day acute phase) component. At the end of this acute phase, patients enter the Markov model (see Figure 12b) in 1 of 5 health states.

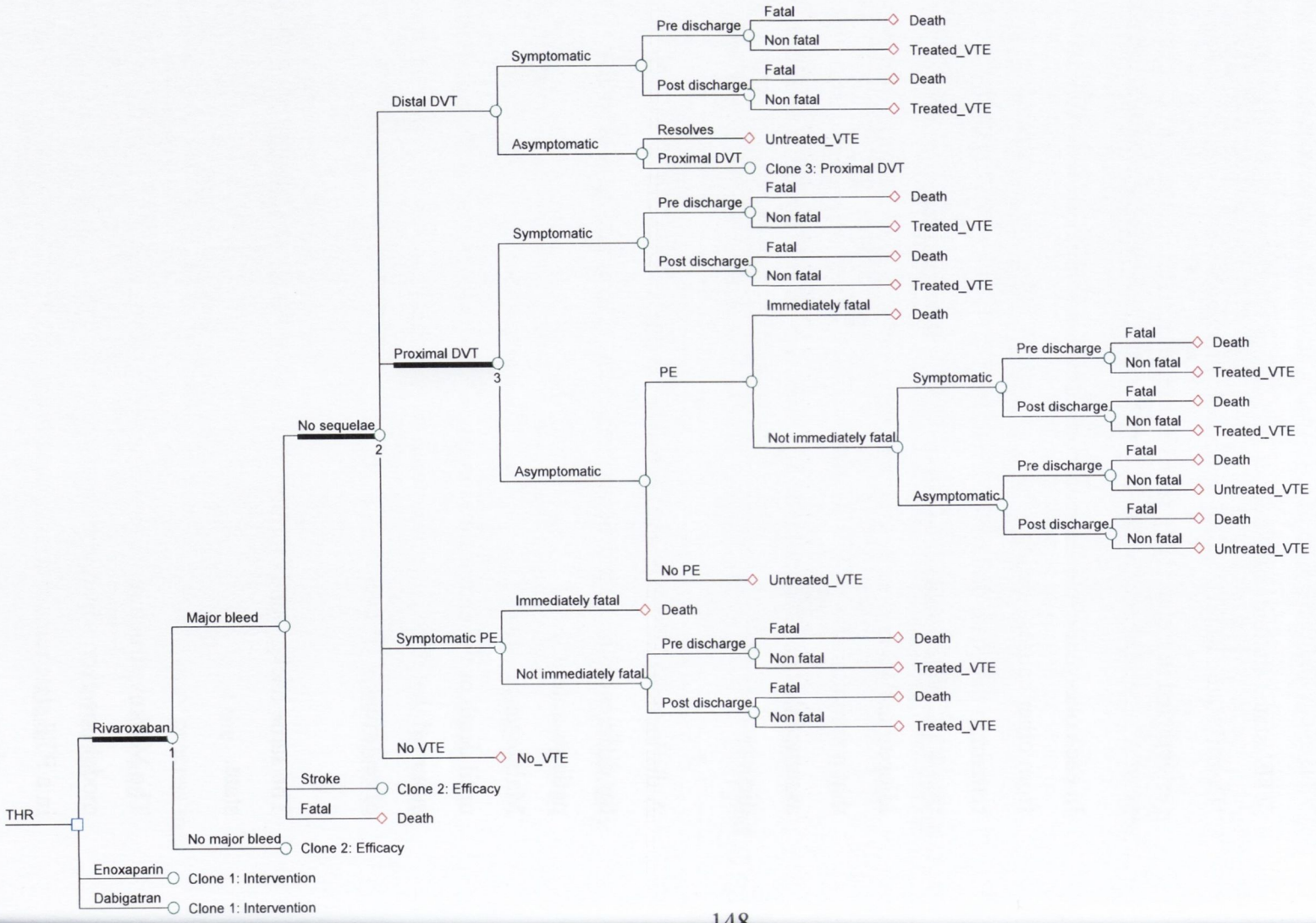


Figure 12 b: Chronic phase Markov model. Patients enter the Markov module in 1 of 5 health states: 'Death', 'Treated VTE', 'Untreated VTE', 'No VTE' or 'Stroke'. There are 2 further states: PTS Year 1 and PTS Maintenance. The 7 health states are represented as circles. Asymptomatic VTE and symptomatic VTE (represented in rectangles) are treated as isolated transient events. Movements between health states are depicted by solid arrows. Movements between states, which occur as a result of transient VTE events, are depicted by dashed arrows. The cycle length is 1 year. The time horizon is patient lifetime. **THR**=total hip replacement; **VTE**=venous thromboembolism; **DVT**=deep vein thrombosis; **PE**=pulmonary embolism; **PTS**=post thrombotic syndrome.

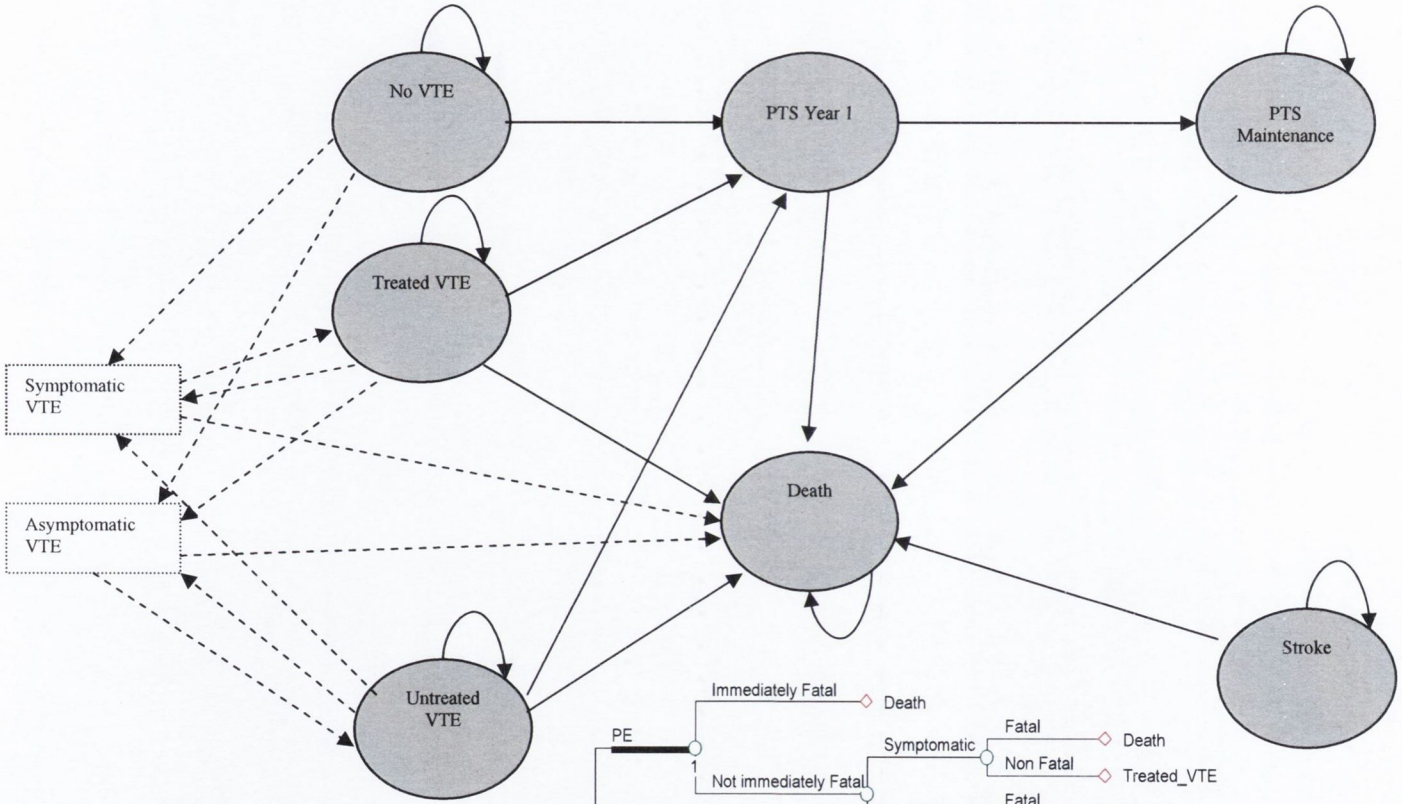
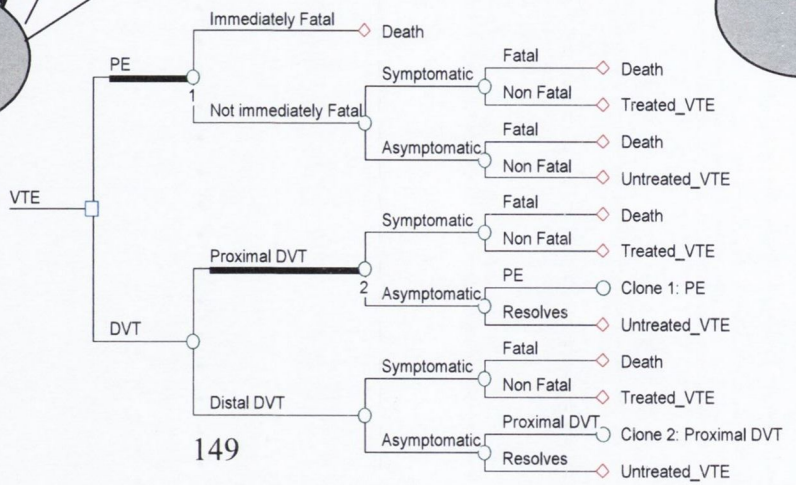


Figure 12c: VTE transition sub-tree. On leaving the sub-tree patients enter the Markov state described.



5.3.2 Age of Modelled Population

The mean age on entering the THR model was 63 years, which is a weighted average of the mean ages in the THR pivotal clinical trials [253, 255]. The weighted average of the mean ages in the TKR pivotal clinical trials was 67.5 years [251, 256]. In the interest of consistency, 63 years was also chosen as the mean age of patients entering into the TKR model.

The time horizon chosen was the full life of the patient, i.e. until either the patient died or reached the age of 100 years.

5.3.3 Clinical Inputs

The probabilities of treatment efficacy (VTE events) and major bleeding for rivaroxaban, dabigatran etexilate and enoxaparin have been described previously (section 4.4.2.1). Briefly, these were derived from pivotal clinical trials [251, 253, 255, 256] and the Bucher method of adjusted indirect comparison was used to determine point estimates [234]. All other probabilities were deemed to be independent of the thromboprophylatic agent.

The thromboprophylatic independent probabilities pertaining to the decision tree module have been described previously (section 4.4.2.2).

The probabilities pertaining to the Markov process were derived from a systematic search of literature published in the English language since 1980. Additional references were identified from the reference lists of published articles. Combinations of the following search terms were used:

For PubMed MeSH: arthroplasty, replacement, knee; arthroplasty, replacement, hip; venous thrombosis; pulmonary embolism; thromboembolism; economics; costs and cost analysis; intracranial hemorrhages; hemorrhage; postthrombotic syndrome; recurrence.

For Embase Thesaurus: hip arthroplasty; knee arthroplasty; deep vein thrombosis; venous thromboembolism; leg thrombosis; lung embolism; pharmacoeconomics; bleeding; brain haemorrhage; postthrombosis syndrome; recurrent disease.

CRD: The databases DARE, NHS EED and HTA were searched for relevant references on anticoagulant prophylaxis relating to TKR and THR.

For NICE: completed health technology appraisals were searched; all appraisals of anticoagulant prophylaxis relating to TKR and THR were retrieved.

5.3.3.1 Probabilities of VTE and PTS in the 'No VTE' State

The probabilities of developing idiopathic PTS and idiopathic VTE among patients in the 'No VTE' state were assumed to be the same as that of the general population.

A literature review by investigators for the 'International Consensus Statement on the Prevention and Treatment of VTE' revealed annual incidence rates of idiopathic DVT and PE, in North America and Europe, of 160 and 70 per 100,000 respectively [130].

The rate of idiopathic PTS was taken from a US population based study. A retrospective study in Olmsted County, Minnesota reviewed the medical records of a community population (1990 population of 106,470) in order to estimate the incidence of PTS. The overall age- and sex-adjusted incidence of PTS was 76.1 per 100,000 person years [327].

5.3.3.2 Probabilities of recurrent VTE and PTS in the 'Treated VTE' state

The annual probabilities of recurrent VTE and PTS in patients with a treated VTE were obtained from a prospective cohort observational study which followed the clinical course of 528 patients with a first episode of symptomatic DVT over an eight year follow up period [85].

The cumulative incidences of recurrent VTE in this cohort, after two, five and eight years were 17.2%, 24.3% and 29.7% respectively [85]. For this Markov process, the annual incidence of recurrent VTE in year one and two was calculated based on the one and two year cumulative incidence rates. The annual incidence for years three to

five was calculated based on the two and five year cumulative incidence rates and the annual incidence for years six to eight was calculated based on the five and eight year cumulative incidence rates. The annual probability of recurrent VTE in this analysis, after year eight, was assumed to be the same as the annual incidence rates of idiopathic VTE in the general population [130].

This cohort study also showed cumulative incidences of PTS of 18.0%, 24.5%, 29.6% and 29.8% after one, two, five and eight years respectively [85]. For this Markov process, the annual incidence of PTS in year one and two was calculated based on the one and two year cumulative incidence rates. The annual incidence for years three to five was calculated based on the two and five year cumulative incidence rates and the annual incidence for years six to eight was calculated based on the five and eight year cumulative incidence rates. The annual incidence of PTS after year eight was assumed to be the same as that of idiopathic PTS in the general population [327].

5.3.3.3 Probabilities of Recurrent VTE and PTS in the 'Untreated VTE' State

No literature was identified which described the incidence of recurrent VTE in patients with asymptomatic, untreated DVT. This risk was thus assumed to be the same as in patients with a treated DVT [85].

The probability of PTS occurring in patients with an untreated VTE was extracted from a published meta-analysis in which the MOS cohorts were followed for a maximum of seven years. The RR of developing PTS in patients who developed an asymptomatic DVT after surgery was 1.58 times greater than those who did not develop a DVT [123]. For this analysis, the probability of developing PTS secondary to an untreated VTE was obtained by multiplying the probability of developing idiopathic PTS by 1.58 [123, 327]. The annual incidence after year seven was assumed to be that of idiopathic PTS in the general population [327].

5.3.3.4 Other Probabilities

No studies were identified which reported the incidence of recurrent VTE after a primary PE. The annual probabilities were therefore assumed to be the same as those after a primary DVT [85].

In the eight year prospective observational study of 528 patients previously mentioned, a total of 101 patients experienced recurrent events. Of these, 21 (20.8%) had experienced a PE [85]. For this economic analysis, it was assumed that 20.8% of recurrent VTE would be a PE.

Another cohort study comprised of 738 patients with treated, confirmed, symptomatic DVT. Of the 738 patients, 591 had a first DVT and 147 had a recurrent event. In total, 97 of the 147 patients (66%) with recurrent events had proximal vein involvement [82]. In this economic analysis, it was assumed that 66% of recurrent DVTs would be proximal.

The probability of death in each yearly cycle of the Markov process was obtained from Irish Life Tables [328].

The probabilities used in the economic evaluation are summarised in Table 23.

Table 23. Probabilities used in the economic evaluations of the lifetime model

		Parameter	Probability
THR	Rivaroxaban [253]	Distal DVT	0.010
		Proximal DVT	0.006
		Symptomatic PE	0.0012
		Major Bleed	0.0008
	Dabigatran etexilate [253, 255]	Distal DVT	0.029[a]
		Proximal DVT	0.036[a]
		Symptomatic PE	0.008[a]
		Major Bleed	0.001[a]
	Enoxaparin sodium [253]	Distal DVT	0.031
		Proximal DVT	0.051
		Symptomatic PE	0.005
		Major Bleed	0.0008
TKR	Rivaroxaban [251, 256]	Distal DVT	0.175[a]
		Proximal DVT	0.015[a]
		Symptomatic PE	0.00[a]
		Major bleed	0.015[a]
	Dabigatran etexilate [256]	Distal DVT	0.334
		Proximal DVT	0.028
		Symptomatic PE	0.00
		Major bleed	0.015
	Enoxaparin sodium [256]	Distal DVT	0.329
		Proximal DVT	0.047
		Symptomatic PE	0.001
		Major bleed	0.013
Decision Tree and Transitory Pathways Parameters			
Proximal DVT is symptomatic [266, 267]			0.40
Distal DVT is symptomatic [266]			0.05
PE is symptomatic (excluding immediately fatal) [281]			0.32
DVT (proximal or distal) fatal during treatment [270]			0.004
PE fatal during treatment [270]			0.015
PE fatal if asymptomatic [282]			0.27
PE immediately fatal [282]			0.22
Distal DVT propagates to the proximal vein [268]			0.18
Proximal DVT propagates to PE [269]			0.53
VTE detected pre-discharge (THR) [133]			0.24
VTE detected pre-discharge (TKR) [133]			0.53
Major bleed results in stroke [157]			0.03
Major bleed results in death [288]			0.008
Annual Markov Process Parameters			
Developing PTS: year 1 [85]			0.18
Developing PTS: year 2 [85]			0.0792[b]
Developing PTS (year 3-5) [85]			0.0230[b]
Developing PTS: (year 6-8) [85]			0.0009[b]
Developing Idiopathic PTS [327]			0.00076
Asymptomatic VTE leads to PTS (year 1-7) [123, 327]			0.0012
Developing recurrent VTE: (year 1-2) [85]			0.0901[b]
Developing recurrent VTE: (year 3- 5)[85]			0.0294[b]
Developing recurrent VTE: (year 6-8) [85]			0.024[b]
Recurrent VTE is a PE [85]			0.2080
Developing Idiopathic VTE [130]			0.0023
Idiopathic VTE is a PE [130]			0.304
Recurrent DVT is a proximal DVT [82]			0.660

a. Derived using the Bucher method of indirect comparison [234]

b. Calculated where annual probability = 1-(1-CP)^(1/t): Where CP=Cumulative Probability and t=Time in Years as reported in Prandoni *et al* [85]

DVT=deep vein thrombosis; **PE**=pulmonary embolism; **VTE**=venous thromboembolism; **THR**=total hip replacement; **TKR**=total knee replacement; **PTS**=post-thrombotic syndrome.

5.3.4 Preference Values

The values pertaining to distal DVT, proximal DVT, PE, QoL in the general population, stroke and death have previously been described (section 4.4.3).

In the Markov process, since VTE events were modelled as transitory events rather than health states, associated effects were assigned only for the duration of treatment. The health states 'No VTE', 'Untreated VTE' and 'Treated VTE' were therefore only awarded the QoL of the general population score [301]. The health states, 'Stroke', 'PTS Year 1'and 'PTS Maintenance' were afforded state preference values, which were then weighted by the QoL in the general population score [301].

5.3.4.1 Post Thrombotic Syndrome

Preference values for PTS were identified via a systematic search of the published literature. Additional references were identified from the reference lists of published articles. Combinations of the following search terms were used:

For Pubmed MeSH: postthrombotic syndrome; varicose ulcer; venous thrombosis; economics; costs and cost analysis; patient preference.
Free text terms: standard gamble; time trade off; SG; TTO; EuroQol; EQ5D; EQ-5D; quality of well being; health utility index; health utilities index; QALY; quality adjusted life year.

For Embase Thesaurus: postthrombosis syndrome; ulcer; skin ulcer; leg ulcer; deep vein thrombosis; venous thromboembolism; leg thrombosis; thromboembolism; cost utility analysis; pharmacoeconomics.
Free text terms: standard gamble; time trade off; SG; TTO; EuroQol; EQ5D; EQ-5D; quality of well being; health utility index; health utilities index; QALY; quality adjusted life year

For NICE: completed HTAs were searched; all appraisals of anticoagulant prophylaxis were retrieved.

The literature search highlighted a lack of good quality preference value data for this population.

One study was identified which estimated the preference values of mild-moderate and severe PTS from 30 community volunteers and 30 physicians. Health state descriptions, adapted from medical text, were presented to the subjects and preferences were elicited using a standard gamble method. The mean preference value for severe PTS (0.93 ± 0.07 (S.D) was lower than that of mild PTS (0.98 ± 0.04 (SD)) [300]. Several cost-effectiveness analyses have referenced PTS preference values to this study [197, 203, 207, 329, 330].

A prospective study was also located in which 79 patients (84 limbs) with an acute first episode of DVT, were reviewed for signs and symptoms of PTS [115]. Three years after the DVT event, the presence of PTS was assessed according to a previously reported scoring system [331]. Where PTS had occurred, it was classified as severe in 36% of cases [115]. For this analysis, the PTS preference value used in the model was weighted accordingly. This PTS preference value was awarded to both the 'PTS Year 1' and the 'PTS Maintenance' states.

The preference values used in the economic evaluation are summarised in Table 24.

Table 24. Preference values used in the economic evaluations of the lifetime model

Parameter	Reported Value	Used in Model
Symptomatic Distal DVT [291]	0.86	0.86 applied for 3 months
Symptomatic Proximal DVT [291]	0.86	0.86 applied for 6 months
Symptomatic PE [291]	0.81	0.81 applied for 6 months
Major Bleed [131, 292]	0	0 applied for 5 days
Stroke [300]	0.6	0.6 applied until death or end of simulation
PTS [115, 300]	0.93 (severe PTS) 0.98 (mild/moderate PTS)	Weighted value (0.962) applied until death or end of simulation
General Population Weight [301]	0.973 (with 0 health conditions) 0.909 (with 1-3 health conditions)	Average value (0.941) applied until death or end of simulation
Death		0

DVT=deep vein thrombosis; **PE**=pulmonary embolism; **PTS**=post-thrombotic syndrome

5.3.5 Direct Medical Costs

The costs pertaining to the 180 day decision tree i.e. primary VTE events (pre- and post- discharge); hospitalisation costs for THR, TKR and GI haemorrhage; acute care of stroke have been described previously (section 4.4.4). The costs associated with recurrent VTE events were assumed to be the same as those associated with a primary post-discharge VTE.

In the Markov process, since VTE events were modelled as transitory events, the associated costs were assigned as transitory costs and not to a health state. Accordingly, the health states 'No VTE', 'Untreated VTE' and 'Treated VTE' were not awarded annual health state costs. Only the health states, 'Stroke', 'PTS Year 1'and 'PTS Maintenance' were afforded annual health state costs.

5.3.5.1 Post Thrombotic Syndrome

The annual cost of PTS was obtained from a 2003 US study that employed a lifetime Markov model to project the long-term complication cost of DVT secondary to THR, from a healthcare provider perspective [197].

The US model simulated the natural history of DVT using published estimates of the incidence and prognosis of PTS and recurrent VTE. Patient care pathways were defined by the literature to identify key cost resource use. Resource use included hospitalisations, surgeries, physician/nurse outpatient visits, diagnostic tests, medical supplies and medications. Inpatient care costs included average Medicare DRG payments and physician fees for the mean DRG length of stay. Outpatient care costs included Medicare reimbursement rates for physicians, laboratory fees and outpatient fees for that procedure.

The model established a distinction between the first and subsequent years after the development of PTS to allow for differences in diagnostic and treatment patterns and associated costs.

The estimated annual costs of mild-to-moderate PTS were $839 in the first year and $341 in subsequent years and of severe PTS were $3,817 in the first year and $1,677

in subsequent years. The reduction in costs from the first year to subsequent years was attributable to a reduction in surgery-related costs [197].

For this economic analysis, a weighted cost was used, whereby it was assumed that 36% of PTS cases would be severe [115]. Costs were converted to Euros (year 2003) and inflated to 2008 using the Irish Consumer Price Index for Health [332, 333].

Here, the annual cost of PTS secondary to TKR was assumed to be the same as that secondary to THR.

5.3.5.2 Stroke

The annual cost of stoke was obtained from a 2003 UK study which used a literature based burden-of-illness Markov model to estimate the cost of treating stroke [334]. In this source, the cost estimates were based on data from a single-blind RCT which included 457 acute-stroke patients and compared alternative strategies of stroke care. Patients were recruited from a population-based stroke register and were excluded if they had had a mild stroke, a very severe stroke, were institutionalised or had severe disability prior to their stroke. The mean age was 76 years.

The data set contained total resource use (inpatient stay, day hospital visits, outpatient care, hospital readmissions, general practitioner and respite care) over 1 year for each patient. The data set also contained the reported costs of occupational therapy, speech and language services, physiotherapy, community services, social services and accommodation for institutionalised patients.

A Markov framework extrapolated the one year data to five years. The model estimated that, for every patient who experiences a stroke, the cost to the healthcare provider is £15,306 over five years [334].

For this economic analysis, costs were converted to Euros and inflated to 2008 using the Irish Consumer price Index for Health [332, 333].

The costs applied to the Markov process of the economic evaluations are summarised in Table 25.

Table 25: Costs applied to the lifetime model

Resource	2008 Unit Cost Data
Rivaroxaban (10mg) DDD	5.15[a]
Dabigatran etexilate (220mg) DDD	5.18[a]
Enoxaparin sodium (40mg) DDD	5.10[b]
Primary Hospitalisation	
THR	13048[c]
TKR	12870[c]
GI Haemorrhage	2555[c]
Acute care for stroke	14961[c]
VTE Diagnosis	
D-dimer	15.00[d]
Doppler ultrasound	130.00[d]
CTPA	113.00[d]
Chest x-ray	47.00[d]
ECG	50.00[d]
VTE treatment	
Warfarin DDD	0.11[c]
Anticoagulant clinic visit	60.00[e]
Graduated compression stockings	15.00[d]
Hospital bed day	500.00[d]
ED visit	200.00[d]
Hospital readmission for DVT	3470[c]
Hospital readmission for PE	5790[c]
Annual Health States	
PTS - First year	1795[f]
PTS - Subsequent years	772[f]
Stroke	4847[g]

All costs are in €, year 2008 values

a. Proposed Health Service Executive (HSE) price (05/08)
b. Monthly Index of Medical Specialities (MIMS) Ireland (10/08)[303]
c. Casemix, Health Service Executive 2007[292]. Costs inflated to 2008 price [193]
d. In-house data base of costs provided by university teaching hospital (average costs used), Dublin (2008 Aug)
e. Expert opinion. Clinical Pharmacology Department, St James's University Teaching Hospital, Dublin
f. Caprini *et al* [197] and Monreal *et al* [115]. Costs inflated to 2008 [193]
g. For this analysis, STG £15,306 (cost from Youman *et al*) [334] was divided by 5 to obtain an annual cost of stroke. This was converted to Euros (STG £1= €1.2707, Oct 2008 exchange rate) [333] and inflated to 2008 using the Consumer Price Index for Health[193].

DDD=daily defined dose; **THR**=total hip replacement; **TKR**=total knee replacement; **GI**= Gastrointestinal; **CTPA**= Computed Tomography Pulmonary Angiogram; **ECG** = electrocardiogram; **ED**=emergency department; **DVT**= Deep vein thrombosis; **PE**=Pulmonary embolism; **PTS**= Post thrombotic syndrome.

5.3.6 Discounting

Normal convention requires that any costs or outcomes occurring beyond one year should be discounted [18]. Costs and outcomes were discounted at 4% per annum as recommended by the Irish Department of Finance [70].

5.3.7 Validation

A hospital clinical team validated the structure of the model and the care pathways. It was also confirmed that the parameter values appeared to be realistic.

5.3.8 Basecase Analysis

The basecase cost-effectiveness of rivaroxaban versus enoxaparin sodium and dabigatran etexilate versus enoxaparin sodium were compared using ICERs according to standard decision rules [304].

5.3.9 Sensitivity Analysis

A one-way SA of all the parameters in the model was performed. Probability parameters were varied to the upper and lower bounds of the 95% CI where these were available; otherwise they were varied ± 50%. The total costs were varied ± 20%, whilst multiplicative preference values were varied ± 10%. The discount rate was varied to 0% and 6%. The impact of using a weighted average cost (assuming a 50:50 notional market share for enoxaparin sodium and tinzaparin) on the ICER was also investigated.

A PSA using second order Monte Carlo simulation was preformed. The Beta distribution was chosen for the probability parameters because of its special relationship with binomial data [306]. Where binomial data was unavailable, Beta distributions were fitted to plausible ranges. The Dirichlet distribution was adopted for mutlibranch nodes [307]. Beta distributions were fitted to ranges for the preference values. Direct medical costs were specified as log-Normal distributions [308]. The associated values of the CoV for both the direct medical costs and the preference values were again obtained via an elicitation exercise [309].

The probabilities pertaining to recurrent VTE, PTS secondary to a primary VTE and the annual all cause mortality were entered into time dependent probability tables and were thus varied with time. The discount rate was fixed.

The PSA distributions applied to the Markov process are summarised in Table 26.

The expected costs and QALYs of all three strategies, for each PSA iteration, were recorded and were combined to form a measure of the expected NMB for each intervention [56, 57]. These simulated values of NMB were used to identify the probability of each option being the most cost effective and to identify the optimal option over the threshold range €0 - €100,000 in order to produce the CEAC [56] and the CEAF respectively [58].

The PSA was run with 50,000 iterations. This number of iterations was chosen as it could be demonstrated that the PSA results did not change appreciably in three successive runs. The non prohibitive running time of five hours was also a consideration. As a further validation of the PSA results, the standard error of the Monte Carlo analysis was also calculated.

Table 26. Summary of distributions used in the probabilistic analysis of the lifetime model

Parameter	Distribution[a]	Source
THR		
Distal DVT, proximal DVT, no VTE, PE occur on rivaroxaban	Dirichlet (10; 6; 850; 2)	[253]
Distal DVT, proximal DVT, no VTE, PE occur on enoxaparin	Dirichlet (28; 45; 795; 5)	[253]
Distal DVT, proximal DVT, no VTE, PE occur on dabigatran	Dirichlet[b] (26.5; 32.2; 811.7; 7.7)	[253, 255]
Major bleed occurs on rivaroxaban	Beta (2,1228)	[253]
Major bleed occurs on enoxaparin	Beta (2,1229)	[253]
Major bleed occurs on dabigatran	Beta (2.2,1145.8)	[253, 255]
TKR		
Distal DVT, proximal DVT, no VTE, PE occur on rivaroxaban	Dirichlet[b] (145.3; 19.6; 662.1; 1)	[251, 256]
Distal DVT, proximal DVT, no VTE, PE occur on enoxaparin	Dirichlet[b] (168.7; 25; 318.6; 1.74)	[256]
Distal DVT, proximal DVT, no VTE, PE occur on dabigatran	Dirichlet[b] (169; 14.9; 322; 1)	[256]
Major bleed occurs on rivaroxaban	Beta (19.75,1202.25)	[251, 256]
Major bleed occurs on enoxaparin	Beta (10,686)	[256]
Major bleed occurs on dabigatran	Beta (11,670)	[256]
Thromboprophylaxis Independent Parameters		
Major bleed results in death, stroke, no sequalae	Dirichlet[b] (3.99; 14; 363.01)	[131, 259]
Proximal DVT is symptomatic	Beta[c] (2.099,3.149)	[266, 267]
Distal DVT is symptomatic	Beta[c] (0.262,4.985)	[266]
PE is symptomatic (excludes immediately fatal)	Beta (15,31)	[281]
DVT (proximal or distal) fatal during treatment	Beta (18,4205)	[270]
PE fatal during treatment	Beta (20,1284)	[270]
PE fatal if asymptomatic	Beta (15,39)	[282]
PE immediately fatal	Beta (14, 47)	[282]
Distal DVT propagates to the proximal vein	Beta (6,24)	[268]
Proximal DVT propagates to PE	Beta (9, 8)	[269]
VTE detected pre-discharge (THR)	Beta (134,424)	[133]
VTE detected pre-discharge (TKR)	Beta (269,241)	[133]
Risk of Recurrent VTE after Treated VTE	Time varying parameter	[85]
Risk of PTS after Treated VTE	Time varying parameter	[85]
Recurrent VTE is a PE	Beta (22,81)	[85]
Recurrent DVT is proximal	Beta (98,50)	[82]
Risk of Idiopathic VTE	Beta (231, 99771)	[130]
Risk of Idiopathic PTS	Beta (77, 99925)	[327]
Idiopathic VTE is a PE	Beta (71,161)	[130]
Risk of PTS post asymptomatic VTE	Time varying parameter	[123, 327]
Annual Mortality Rate	Time varying parameter	[328]
Total Costs	Lognormal, SD=0.2	
Preference Values	Beta[c], SD=0.2	[115, 131, 291, 300, 301]

a. The ordering of the parameters of the Dirichlet distribution, as shown in the parenthesis, refers to the same ordering of the parameters described in the first column. The alpha and beta parameters of the Beta distribution are described in parentheses.

b. Where the sample size for each event is different the Dirichlet distribution was calculated based on a common denominator.

c. In the absence of other information, standard deviation for the Beta distribution was fixed at 0.2 during the fitting process.

DVT=deep vein thrombosis; **VTE**=venous thromboembolism; **PE**=pulmonary embolism; **THR**=total hip replacement; **TKR**=total knee replacement; **PTS**=post thrombotic syndrome; **SD**=standard deviation.

5.4 Results

5.4.1 Basecase Analysis

5.4.1.1 Total Hip Replacement

The basecase CEA and CUA indicate that the 35 day rivaroxaban strategy dominates both 35 days of dabigatran etexilate and 14 days of enoxaparin sodium. The ICERs for dabigatran etexilate relative to enoxaparin sodium were €3,051 per LYG and €2,935 per QALY.

5.4.1.2 Total Knee Replacement

The basecase CEA and CUA indicate that the 14 day rivaroxaban strategy dominates both 10 days of dabigatran etexilate and 14 days of enoxaparin sodium. Dabigatran etexilate also dominates enoxaparin sodium.

The basecase results are summarised in Table 27.

Table 27. Results of the basecase analyses of the lifetime model

Strategy	Cost (€)	Incremental Cost (€)	Effect (QALY)	Incremental Effect (QALY)	ICER (QALY)	Effect (LYG)	Incremental Effect (LYG)	ICER (LYG)
THR								
Rivaroxaban	13483		10.4654			11.1265		
Enoxaparin sodium	13606	123	10.3908	-0.0746	Dominated by rivaroxaban	11.0549	-0.0716	Dominated by rivaroxaban
Dabigatran etexilate	13660	177	10.4092	-0.0561	Dominated by rivaroxaban	11.0726	-0.0539	Dominated by rivaroxaban
TKR								
Rivaroxaban	13516		10.3897			11.0558		
Dabigatran etexilate	13744	228	10.3140	-0.0758	Dominated by rivaroxaban	10.9823	-0.0734	Dominated by rivaroxaban
Enoxaparin sodium	13752	236	10.3078	-0.0819	Dominated by rivaroxaban	10.9762	-0.0796	Dominated by rivaroxaban

Costs are €, year 2008 values

QALY=quality adjusted life year; **ICER**=incremental cost-effectiveness ratio; **LYG**=life years gained; **THR**=total hip replacement; **TKR**= total knee replacement.

5.4.2 One-Way Sensitivity Analysis

All model parameters were varied in a one-way SA.

5.4.2.1 Total Hip Replacement

Rivaroxaban versus both comparators

Rivaroxaban continued to dominate both comparators in all instances of parameter variation.

Dabigatran etexilate versus enoxaparin sodium

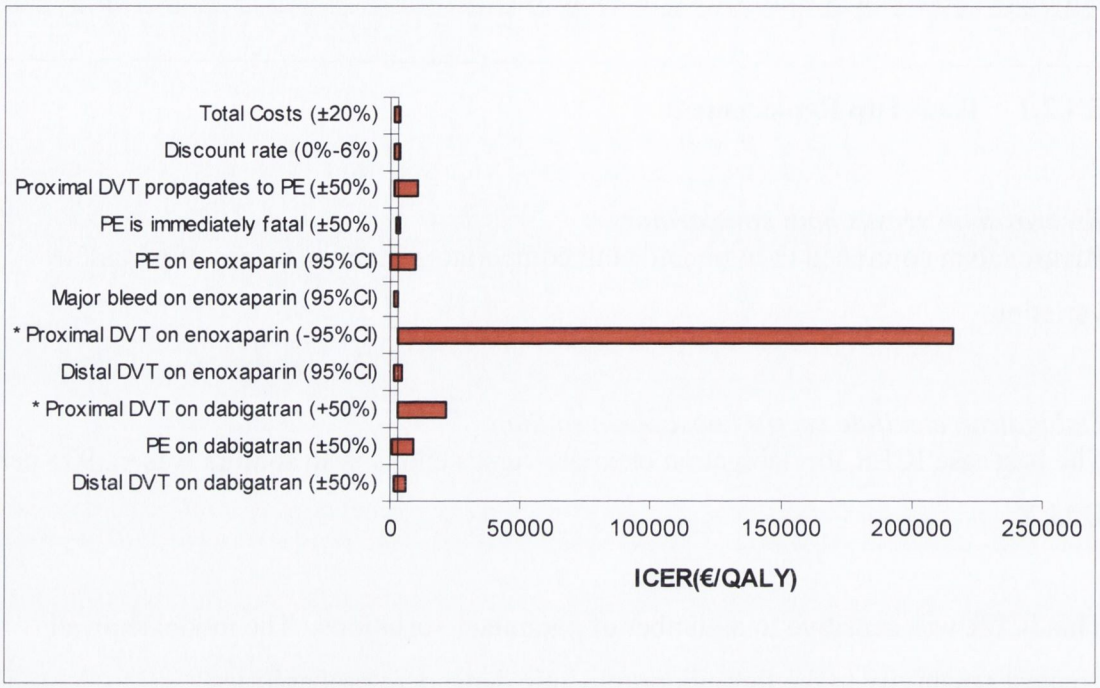
The basecase ICER for dabigatran etexilate versus enoxaparin sodium was €2,935 per QALY.

This ICER was sensitive to a number of parameter variations. The model showed greatest sensitivity to the thromboprophylatic dependent probabilities.

Dabigatran etexilate dominated enoxaparin sodium in two instances: when the probabilities that a proximal DVT will occur on dabigatran etexilate or enoxaparin sodium were decreased (by 50%) or increased (to the 95% CI upper limit) respectively.

The ICER was sensitive to a number of other parameter variations, the most significant of which are shown in Figure 13. The €45,000 per QALY threshold was reached on one occasion; when the probability that a proximal DVT on enoxaparin sodium was decreased to the lower limit of the 95%CI, the ICER increased to €216,000/QALY. The €20,000 per QALY threshold was reached when the probability that a proximal DVT will occur on dabigatran etexilate was increased by 50% (ICER = €21,818/QALY).

Figure 13: Total hip replacement lifetime model: Tornado diagram for the one-way sensitivity analysis showing the variation around the ICER (€2,935/QALY) for the basecase of dabigatran vs. enoxaparin (€, year 2008 values)



THR=total hip replacement; **ICER**=incremental cost effectiveness ratio; **DVT**=deep vein thrombosis; **PE**=pulmonary embolism.
* Dabigatran dominates when: [1] proximal DVT on dabigatran is decreased by 50% [2] proximal DVT on enoxaparin is increased to the 95% CI upper limit

5.4.2.2 Total Knee Replacement

Rivaroxaban versus both comparators
Rivaroxaban continued to dominate both comparators in all instances of parameter change.

Dabigatran etexilate versus enoxaparin sodium
Dabigatran etexilate continued to dominate enoxaparin sodium in all but six instances. The model showed greatest sensitivity to the thromboprophylatic dependent probabilities.

Enoxaparin sodium dominated dabigatran etexilate when the probabilities that a distal or a proximal DVT will occur on dabigatran etexilate were individually increased by 50% and when the probabilities that a distal or a proximal DVT will occur on enoxaparin sodium were individually decreased by 50%.

Also, when the probability that a major bleed will occur on enoxaparin sodium was decreased to the 95% CI lower limit, the ICER of dabigatran etexilate relative to enoxaparin sodium was €5,000/QALY. When the probability that a major bleed will occur on dabigatran etexilate was increased to the 95% CI upper limit, the ICER was €12,250/QALY.

5.4.3 Probabilistic Analysis

5.4.3.1 Total Hip Replacement

The mean PSA outcomes were compared to the results of the deterministic analysis and are shown in Table 28. The results of the PSA did not change appreciably over three successive PSA runs.

Table 28. Total hip replacement lifetime. ICERs for the deterministic and probabilistic (50,000 simulations) analyses.

	Cost (€)	Effect (QALY)	ICER (€/QALY)
Basecase Results			
Rivaroxaban	13483	10.4654	Rivaroxaban dominates enoxaparin Rivaroxaban dominates dabigatran
Enoxaparin sodium	13606	10.3908	
Dabigatran etexilate	13660	10.4092	Dabigatran vs. enoxaparin = 2935
PSA Mean Results			
Rivaroxaban	13780	10.4497	Rivaroxaban dominates enoxaparin Rivaroxaban dominates dabigatran
Enoxaparin sodium	13916	10.3737	
Dabigatran etexilate	13968	10.3912	Dabigatran vs. enoxaparin = 2971
PSA run 2. Mean results			
Rivaroxaban	13814	10.4484	Rivaroxaban dominates enoxaparin Rivaroxaban dominates dabigatran
Enoxaparin sodium	13904	10.3727	
Dabigatran etexilate	13960	10.3906	Dabigatran vs. enoxaparin = 3128
PSA run 3. Mean results			
Rivaroxaban	13792	10.4578	Rivaroxaban dominates enoxaparin Rivaroxaban dominates dabigatran
Enoxaparin sodium	13909	10.3817	
Dabigatran etexilate	13960	10.3993	Dabigatran vs. enoxaparin = 2898

Costs are in €, year 2008 values

ICER=incremental cost effectiveness ratio; **PSA**=probabilistic analysis; **QALY**=quality adjusted life year.

With 50,000 iterations the MC error (at €45,000 per QALY) was 1.28% of the mean opportunity loss.

The cost-effectiveness plane for THR, illustrating the individual scatterplots for rivaroxaban compared with enoxaparin sodium and dabigatran etexilate compared with enoxaparin sodium is shown in Figure 14a.

The CEAC, derived from the PSA, for the comparison between the three strategies is illustrated in Figure 15a. Rivaroxaban has the highest probability of being the most cost-effective strategy over the threshold range of €0 - €100,000 per QALY. At a threshold of €45,000 per QALY, the probability that rivaroxaban is the most cost effective strategy was 69%, followed by dabigatran etexilate at 18% and enoxaparin sodium at 13%.

The CEAF (also depicted in Figure 15a) highlights that rivaroxaban is the optimal strategy over the entire threshold range.

5.4.3.2 Total Knee Replacement

The mean ICERs for the PSA analysis were compared to the results of the deterministic analysis and are shown in Table 29.

On repeated runs of the PSA, the results did not change appreciably.

Table 29. Total knee replacement lifetime. ICERs for the deterministic and probabilistic (50,000 simulations) analyses

	Cost (€)	Effect (QALY)	ICER (€/QALY)
Basecase Results			
Rivaroxaban	13516	10.3897	Rivaroxaban dominates enoxaparin Rivaroxaban dominates dabigatran
Dabigatran etexilate	13744	10.3140	Dabigatran dominates enoxaparin
Enoxaparin sodium	13752	10.3078	
PSA Mean Results			
Rivaroxaban	13853	10.3781	Rivaroxaban dominates enoxaparin Rivaroxaban dominates dabigatran
Dabigatran etexilate	14080	10.2935	Dabigatran dominates enoxaparin
Enoxaparin sodium	14085	10.2852	
PSA run 2. Mean results			
Rivaroxaban	13845	10.3801	Rivaroxaban dominates enoxaparin Rivaroxaban dominates dabigatran
Dabigatran etexilate	14090	10.2952	Dabigatran dominates enoxaparin
Enoxaparin sodium	14097	10.2871	
PSA run 3. Mean results			
Rivaroxaban	13819	10.3699	Rivaroxaban dominates enoxaparin Rivaroxaban dominates dabigatran
Dabigatran etexilate	14084	10.2860	Dabigatran dominates enoxaparin
Enoxaparin sodium	14105	10.2776	

Costs are €, year 2008 values

ICER=incremental cost effectiveness ratio; **PSA**=probabilistic analysis; **QALY**=quality adjusted life year.

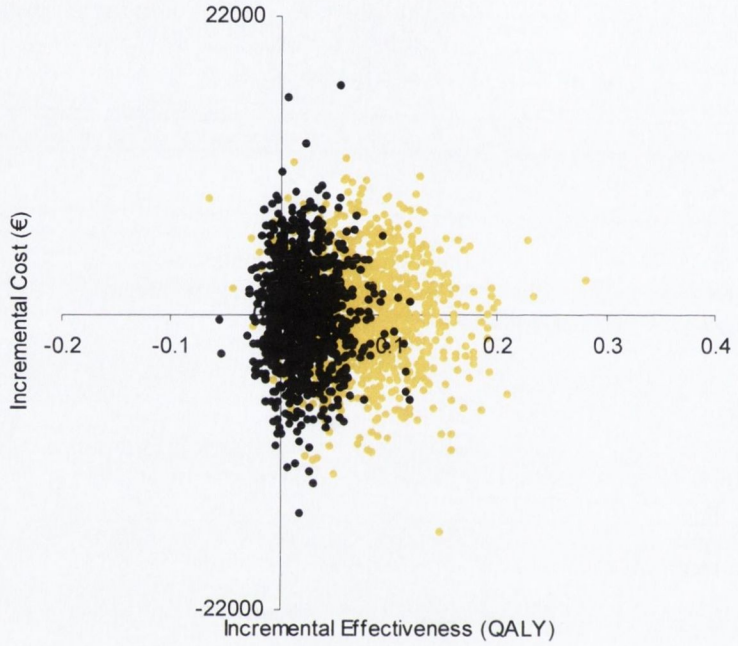
With 50,000 PSA iterations, the MC error (at €45,000 per QALY) was 1.18% of the mean opportunity loss.

The cost-effectiveness plane for TKR is shown in Figure 14b. The results of the PSA are also presented on the CEAC in Figure 15b; rivaroxaban has the highest probability of being the most cost-effective strategy over the threshold range of €0 - €100,000 per QALY. At a threshold of €45,000 per QALY, the probability that rivaroxaban is the most cost effective strategy was 79%, followed by dabigatran etexilate at 13% and enoxaparin sodium at 8%.

Rivaroxaban is the optimal strategy over the entire threshold range as depicted by the CEAF in Figure 15b.

Figure 14: Cost-effectiveness plane for the lifetime model
Rivaroxaban and dabigatran etexilate compared with enoxaparin sodium after (**a**) total hip replacement and (**b**) total knee replacement; showing 1000 points drawn from 50,000 for each drug. Costs are in €, year 2008 values

(a) Total Hip Replacement



(b) Total Knee Replacement

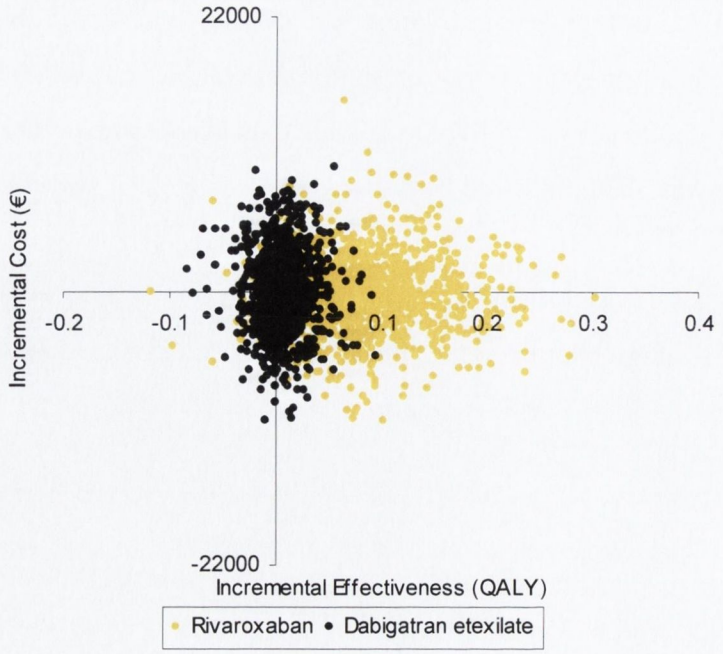
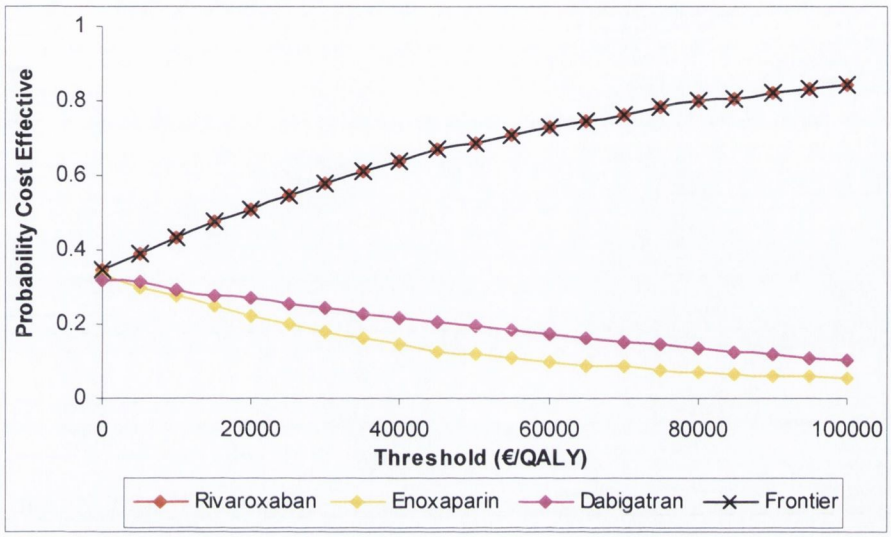
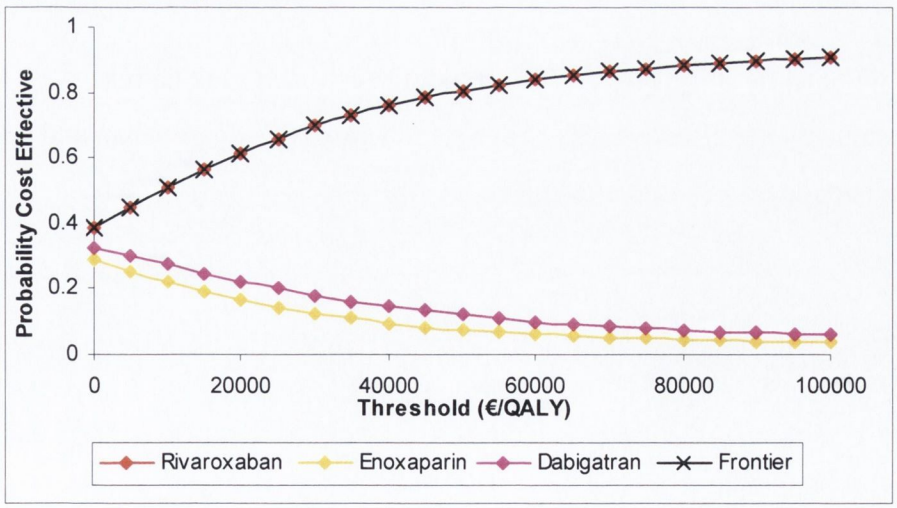


Figure 15: Cost-effectiveness acceptability curve and frontier for the lifetime model (**a**) total hip replacement and (**b**) total knee replacement. The cost-effectiveness acceptability frontier shows the optimal strategy over the range of threshold values. Costs are in €, year 2008 values.

(a) Total Hip Replacement



(b) Total Knee Replacement



5.5 Structural Uncertainty within the THR Model

It has been recognised elsewhere that, compared to standard duration LMWH, extended duration LMWH significantly reduces the frequency of symptomatic VTE after THR [259] but not after TKR [135, 259].

For the THR economic models (sections 4.4 and 5.3) efficacy point estimates were obtained from a Bucher *et al* indirect comparison (Table 11). This indirect comparison assumed that 28 to 35 days of enoxaparin sodium (in RE-NOVATE [255]) and 10 to 14 days of enoxaparin sodium (in RECORD 2 [253]) were equally efficacious. It is therefore possible that this indirect comparison is biased towards demonstrating superior efficacy (and subsequent superior cost-effectiveness) of rivaroxaban relative to dabigatran etexilate after THR.

This Bucher *et al* [234] indirect comparison was unable to account for the difference durations of enoxaparin sodium in the pivotal trials. The resulting uncertainty (in the cost-effectiveness analysis) that exists due to the method used to ascertain the efficacy parameters can be referred to as structural uncertainty [335]. In order to decrease this uncertainty, it is possible to incorporate all relevant evidence simultaneously in a MTC model [102, 230].

5.5.1 Objective

To illustrate the application of a Bayesian MTC model to estimate the relative efficacy and subsequent cost-effectiveness of dabigatran etexilate, rivaroxaban and standard duration enoxaparin sodium after THR.

5.5.2 Method

5.5.2.1 Literature Review

The probabilities pertaining to the use of standard- and extended duration LMWH as thromboprophylaxis after THR were obtained from a systematic literature search. Only RCTs published in the English language since 1980 were included. Additional references were identified from the reference lists of published articles. Combinations of the following search terms were used in combination with generic and trade names of individual LMWH preparations:

For PubMed MeSH: arthroplasty, replacement, hip; venous thrombosis; pulmonary embolism; thromboembolism; heparin, low molecular weight; randomized controlled trial; meta-analysis.
For Embase Thesaurus: hip arthroplasty; deep vein thrombosis; venous thromboembolism; leg thrombosis; lung embolism; low molecular weight heparin; randomized controlled trial; meta analysis.
CRD: The databases DARE, NHS EED and HTA were searched for relevant references on anticoagulant prophylaxis relating to THR.

For dabigatran etexilate and rivaroxaban, only those phase III trials in which enoxaparin sodium had been given at the EU-licensed dose of 40mg OD were considered [252, 253, 255]. RECORD 1 compared 31 to 39 days of rivaroxaban and enoxaparin sodium [252]. RECORD 2 compared 31 to 39 days of rivaroxaban to 10 to 14 days of enoxaparin sodium [253]. RE-NOVATE compared 28 to 35 days of dabigatran etexilate and enoxaparin sodium [255].

5.5.2.2 Statistical Analysis

Analysis by Ms Susanne Schmitz, PhD candidate, Department of Statistics, Trinity College Dublin, Dublin, Ireland.

The Bayesian inference software program WinBUGS (a software package using Markov chain Monte Carlo techniques) [336] was used to combine evidence (for the outcomes of distal DVT, proximal DVT and symptomatic PE) from the relevant trials in a fixed treatment effects model [102]. The model estimates all pair wise RRs; for this analysis the following comparisons were of interest: (a) dabigatran vs. enoxaparin (standard duration), (b) rivaroxaban vs. enoxaparin (standard duration) and (c) rivaroxaban vs. dabigatran etexilate. The full WinBUGS code for the evidence synthesis is presented in Appendix 2.

By applying the mean RRs derived from the MTC, efficacy point estimates (for the outcomes distal DVT, proximal DVT and symptomatic PE) for rivaroxaban and dabigatran etexilate were then calculated relative to the baseline risks for enoxaparin sodium (standard duration) taken from RECORD 2 [253].

5.5.2.3 Economic Evaluation

Efficacy point estimates, for the three thromboprophylatic strategies, obtained from the MTC were input into the THR lifetime economic model. Deterministic and probabilistic analyses were repeated.

The lifetime economic model was chosen for this analysis since both the acute VTE events and their long term consequences were deemed to be of interest to the decision maker.

5.5.3 Results

5.5.3.1 Literature Review

The literature search revealed one MTC and eight RCTs which compared extended- with standard duration LMWH after THR [135, 337-345]. The MTC was excluded; it had included RTCs which had compared extended and standard duration UH [337]. Seven RTCs were excluded [135, 337, 338, 340-345]. Heit *et al* had investigated the efficacy of ardeparin which was withdrawn in 2000 [135]. Comp *et al* had investigated enoxaparin sodium at the non-EU licensed dose of 30mg BD [342]. Manganelli *et al* had not performed bilateral venography at completion of treatment [338, 340, 341, 345]. In five studies, the standard-duration of prophylaxis was not reflective of current practice in Ireland; in four this was six to 10 days [343], in one it was 16 to 17 days [346].

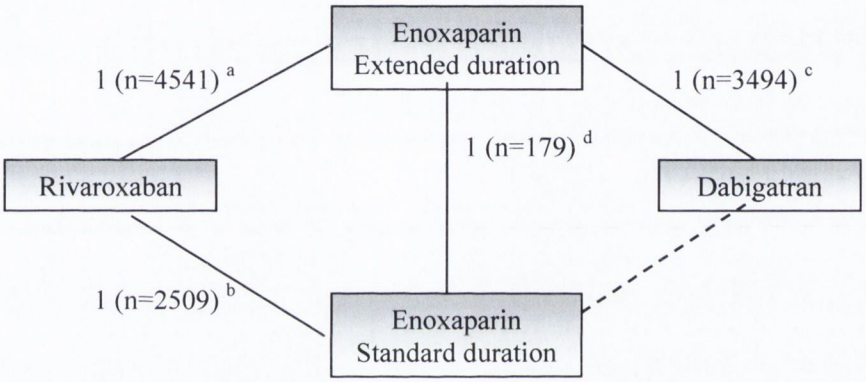
Planes *et al* randomly assigned 179 consecutive THR patients at hospital discharge (13 to 15 days after surgery) to SC enoxaparin sodium (40 mg OD; n=90) or placebo (n=89) for 21 days [339]. All patients had received enoxaparin sodium during inpatient stay. In the ITT analysis the rate of DVT at day 21 after discharge was significantly lower in the enoxaparin sodium group (7.1% vs. 19.3%, p=0.018). Distal DVT was detected in 1.2% and 11.4% of the enoxaparin sodium and placebo groups respectively (p=0.006). The respective rates of proximal DVT were 5.9% and 7.9% (p=0.592). There were no cases of PE.

5.5.3.2 Statistical Analysis

Analysis by Ms Susanne Schmitz, PhD candidate, Department of Statistics, Trinity College Dublin, Dublin, Ireland.

A fixed effects Bayesian MTC model was fitted for each of the outcome measures (distal DVT, proximal DVT and symptomatic PE) to calculate pair wise RRs. A fixed effect model was used as there is one RCT in each arm of the network. The network diagram is shown in Figure 16.

Figure 16: Network diagram of randomised controlled trials of thromboprophylaxis after total hip replacement
Each treatment strategy is a node in the network. The bold lines refer to the direct comparisons. The numbers along these lines indicate the number of trials (and the number of patients included) for that link in the network. The dotted line refers to a lack of direct evidence.



Where:

a. RECORD 1 (rivaroxaban (31-39) days vs. enoxaparin (31-39days)) [252]
b. RECORD 2 (rivaroxaban (31-39 days) vs. enoxaparin (10-14 days)) [253]
c. RE-NOVATE (dabigatran (28-35 days) vs. enoxaparin (28-35 days)) [255]
d. Planes *et al* (enoxaparin (13-15 days) vs. enoxaparin (34-36 days)) [339]

The mean RRs (with SD) obtained from the Bayesian MTC model, for the outcome measures (distal DVT, proximal DVT and symptomatic PE) are described in Table 30.

Table 30: Mean efficacy relative risks (with standard deviation) for the THR economic evaluation derived from the Bayesian MTC model.

Comparison	**Distal DVT**	**Proximal DVT**	**Symptomatic PE**
Enoxaparin (extended) vs. Enoxaparin (standard)	0.359 (0.42)	1.072 (0.48)	0.031 (1.87)
Enoxaparin (extended) vs. Rivaroxaban	1.553 (0.32)	14.417 (0.53)	0.185 (1.32)
Enoxaparin (extended) vs. Dabigatran	1.074 (0.30)	1.450 (0.27)	0.560 (0.78)
Rivaroxaban vs. Enoxaparin (standard)	0.231 (0.36)	0.074 (0.48)	0.168 (1.44)
Dabigatran vs. Enoxaparin (standard)	0.334 (0.52)	0.739 (0.55)	0.056 (2.02))
Rivaroxaban vs. Dabigatran	1.446 (0.44)	9.946 (0.59)	0.331 (1.54)

DVT= deep vein thrombosis; **PE**=pulmonary embolism; **extended** = 28-35 days prophylaxis; **standard** = 10-14 days prophylaxis.

For the economic evaluation, efficacy point estimates (distal DVT, proximal DVT and symptomatic PE) for enoxaparin sodium (standard duration) were obtained from RECORD 2 [253]. Point estimates for dabigatran etexilate were calculated by multiplying the enoxaparin point estimates by the RR (dabigatran vs. enoxaparin (standard duration)). Likewise point estimates for rivaroxaban were calculated by multiplying the enoxaparin sodium point estimates by the RR (rivaroxaban vs. enoxaparin (standard duration)). The point estimates input into the THR lifetime model are described in Table 31.

Table 31: Efficacy point estimates for the THR economic evaluation derived from the Bayesian MTC model

Strategy	Distal DVT	Proximal DVT	Symptomatic PE
Enoxaparin [a]	0.031	0.051	0.005
Rivaroxaban [b]	0.007	0.004	0.001
Dabigatran [c]	0.010	0.037	0.003

a. Enoxaparin point estimates from RECORD 2.
b. Calculated by multiplying the enoxaparin point estimates by RR (rivaroxaban vs. enoxaparin (standard duration)).
c. Calculated by multiplying the enoxaparin point estimates by RR (dabigatran vs. enoxaparin (standard duration)).

DVT = deep vein thrombosis; **PE** = pulmonary embolism; **PSA** = probabilistic analysis; **RR**= relative risk.

These point estimates were input into the THR lifetime model. Deterministic and probabilistic analyses were repeated.

5.5.3.3 Economic Evaluation

In the basecase analysis rivaroxaban continued to dominate both comparators. Dabigatran etexilate also dominated enoxaparin sodium.

The cost-effectiveness plane is shown in Figure 17. The CEAC and the CEAF, derived from the PSA are illustrated in Figure 18. Rivaroxaban continued to have the highest probability of being optimal and had the highest expected NMB over the entire threshold range. At €45,000 per QALY, the probability that rivaroxaban is the most cost-effective strategy was 65%, followed by dabigatran etexilate at 24% and enoxaparin sodium at 11%.

Figure 17: Cost-effectiveness plane for the lifetime THR model; efficacy point estimates derived from the Bayesian MTC model.
Rivaroxaban and dabigatran etexilate compared with enoxaparin sodium; showing 1000 points drawn from 50,000 for each drug. Costs are in €, year 2008 values.

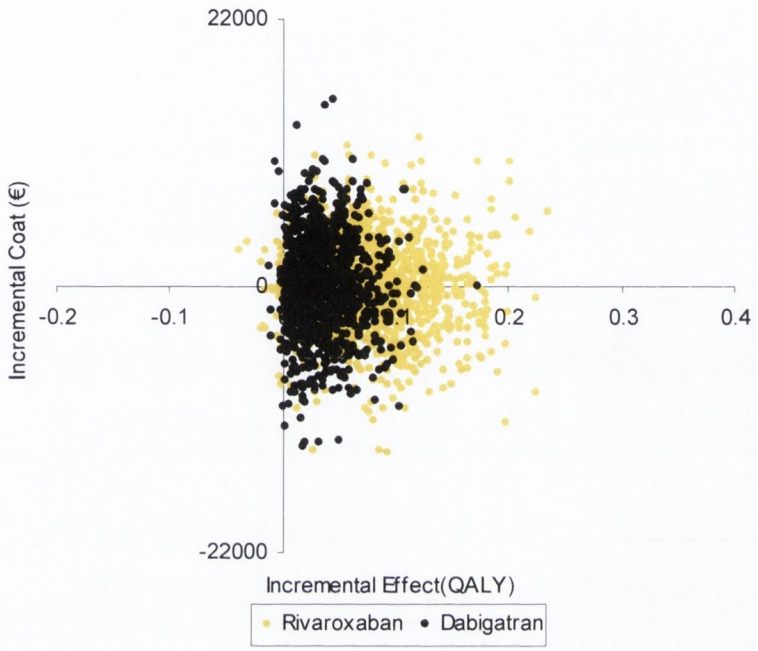
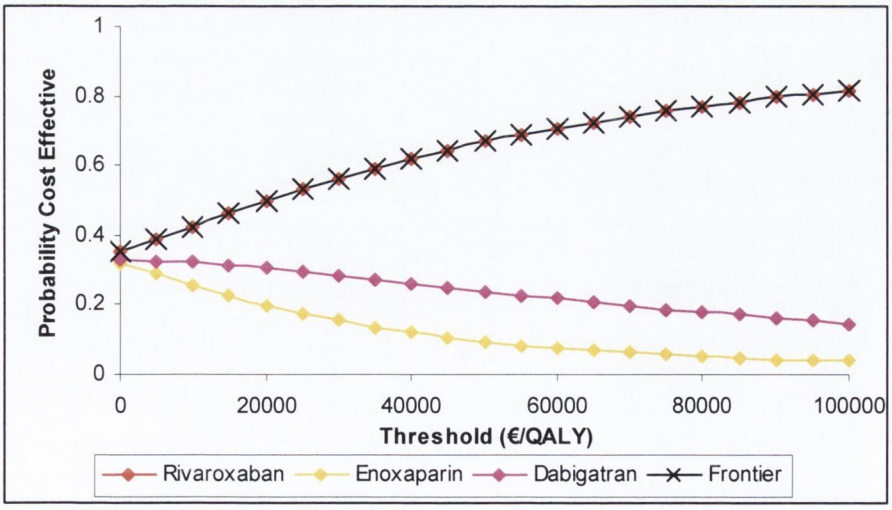


Figure 18: Cost-effectiveness acceptability curve and frontier for the lifetime THR model; efficacy point estimates derived from the Bayesian MTC model
Costs are in €, year 2008 values.



5.6 Discussion

VTE is a disease with long-term costs and consequences, including the risk of recurrences and the development of PTS [82-89]. Likewise, there are long-term costs and consequences associated with stroke [334]. The 180 day model considers acute VTE events and thromboprophylaxis related acute major bleed events only. The lifetime model considers these events and also their associated long-term consequences.

The results of the lifetime model are compared to those of the 180 day model (section 4.5).

Total Hip Replacement: In the deterministic basecase analyses, rivaroxaban dominated both comparators when either time horizon was considered. ICERs for dabigatran etexilate compared to enoxaparin sodium fell from €50,625 to €3,051 per LYG and from €33,750 to €2,935 per QALY when the time horizon was extended from 180 days to lifetime. Hence, the cost-effectiveness of dabigatran etexilate becomes more favourable as the time horizon is extended.

All model parameters were varied in a one-way SA. In the 180 day model, rivaroxaban continued to dominate both comparators in all but four instances of parameter change. When the time horizon was extended to lifetime, rivaroxaban dominated both comparators in all instances of parameter variation. The results of the lifetime model were therefore more robust to parameter variation.

Dabigatran etexilate and enoxaparin sodium were also compared. In the 180 day model, the ICER (€33,750 per QALY) was sensitive to a number of parameter changes; it increased beyond the €45,000 per QALY threshold in five instances. Also, enoxaparin sodium dominated when the risk of a proximal DVT occurring on enoxaparin sodium was decreased. When this parameter was decreased in the lifetime model, the ICER instead increased to €216,000 per QALY. This can be explained; in the 180 day model, basecase results (Table 19) reveal that the expected QALY gain with dabigatran etexilate is only 0.0024 more that that expected with enoxaparin sodium. Table 27 reveals that this difference is greater (at 0.0184) in the lifetime model. When the expected effect of enoxaparin sodium is increased in the 180 day

model, it surpasses the expected effect of dabigatran etexilate and enoxaparin sodium dominates. When the expected effect of enoxaparin sodium is increased in the lifetime model, it does not manage to surpass the expected effect of dabigatran etexilate.

The lifetime model was further sensitive to a number of other parameter variations; however the €45,000 per QALY threshold was not reached again. Indeed dabigatran etexilate dominated enoxaparin sodium on two occasions. Hence, although both models show some degree of uncertainty, the cost-effectiveness of dabigatran etexilate remains more favourable in the one-way SA of the lifetime model.

The respective CEACs and CEAFs (Figure 11a and Figure 15a) indicate that, when both time horizons were considered, rivaroxaban was the optimal strategy over the threshold range €0 - €100,000 per QALY. The probability that rivaroxaban is the most cost-effective option increased from 39% in the 180 day model (Figure 11a) to 69% in the lifetime model (Figure 15a). This increased probability might influence the decision maker's confidence in making a reimbursement decision.

Total Knee Replacement: In the basecase analyses, rivaroxaban dominated both comparators and dabigatran etexilate dominated enoxaparin sodium when either time horizon was considered.

The robustness of these results was examined in a one-way SA. In the 180 day model rivaroxaban dominated both comparators in all but two instances; in neither of these was the €45,000 per QALY threshold reached. Rivaroxaban continued to dominate both comparators with all changes of parameter in the lifetime model. The lifetime model was therefore robust.

Dabigatran etexilate and enoxaparin sodium were also compared in a one-way SA. In the short-term model enoxaparin sodium dominated dabigatran etexilate in five instances. In three further instances the ICER for dabigatran etexilate versus enoxaparin sodium ranged from €22,857 to €31,000 per QALY. In the long-term model, enoxaparin sodium dominated dabigatran etexilate in four instances and the ICERs were €5,000 and €12,250 per QALY in a further two. Both models therefore

remain sensitive to parameter change, although the €20,000 per QALY threshold is not surpassed in the one way SA of the lifetime model.

The CEACs and CEAFs (Figure 11b and Figure 15b) can be reviewed. With either time horizon, PSA indicated that rivaroxaban was the optimal strategy over the €0 - €100,000 threshold. The probability that rivaroxaban was the most cost-effective option increased from 42% (Figure 11b) to 79% (Figure 15b) with the extended horizon. Again, this increased probability might be expected to influence the decision maker's confidence in strategy choice.

The cost-effectiveness planes for THR and TKR clearly show that more favourable cost-effectiveness seen with rivaroxaban and dabigatran etexilate in the lifetime models (Figure 14) as compared to the 180 day models (Figure 10) is driven by an increase in incremental effectiveness compared to enoxaparin sodium. There is some overlap in the cost-effectiveness planes pertaining to both the 180 day models (Figure 10) and the lifetime models (Figure 14); this indicates that there is some uncertainty that rivaroxaban is more cost-effective than dabigatran etexilate when both are compared to enoxaparin sodium with either model time horizon.

In summary, there is an increased probability that rivaroxaban is the most cost-effective agent after THR and TKR with the longer time horizon model. Decision certainty is also improved. The increased probability that rivaroxaban is the most cost-effective strategy, seen when the model time horizon is extended, is not unexpected. According to the lifetime model, the strategy associated with the lowest risk of VTE events would also be associated with a lower incidence of recurrent VTE and of PTS. Likewise the strategy with the lowest incidence of major bleed would be associated with a lower incidence of chronic stroke.

The Markov modelling skills that I have developed in this study will be beneficial in future analyses within other therapeutic areas. The Markov model is a commonly used approach, in decision analysis, to handle the complexity of modelling options with a multiplicity of possible consequences [320]. They are particularly useful when a decision problem involves exposure to risks or events over time, ongoing exposures or situations where the specific timing of an event is regarded as important or uncertain.

There are two main limitations of Markov models. First, state transitions can occur only at the end of a cycle and this can create some biases. Second, Markov cycle time may force the analyst to make simplifying assumptions regarding transition probabilities [347].

There are a number of limitations to this analysis.

The limitations of the indirect comparison, from which the efficacy point estimates for this evaluation were derived, have been discussed (section 3.4.5). Of most concern is the difference in the duration of enoxaparin sodium between the THR trials (Table 11). This indirect comparison may be biased towards demonstrating superior efficacy of rivaroxaban relative to dabigatran etexilate. In order to decrease the resulting structural uncertainty, all relevant efficacy evidence was simultaneously incorporated in a MTC model [102, 230]. Deterministic and probabilistic analyses were repeated. Rivaroxaban continues to dominate in the basecase. The ICER of dabigatran etexilate (compared to enoxaparin) was €2,935 per QALY in the original analysis; dabigatran etexilate dominated in the MTC analysis. The probability that rivaroxaban and dabigatran etexilate were the most cost-effective strategies decreased to 65% (from 69%) and increased to 24% (from 18%) respectively. The respective cost-effectiveness planes (Figure 14(a) and Figure 17) indicates that the more favourable cost-effectiveness seen with dabigatran etexilate in the MTC analysis is driven by an increase in its efficacy. It is encouraging that this small change in results would be unlikely to impact on the health payer's decision.

It was considered pragmatic to accept a higher standard error of the Monte Carlo analysis in the lifetime models in order to retain a non-prohibitive running time. Reassuringly, the mean expected costs and QALYs were comparable on successive runs of the PSA.

There are no direct RCTs that investigate these long-term outcomes in the three strategies under investigation. There is also a lack of published literature which describes VTE progression rates in patients who have undergone THR or TKR. As such, the lifetime model relies upon literature based extrapolation. It is therefore subject to an increased structural uncertainty as compared to the 180 day model.

Therefore, although the lifetime model offers a more favourable probability that rivaroxaban is the most cost-effective option and the model results appear to be more robust, this uncertainty associated with extrapolation should be considered in the decision making process.

VTE-related mortality is not removed from the general age-specific mortality rate in the model. This does not lead to double counting since the same background mortality risk is assumed for all individuals regardless of health state. It is noted however that a number of studies however have investigated the long-term prognosis after stroke. They conclude, that persons who survive a stroke have a continuing excess risk of death, which remains at least double that of the background population [348-351]. There is also evidence to suggest that the long-term survival of patients who have experienced a DVT is compromised [85].

It is assumed that patients who develop a stroke in the decision tree remain permanently disabled until death or the end of the simulation. The model has no facility to allow improvement in disability level over patient lifetime. The important role of rehabilitation in stroke in reducing functional disability has however been well established [352-354]. The model assumption is likely to overestimate the costs and consequences associated with stroke. To compound this, the annual cost of stroke was obtained from a study that collected data over the one year period following an acute stroke and then extrapolated these costs over five years. It is likely that these costs will represent an overestimation of the annual costs incurred over a lifetime. The impacts of changing the preference value of stroke to '0' and to '1' were tested in a one-way SA. Rivaroxaban continued to dominate both comparators in both analyses. Rivaroxaban also continued to dominate when the annual cost of stroke and the utility value of stroke were jointly changed to '0'.

It was assumed that those patients who enter the 'Stroke' state remain there until death or the end of the simulation. For model simplification purposes, patients in the 'Stroke' state are not at risk of recurrent VTE and PTS. It was assumed that the costs and QoL impacts associated with any VTE or PTS events would be minimal compared to those of the 'Stroke' state. This model simplification will underestimate the number of VTE and PTS events likely to occur.

The model assumed that once patients entered the PTS health states, they were no longer at risk of recurrent VTE events. This assumption is likely to be conservative for rivaroxaban (the strategy of choice) since there is a lower probability that patients on rivaroxaban will enter the PTS health states. A lower percentage of rivaroxaban patients therefore are at no further risk of recurrence compared to the other strategies.

The model assumes that patients who develop PTS may not transition between the mild-to-moderate PTS and severe PTS states. This model simplification was based on the fact that although an ulcer can heal, the underlying condition remains as the damage to the venous system is serious and irreversible [197]. This assumption is likely to have resulted in an overestimation of the costs and consequences associated with PTS.

No literature was identified which described the incidence of recurrent VTE in patients with asymptomatic, untreated DVT. In this analysis, this risk was assumed to be the same as in patients with a treated DVT. This assumption is likely to decrease the cost-effectiveness of the less effective strategies (i.e. enoxaparin sodium and dabigatran etexilate).

There is a lack of Irish cost and preference data pertaining to VTE disease. As such, values from disparate sources from a range of jurisdictions have been used. However, these values were subjected to extensive SA in acknowledgement of this.

The probabilities pertaining to 'Recurrent VTE after Treated VTE', 'PTS after Treated VTE', 'PTS after asymptomatic VTE' and 'Annual Mortality Rate' are all entered into Time Dependent Probability tables within TreeAge Pro. The feasibility of attaching distributions to these time dependent probabilities has been discuseed with the TreeAge Support Team. They have confirmed that 'there is no obvious way to have sampling uncertainty with time-dependent probability tables within TreeAge Pro' [355]. It is a limitation of this model that the uncertainty associated with these parameters has not been explored.

In Ireland, data on discharges from acute public hospitals are recorded in the HIPE data using the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Australian Modification (ICD-10-AM) codes. A review of the HIPE data (1st January 2009 to 31st December 2009) has revealed that the average age of patients who underwent a THR (ICD-10-AM: 4752200*, 4931500*, 4931800*, 4931900) was 71.5 years and a TKR (ICD-10-AM: 49527*) was 67 years [356]. This is at odds with the average age of 63 years used here in both the THR and TKR economic models. This discrepancy is likely to overestimate the cost-effectiveness of dabigatran etexilate and rivaroxaban as compared to enoxaparin sodium.

Enoxaparin sodium was used as the comparator in this analysis. As mentioned previously, other LMWHs are also available for use in Ireland. The impact of using a weighted average cost (assuming a 50:50 notional market share for enoxaparin sodium and tinzaparin) on the ICER was investigated. Both the THR and TKR models were robust to this change; rivaroxaban continued to dominate both comparators.

Finally, because this analysis was performed from the perspective of the Irish HSE, the results may not be generalisable to other health systems.

Subsequent to this analysis, Kunnskapssenteret (The Norwegian Knowledge Centre for the Health Services) [223] evaluated dabigatran etexilate and rivaroxaban compared to enoxaparin sodium after THR or TKR from the Norwegian health payer perspective. At a cost effectiveness threshold of Norwegian Krone 500,000 (about €56,000) per QALY, rivaroxaban had the highest probability of being cost-effective (38%) after THR and enoxaparin sodium had the highest probability (34%) after TKR. They compared their results to those of our analysis. They concluded that it was a difference in the assumptions used for their estimation of efficacy and safety data which was largely responsible for the difference in results. Unlike our analysis, they had included and combined studies (phase II and phase III), across all doses of drugs and treatment lengths in meta-analyses. Our analysis was performed for a 220mg dose of dabigatran etexilate and 40mg of dose of enoxaparin only.

The results of our analysis have been compared to the published evaluation by Wolowacz *et al* [206]. In their analysis (UK NHS perspective), dabigatran etexilate 220mg OD dominated enoxaparin 40 mg OD after both THR and TKR. This model was used in Boehringer Ingelheim Ltd.'s submission to the NCPE. Likewise, from the HSE's perspective, the dabigatran etexilate dominated in both disease states. The structure of their lifetime model was similar to ours, however all patients on LMWH were at risk for HIT. In our evaluation dabigatran etexilate dominated after TKR; the ICER (dabigatran vs. enoxaparin sodium) after THR was €2,935 per QALY. However, dabigatran etexilate also dominated after THR when the efficacy point estimates were obtained from the MTC [357]. Likewise, the NCPE has assessed Bayer Ltd.'s economic evaluation of rivaroxaban, compared to enoxaparin sodium, as thromboprophylaxis after THR and TKR. Similar to our analysis, rivaroxaban dominated in both disease states. The time horizon of their economic model was five years [358].

5.7 Conclusions

When the lifetime thromboprophylaxis model is considered, basecase analysis indicates that when rivaroxaban, dabigatran etexilate and enoxaparin sodium are evaluated, rivaroxaban is the less costly and more effective option following THR and TKR. PSA indicates that rivaroxaban is the most cost-effective strategy at a cost-effectiveness threshold of €45,000 per QALY.

Compared to the 180 day model, the lifetime model offers a more favourable probability that rivaroxaban is the most cost-effective agent. This increased probability is not unexpected. However, the lifetime model relies upon literature based extrapolation and is therefore associated with greater uncertainty.

Chapter 6

Value of Information Analysis to Reduce Decision Uncertainty Associated with the Choice of Thromboprophylaxis after Total Hip- and Total Knee- Replacement

6 Value of Information Analysis to Reduce Decision Uncertainty Associated with the Choice of Thromboprophylaxis after Total Hip- and Total Knee-Replacement

6.1 Introduction

Treatment choices have to be made in the face of uncertainty about effectiveness, safety and economic implications [359]. Given that the decision about cost-effectiveness is uncertain, there is always a chance that the wrong decision has been made with subsequent opportunity loss [360].

To reduce uncertainty, decision makers could opt to commit resources to collecting additional economic evidence on the technologies under investigation [360]. A number of methods for setting priorities in research and development of health care technologies have been proposed. These include measures of the burden of disease and estimates of welfare losses due to variations in clinical practice. All such methods view research as a means of changing clinical practice, rather than reducing uncertainty about what is appropriate clinical practice. Therefore they assume that there is no uncertainty surrounding the decision. They also endeavour to identify research priorities using aggregate measures across broad clinical areas. Simply because such measures suggest a clinical area is a high priority, it does not mean that specific research relating to any one clinical decision will be valuable [57].

Policy makers are keen to understand the level of decision uncertainty and many HTA guidelines recommend PSA [50]. The CEAC derived from the PSA provides a measure of this uncertainty. Here, uncertainty is characterised by estimating the probability that an option is cost-effective at different levels of the cost-effectiveness threshold. However, the option with the highest probability of being cost-effective will not necessarily have the highest expected NMB. Instead, the CEAF plots the option which is optimal (has the highest expected NMB) at different values of the cost-effectiveness threshold [58]. However, the importance of uncertainty is not reflected as the consequences of not selecting the 'true' preferred alternative are ignored [61]. To overcome this problem, it is necessary to use a measure that

incorporates the magnitude of the difference between the true preferred and alternative decisions, rather than merely counting probabilities. Value of Information (VOI) methods seem appropriate for this purpose [361, 362].

VOI provides a framework that can be used to explicitly estimate the expected benefit of future research [359]. It offers a Bayesian approach, such that current knowledge is taken, proposed information to be collected is added in, and a posterior distribution, based on all available information, is produced [363].

6.1.1 Expected Value of Perfect Information

The expected value of perfect information (EVPI) estimates the value of simultaneously eliminating all uncertainty of all uncertain parameters related to the decision [62]. Any additional research to decrease uncertainty will never resolve all the uncertainties, but the EVPI places an upper bound on the value of this additional evidence [50, 63]. Essentially, if the EVPI exceeds the expected costs of further investigation, then it is potentially cost-effective to conduct additional research on the technology [65].

The EVPI can be determined directly from the PSA with each iteration representing a possible future resolution of the existing uncertainty for which the optimal decision can be identified [63]. It combines both the probability of the wrong decision being made and the consequences of the wrong decision in terms of the net benefit (NB) forgone [254] and it can be expressed in health or monetary values [50].

6.1.2 Expected Value of Perfect Parameter Information

If the EVPI suggests that more research is justified, the expected value of perfect parameter information (EVPPI) can identify the key parameters whose uncertainty drives the decision uncertainty. This can allow further research to be prioritised [62, 63, 66]. In an economic evaluation, it is possible that only a few parameters account for virtually all the decision uncertainty [62].

The EVPPI is the expected value of obtaining perfect knowledge about the 'true' values of one or more parameters [62, 66, 364]. It is the difference between the expected

value of the decision made on the basis of existing information and the value of the decision made with perfect information about the parameter(s) of interest and current information about the remaining parameters averaged over all possible realisations of uncertainty about the parameter(s) of interest [57, 63, 315, 365].

EVPPI can be expressed in health or monetary values [50]. When expressed in monetary terms, it can be directly compared with the expected opportunity costs of the type of research that might be needed to provide the evidence. Some uncertainties are relatively inexpensive to resolve (in terms of time and resource), compared with others (e.g. an observational study compared with a RCT) [50].

The EVPPI values associated with model inputs will change with the cost-effectiveness threshold. Specifically, those inputs which are more closely related to differences in expected costs will be relatively more important at low threshold values, and those more closely related to differences in outcomes will be more important at high values [315].

The EVPPI value is necessarily positive and is also necessarily less than the overall EVPI [66].

6.1.3 Population Expected Value of Perfect Information

Information is a public good; as such generation of perfect information for one instance of a decision ensures that the information is available for other instances of the decision. Hence, the overall value of perfect information surrounding a health care policy decision depends on the number of times that the decision is faced over the lifetime of the technology [365].

The expressions for EVPI and EVPPI refer to the maximum value that can be placed on additional information to inform treatment choice for an individual patient [365]. The population-level estimates are determined by scaling up the individual estimates according to an assessment of the time horizon for the information, estimates of incidence over this period and a discount rate [63, 365, 366].

A judgement by the analyst is required about the time over which additional evidence that can be acquired in the near future is likely to be useful and relevant [367]. Even if the time horizon is not chosen arbitrarily but is based on evidence or formal priors, it will remain a proxy [366]. Fixed time horizons of 10,15 and 20 years have commonly been used in the health literature [367]. There is some empirical evidence that suggests that clinical information may be valuable for much longer (a half-life of 45 years) [368], although this has been regarded as an overestimation by others [369].

With a positive discount rate, population level VOI estimates will be finite [364].

Investigations of EVPI and EVPPI can be applied to allow policy and decision makers to more efficiently design and prioritise healthcare research [370].

6.1.4 Health Technology Assessment in Ireland

In Ireland, the NCPE appraises the cost-effectiveness of technologies, for reimbursement purposes, in response to requests from the HSE or the DoHC. Since September 2009, in collaboration with the HSE, the centre considers the cost-effectiveness of all new medicines introduced to Ireland. Assessments are conducted in accordance with the existing agreed Irish HTA Guidelines [18]. These guidelines do not specify a formal analysis of VOI as part of the 'reference case'.

It has been recognised elsewhere that a framework for reimbursement is needed in which the decision about whether to reimburse, based on existing data, needs to be taken simultaneously with the decision regarding whether additional research is to be undertaken [315].

6.2 Objective

The objective of this study was to establish the level of decision uncertainty associated with the choice of thromboprophylaxis after THR and TKR. Also, to demonstrate the benefits of using VOI analysis in decreasing decision uncertainty.

A further aim was to examine the viability of applying these techniques as part of the formal HTA process for reimbursement purposes within the Irish Healthcare System.

6.3 Method

VOI analysis was undertaken on all four thromboprophylaxis models i.e., the TKR and THR (180 day- and lifetime-) models. All models evaluated the cost-effectiveness of rivaroxaban, dabigatran etexilate and enoxaparin sodium as thromboprophylaxis.

All analyses were performed using TreeAge Pro 2008® (TreeAge Software Inc, Williamstown, MA, USA).

The analyses were conducted from the Irish HSE perspective. A cost-effectiveness threshold of €45,000 per QALY was considered [4].

6.3.1 Expected Value of Perfect Information

To characterise decision uncertainty, PSA uses Monte Carlo simulation to repeatedly sample from the prior distributions assigned to all the uncertain model parameters (θ). For each iteration, the expected costs ($E_\theta C(j, \theta)$) and QALYs ($E_\theta Q(j, \theta)$) for all three strategies (j) were combined to form a measure of NMB ($E_\theta NMB(j, \theta)$).

The NMB is given by: [56, 57]

$$E_\theta NMB\ (j, \theta) = (E_\theta Q(j, \theta) \times \lambda) - E_\theta C(j, \theta)$$

Where:
NMB=net monetary benefit
$E_\theta Q(j, \theta)$ =expected QALYs
$E_\theta C(j, \theta)$ =expected Costs
λ =cost-effectiveness threshold
j =all strategies under investigation
θ =all uncertain model parameters

The output of these simulations represents the possible values of the NMB for all possible realisations of the uncertain parameters (θ) [364, 365].

The EVPI is the difference between the expected NMB with perfect information and the expected NMB with current information. The optimal decision with current information would be to choose the intervention that generates the maximum expected NMB ($\max_j E_\theta NMB(j, \theta)$). With perfect information, we would know how the

uncertainties would resolve and we could select the alternative that maximises the NMB for a particular value of θ (max_j NMB (j, θ)). However, the true values of θ are unknown, so the expected value of a decision taken with perfect information is found by averaging the maximum NMB over the joint distribution of θ.

The EVPI is therefore calculated as the average of the maximum NMBs across all model iterations (i.e. the expected NMB using perfect information), minus the maximum of the average expected NMBs across all strategies (i.e., the expected NMB using the currently available information) [57, 364, 365].

The EVPI is calculated as: [57]

$$EVPI = E_\theta max_j NMB\ (j, \theta) - max_j E_\theta NMB\ (j, \theta)$$

Where:
$E_\theta max_j$ NMB (j, θ) = expected NMB with perfect information about θ
$max_j E_\theta$NMB (j, θ)= expected NMB of strategy of choice with current information about θ
NMB=net monetary benefit

EVPI was calculated on 30,000 PSA iterations for the 180 day models and 50,000 iterations for the lifetime models. This number of PSA iterations was chosen as it had previously been demonstrated that the PSA results did not change appreciably in three successive PSA runs (see Table 20, Table 22, Table 28 and Table 29).

EVPI estimates were calculated over a cost-effectiveness threshold range of €0-€100,000 per QALY.

The method of EVPI calculation is illustrated in Table 32. The example shown is the THR 180 day model.

Table 32 The calculation of expected value of perfect information given perfect information on θ. Example shown is the THR 180 day model, with 30,000 PSA iterations.

	NMB (where λ=€45,000/Qaly)			
Iteration	Rivaroxaban	Enoxaparin	Dabigatran	Max NMB
1	33018	28412	25392	33018
2	26841	32072	25015	32072
3	35296	33277	29379	35296
4	29472	33976	32898	33976
5	27194	29349	32922	32922
6	31525	33310	34552	34552
n=30,000				
Mean NMB	28609[a] $\max_j E_\theta NMB(j, \theta)$	28148	28187	30462[b] $E_\theta \max_i NMB(j, \theta)$ EVPI=1852[c]

a. Rivaroxaban has the highest expected NMB, $[\max_j E_\theta NMB(j, \theta)]$ and is the optimal strategy with current information.
b. The mean of the maximum expected NMBs across all model iterations is $[E_\theta \max_j NMB(j, \theta)]$ i.e. the expected NMB with perfect information.
c. EVPI is calculated as the average gain in NMB across the model iterations; $EVPI = E_\theta \max_j NMB(j, \theta) - \max_j E_\theta NMB(j, \theta)$ i.e. (30462- 28609) = 1852

NMB=net monetary benefit; **EVPI**=expected value of perfect information; **λ**=cost-effectiveness threshold; **θ**=all uncertain model parameters; **j**=the 3 strategies under investigation.

6.3.2 Expected Value of Perfect Parameter Information

The four thromboprophylaxis economics models share the same subsets of parameters: probabilities, preference weights and direct medical costs. EVPPI estimates for the three subsets were calculated for each model.

If the uncertain parameters (θ) are divided into two parameter subsets, φ and its complement ψ, then the value of perfect information about a parameter or a subset (φ) can be calculated. It is the difference between the expected NMB with perfect information about φ and the NMB with current information about φ.

With perfect information, the value of φ is known and the expected NMBs are calculated over the remaining uncertainties ψ ($\max_j E_{\psi|\varphi} NMB(j,\varphi,\psi)$). However, the true values of φ are unknown and the expected value of a decision taken with perfect information is found by averaging these maximum expected NMBs over the distribution of φ ($E_\varphi \max_j E_{\psi|\varphi} NMB(j,\varphi,\psi)$).

The expected value with current information is the same as before ($max_j E_\theta NMB(j,\theta)$) since $\varphi \cup \psi = \theta$ [320].

Therefore, the EVPPI is calculated as: [57, 66, 254, 315, 371]

$$EVPPI(\varphi) = E_\varphi max_j E_{\psi|\varphi} NMB(j,\varphi,\psi) - max_j E_\theta NMB(j,\theta)$$

Where:
$E_\varphi max_j E_{\psi|\varphi} NMB(j,\varphi,\psi)$ = expected NMB with perfect information about φ
$max_j E_\theta NMB(j,\theta)$ =expected NMB of strategy of choice with current information about φ

The two-stage sampling algorithm, which uses two nested levels of Monte Carlo sampling over the plausible ranges for both the parameters of interest (φ) and the remaining uncertain parameters (ψ) was implemented [66]. This method is illustrated in Table 33. The example shown is the THR 180 day economic model, parameter subset of interest (φ) is direct medical costs.

EVPPI on the 180 day models was calculated on 30,000 inner- and 1000 outer-loops. The running time per parameter group was approximately four computational hours. For the lifetime models, the number of runs was reduced to 1000 inner- and 1000 outer-loops due to the computationally expensive nature of the analyses. The running time per parameter group in the lifetime model investigations was about 100 computational hours.

EVPPI estimates were calculated over a cost-effectiveness threshold range of €0-€100,000 per QALY.

Table 33: Illustration of the two stage Monte Carlo algorithm (with 30,000 inner- and 1000 outer-loops) given perfect information on φ. Example shown is the THR 180 day model, parameter subset of interest (φ) is the 'direct medical costs' subset.

Inner Loop Simulations

Iteration	$E_{\psi\|\varphi}NMB(\varphi,\psi)$ where λ=€45,000/Qaly		
	Rivaroxaban	Enoxaparin	Dabigatran
1	29057	22883.	27519
2	29257	30886	26962
3	27477	29433	29454
4	25873	32180	30883
5	28461	28824	27419
n =30,000			
Mean $E_{\psi\|\varphi}NMB(\varphi,\psi)$	28618[a] Max $E_{\psi\|\varphi}NMB(\varphi,\psi)$	28151	28225

Outer Loop Simulations

	Mean $E_{\psi\|\varphi}NMB(\varphi,\psi)$ where λ=€45,000/Qaly			
Inner Loop Number	Rivaroxaban	Enoxaparin	Dabigatran	Max $E_{\psi\|\varphi}NMB(\varphi,\psi)$
1	28618	28151	28225	28618
2	32651	28655	28877	32651
3	29738	29046	29989	29989
4	30122	27248	26272	30122
5	27084	26082	29639	29639
n=1000				
Mean	28602[c] $\max_j E_\theta NMB(j,\theta)$	28079	28100	30400[b] $E_\varphi \max_j E_{\psi\|\varphi}NMB(j,\varphi,\psi)$ EVPPI=1798[d]

a. Inner-loop simulations: Parameters of interest (φ) were sampled once from their prior distributions and were held fixed at their sampled values. All other model parameters (ψ) were varied according to their prior uncertainty (30,000 PSA iterations). The maximum of the average NMB across all treatment strategies was recorded (Max $E_{\psi|\varphi}NMB(\varphi,\psi)$).

b. Outer-loop simulations: The previous step was repeated 1000 times and the average of the maximums from the previous step was calculated ($E_\varphi \max_j E_{\psi|\varphi}NMB(j,\varphi,\psi)$).

c. The average NMB of the policy of choice, rivaroxaban is calculated ($\max_j E_\theta NMB(j,\theta)$).

d. The EVPPI is the difference between $E_\varphi \max_j E_{\psi|\varphi}NMB(j,\varphi,\psi)$ and the average NMB of the policy of choice ($\max_j E_\theta NMB(j,\theta)$) i.e. EVPPI (direct medical costs) = 30400 - 28602 =1798

NMB=net monetary benefit; **EVPI**=expected value of perfect information; **EVPPI**=expected value of partial perfect information; **λ**=cost effectiveness threshold; **j**=3 strategies; **φ**= parameter subset of interest; **Ψ**= remaining uncertain parameters.

6.3.3 Population Expected Value of Perfect Information

EVPI and EVPPI estimates were scaled up to population level according to the incidence of the decision [63]. This was calculated based on the 5,023 THR (for the THR models) and 1,864 TKR (for the TKR models) procedures preformed in acute

public hospitals in Ireland in 2008 [372] and the ENDORSE study which revealed that 64% of at risk surgical patients in Ireland receive ACCP-recommended prophylaxis [161]. The assumed uptake rate of the policy of choice with current information was 50%. A discount rate of 4% was applied. A conservative assumption that the information would be valuable for 10 years was used as the basecase. Alternative assumptions of 5 and 15 years were also explored.

PEVPI is calculated as: [365, 366]

$$PEVPI = EVPI \times \sum_{t=1}^{T} (I_t/(1+r)^t)$$

Where PEVPI=population level expected value of perfect information
T = time horizon
I_t = incidence estimate over time period
r = discount rate

6.4 Results

VOI estimates on the four thromboprophylaxis models at €45,000 per QALY, (with a decision time horizon of 10 years, an uptake rate of 50% and a discount rate of 4%), are described in Table 34. This table highlights that, consistent across all models, virtually all the decision uncertainty is associated with the direct medical costs parameter subset.

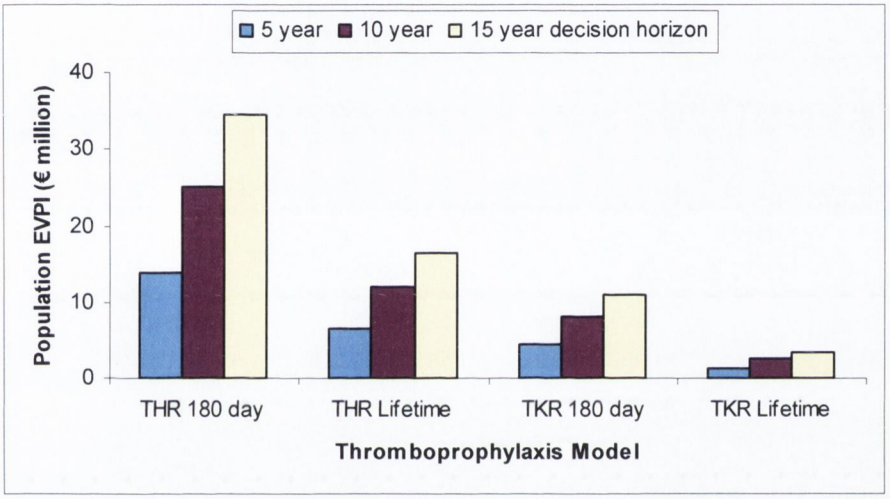
Table 34: EVPI and EVPPI estimates for each thromboprophylaxis model (where λ= €45,000/QALY), given a 10 year decision time horizon, an assumed uptake rate of the policy of choice of 50% and a 4% discount rate. (Costs are in €, year 2008 values).

Disease State	Model	Patient Level EVPI (€)	Population Level (€ million)			
			EVPI	EVPPI		
				Direct Costs	Probabilities	Preferences
THR	180 day	1852	25.12	24.39	0.00	0.08
	Lifetime	882	11.96	9.00	0.00	0.01
TKR	180 day	1593	8.02	7.80	0.00	0.01
	Lifetime	494	2.49	1.48	0.00	0.03

λ = cost-effectiveness threshold; **EVPI**=expected value of perfect information; **EVPPI**=expected value of perfect parameter information; **THR**=total hip replacement; **TKR**=total knee replacement.

A conservative assumption, of a 10 year decision time horizon, was used in the basecase population EVPI estimates. The influence of this assumption on these values is shown in Figure 19. Taking the THR 180 day model as an example, there is a considerable range in the estimates from €13.79 million (when a 5 year decision time horizon is assumed) to €34.43 million (with a 15 year decision time horizon).

Figure 19: Population EVPI estimates associated with each thromboprophylaxis model given 5, 10 and 15 year time horizons for the decision, where λ = €45,000/QALY (Costs are in €, year 2008 values).

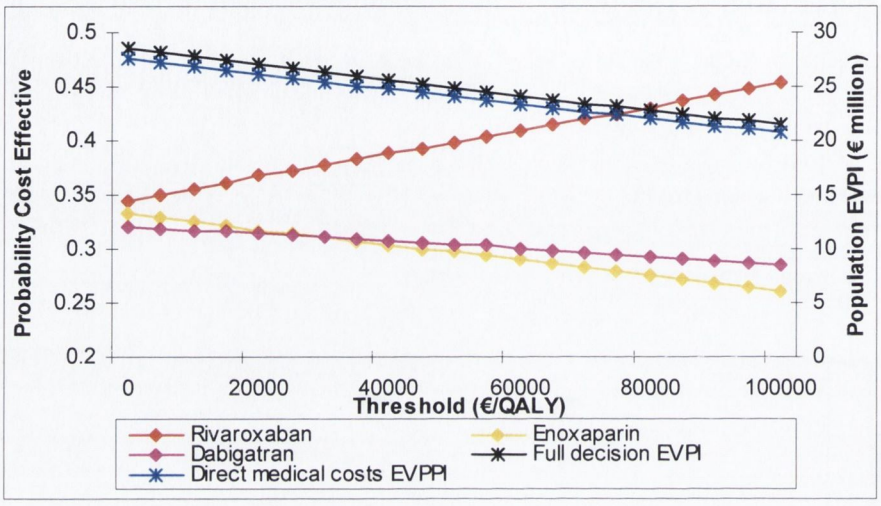


EVPI=expected value of perfect information; **λ**=cost-effectiveness threshold; **THR**=total hip replacement; **TKR**=total knee replacement.

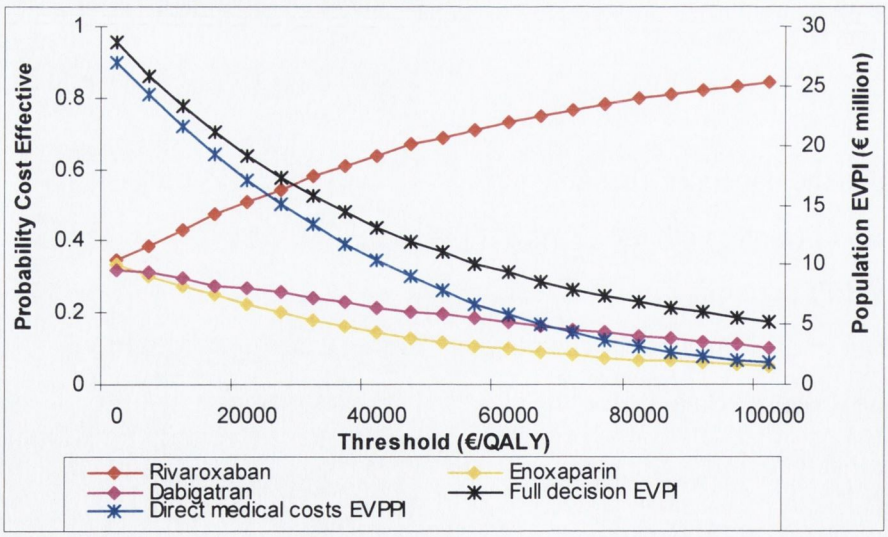
Figure 20 highlights the impact of changing the cost-effectiveness threshold on the population level EVPI (along with the CEAC) for each thromboprophylaxis model. The population EVPPI pertaining to the direct medical costs subset is also shown. This highlights that, in all four models, the majority of the decision uncertainty is associated with the direct medical costs subset, at any given threshold.

Figure 20: Cost-effectiveness acceptability curves with EVPI curves for all models (costs are in €, year 2008 values) for (**a**) THR 180 day model, (**b**) THR Lifetime model, (**c**) TKR 180 day model and (**d**) TKR Lifetime model. EVPI curves are depicted as a function of λ (€0 - €100,000/QALY), assuming a 10 year time horizon for the decision

(a): Total Hip Replacement (180 day)

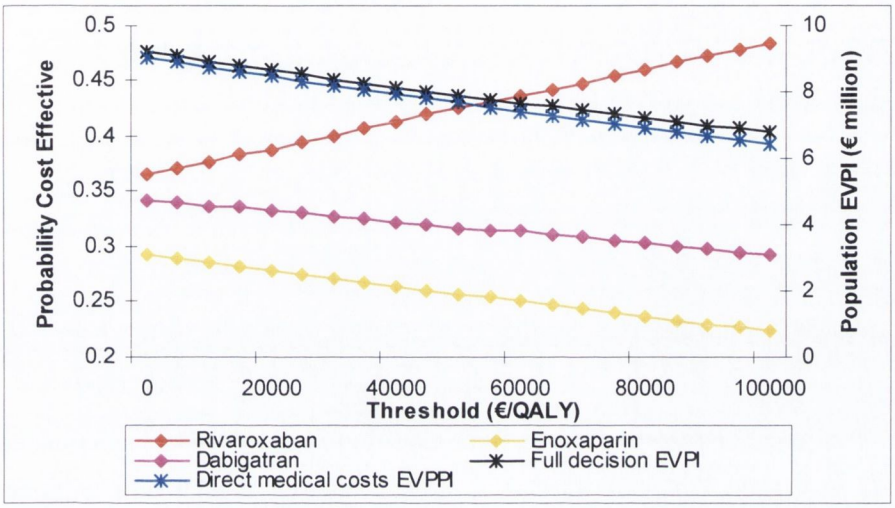


(b): Total Hip Replacement (Lifetime)

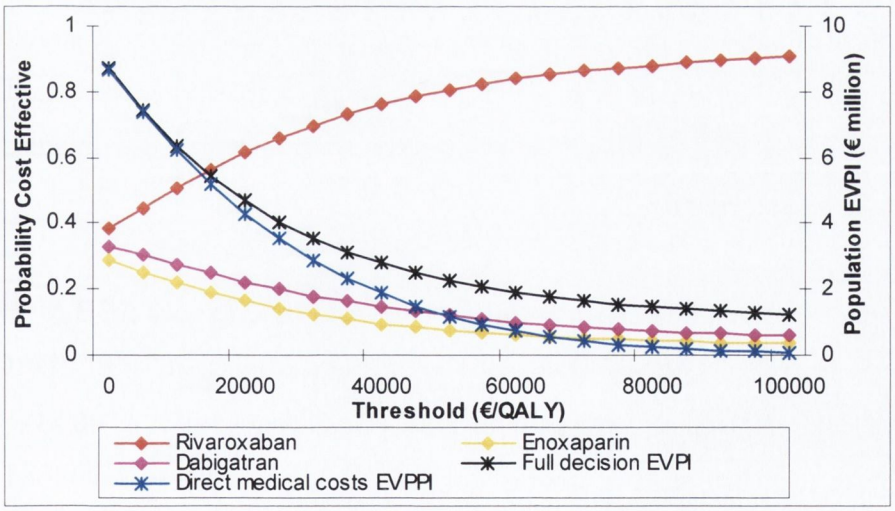


THR=total hip replacement; **PSA**=probabilistic analysis; **EVPI**=expected value of perfect information; λ=cost-effectiveness threshold.

(c): Total Knee Replacement (180 day)



(d): Total Knee Replacement (Lifetime)



THR=total hip replacement; **TKR**=total knee replacement; **PSA**=probabilistic analysis; **EVPI**=expected value of perfect information; **λ**=cost-effectiveness threshold.

6.4.1 Further Research

It was considered pragmatic, from a decision maker's perspective, to direct further research towards the THR disease state. Table 34 highlights that population EVPI estimates associated with the THR models are higher than those associated with the respective TKR models, indicating greater decision uncertainty. Also, the uncertainty associated with both the acute events (VTE and thromboprophylaxis related bleeds) and their long-term consequences was deemed to be of interest to the decision maker. Thus the lifetime THR- (rather than the 180 day THR-) model was chosen for further analysis.

EVPPI analysis identified that research should be targeted towards the direct medical costs input into the model. A more detailed costing study was undertaken. Updated costs were obtained through a systematic literature search, use of updated Casemix data and the use of Irish cost of care studies where available [373, 374]. The subsequent analysis was termed the 'revisited' analysis in order to differentiate it from the 'original' analysis.

6.4.1.1 Direct Medical Costs Input into the Revisited Analysis

In July 2010, the NCPE introduced guidelines for inclusion of drug costs in pharmacoeconomic evaluations [375]. These guidelines specify that drug prices should be obtained from the reimbursement files of the PCRS which represent the price paid to pharmacists by the HSE [305]. In the revisited analysis, all drug costs were obtained from the PCRS reimbursement files [305].

The weighted average costs of hospital stay for elective THR (DRG codes I03B & I03C), GI haemorrhage (DRG codes G61A &G61B), hospital admission for PE (DRG codes E61A & E61B) and hospital admission for DVT (DRG codes F63A & F63B) were calculated from the 2010 updated Irish HSE DRGs Casemix data. Hospital bed stay and ED visit costs were also obtained from this source [376]. Neither hospital bed stay nor ED visit costs had been included in the 2007 Irish HSE DRGs Casemix data, [292] which had been used for the original analysis.

The direct costs for the acute hospital care of stroke and for the annual health state cost of stroke were obtained from the Irish Heart Foundation Cost of Stroke in Ireland (COSI) report [374]. This prevalence based cost-of-illness study used the Casemix approach to estimate the economic burden of stroke in Ireland over a one year period in the year 2007.

A systematic literature search revealed no up-to-date references detailing costs associated with PTS. For the revisited analysis, the annual cost of PTS was obtained from the 2003 US study which had been used in the original analysis [197]. Similar to the original analysis, the PTS costs were weighted under the assumption that 36% of PTS cases would be severe [115]. For the revisited analysis, costs were inflated to 2010 [193].

A systematic search of published literature revealed a lack of good quality data pertaining to the cost of INR monitoring in Ireland. A published systematic literature review of INR monitoring also failed to identify any costing studies relating to Ireland [377]. The COSI report states that there is limited up-to-date evidence on the cost of anticoagulation services [374].

A 2009 micro-costing study of patient attendance at an anticoagulation clinic in an Irish General Practice (GP) practice was located [373]. This study was based on 10 randomly selected patients in the practice who were on warfarin for atrial fibrillation (AF). All patients were under warfarin management in the practice for at least 12 months. Costs included staff (doctor, nurse and clerical), overhead (rent, electricity, heating and computer) and equipment (including gloves, alcohol wipes, needle and vacutainer) costs. The laboratory cost was an estimated cost received from the hospital where INR analysis was undertaken. Direct costs per visit were estimated to be €28.97 [373].

Updated costs pertaining to a d-dimer blood test, Doppler ultrasound, chest X-ray, E.C.G, CTPA and graduated compression stockings were obtained from a university teaching hospital 2010 in-house data-base of costs.

For this revisited analysis, all costs were inflated to 2010 cost values [193].

Table 35 describes the disaggregated costs applied to the original and revisited analyses. The costs applied to the original analysis are summarised in the column marked '2008 Unit Cost Data', whilst those applied to the revisited analysis are summarised in the column marked '2010 Unit Cost data'.

In order to obtain the updated CoV associated with the direct medical costs, the elicitation exercise previously performed (section 4.4.8), was repeated with the up-dated costs [309]. Predictive probability distributions for the up-dated costs were constructed by varying the values of the CoV. The analyst (who had also selected the CoV associated with the original costs) selected the distribution that most closely matched the uncertainty associated with the updated costs at the time that they had been obtained. The resultant associated value of the CoV was 0.1. As a result, in the PSA, the CoV on the log-Normal distribution on the costs was decreased from 0.2 to 0.1. Deterministic, probabilistic and VOI analyses were repeated.

Table 35: Total hip replacement lifetime model. Costs applied to the economic evaluation for the original and revisited analysis.

Resource	2008 Unit Cost Data (€)	2010 Unit Cost Data (€)
Rivaroxaban (10mg) DDD	5.15[a]	5.67[b]
Dabigatran etexilate (220mg) DDD	5.18[a]	5.27[b]
Enoxaparin sodium (40mg) DDD	5.10[c]	5.60[b]
Primary Hospitalisation		
THR	13048[d]	14634[e]
GI Haemorrhage	2555[d]	3051[e]
Acute care for stroke	14961[d]	9057[f]
VTE Diagnosis		
D-dimer	15.00[g]	15.00[h]
Doppler ultrasound	130.00[g]	130.00[h]
CTPA	113.00[g]	113.00[h]
Chest x-ray	47.00[g]	25.00[h]
ECG	50.00[g]	50.00[h]
VTE treatment		
Warfarin DDD	0.11[c]	0.11[b]
Anticoagulant clinic visit	60.00[i]	29.00[j]
Graduated compression stockings	15.00[g]	15.00[h]
Hospital bed day	500.00[g]	874.00[e]
ED visit	200.00[g]	277.00[e]
Hospital readmission for DVT	3470[d]	3705[e]
Hospital readmission for PE	5790[d]	7482[e]
Annual Health States		
PTS - First year	1795[k]	1870[l]
PTS - Subsequent years	772[k]	804[l]
Stroke	4847[m]	9694[f]

DDD=daily defined dose; **THR**=total hip replacement; **GI**= Gastrointestinal; **CTPA**= Computed Tomography Pulmonary Angiogram; **ECG** = electrocardiogram; **ED**=emergency department; **DVT**= Deep vein thrombosis, **PE**=Pulmonary embolism, **PTS**= Post thrombotic syndrome.

a. Proposed Health Service Executive (HSE) price (05/08)
b. Health Services Executive (HSE). Reimbursable Items. Primary Care Reimbursement Service (PCRS) 2010 [305]
c. Monthly Index of Medical Specialities (MIMS) Ireland (10/08)[303]
d. Casemix, Health Service Executive 2007[292]. Costs inflated to 2008 price [193]
e. Casemix, Health Service Executive 2010 [376]
f. Irish Heart Foundation. Cost of Stroke in Ireland Report. 2010 [374]
g. Inhouse data base of costs provided by university teaching hospital (average costs used), Dublin (2008 Aug)
h. Inhouse data base of costs provided by university teaching hospital (average costs used), (Dublin (2010 Jan)
i. Expert opinion. Clinical Pharmacology Department, St James's University Teaching Hospital, Dublin
j. Micro-costing of an Irish anticoagulant clinic 2009 [373] . Costs inflated to 2010 [193]
k. Caprini *et al* [197] and Monreal *et al* [115]. Costs inflated to 2008 [193]
l. Caprini *et al* [197] and Monreal *et al* [115]. Costs inflated to 2010 [193]
m. For this analysis, STG £15,306 (cost from Youman *et al*) [334] was divided by 5 to obtain an annual cost of stroke. This was converted to Euros (STG £1= €1.2707, Oct 2008 exchange rate) [333] and inflated to 2008 using the Consumer Price Index for Health[193].

6.5 Revisited Analysis Results

The results of the revisited analysis are compared to those of the original analysis (section 5.4.1.1 and section 5.4.3.1). Basecase analysis reveals that rivaroxaban continues to dominate both comparators. The ICER for dabigatran etexilate relative to enoxaparin sodium decreased from €2,935 per QALY in the original to €1,558 per QALY in the revisited analysis.

The CEAC, CEAF and the population EVPI estimates (over the threshold €0 - €100,000 per QALY), for both the original and the revisited analyses are depicted in Figure 21. In the revisited analysis, rivaroxaban continued to have the highest probability of being optimal and had the highest expected NMB over the entire threshold range. At €45,000 per QALY, the probability that rivaroxaban is the most cost-effective strategy increased to 81% (from 69%), followed by dabigatran etexilate (decreased to 13%) and enoxaparin sodium (decreased to 6%).

Population EVPI and EVPPI levels (assuming a 10 year decision time horizon, at €45,000 per QALY) pertaining to the original cost data analysis and the revisited cost data analysis are summarised in Table 36. Population EVPPI estimates associated with the three parameter subsets, as a function of the threshold (€0 - €100,000 per QALY) are shown in Figure 22.

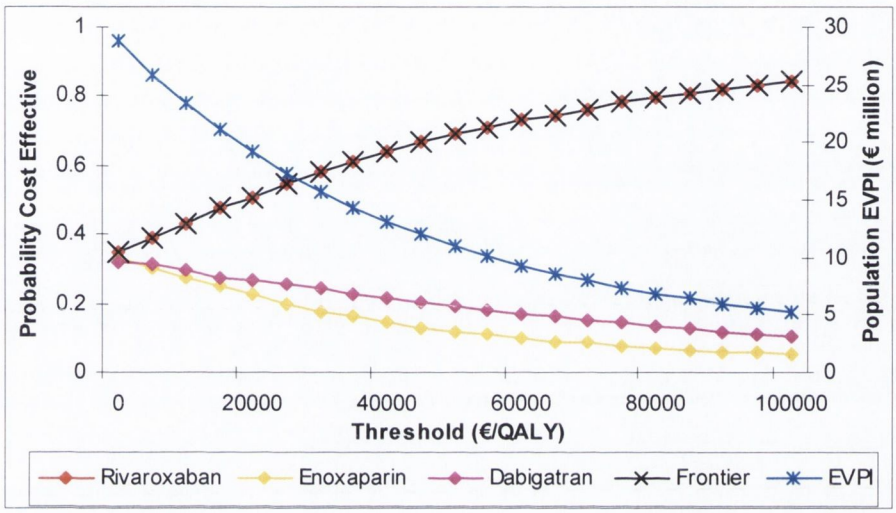
Table 36: Total hip replacement lifetime model (original and revisited). EVPI and EVPPI estimates pertaining to the original analysis (costs are in €, year 2008 values) and the revisited analysis (costs are in €, year 2010 values). The analyses assume a 10 year decision time horizon, where λ= €45,000/QALY.

THR Lifetime Model	**Patient Level EVPI (€)**	**Population Level (€ million)**			
		EVPI	**EVPPI**		
			Direct Costs	**Probabilities**	**Preferences**
Original	882	11.96	9.00	0	0.01
Revisited	253	3.43	1.72	0	0.06

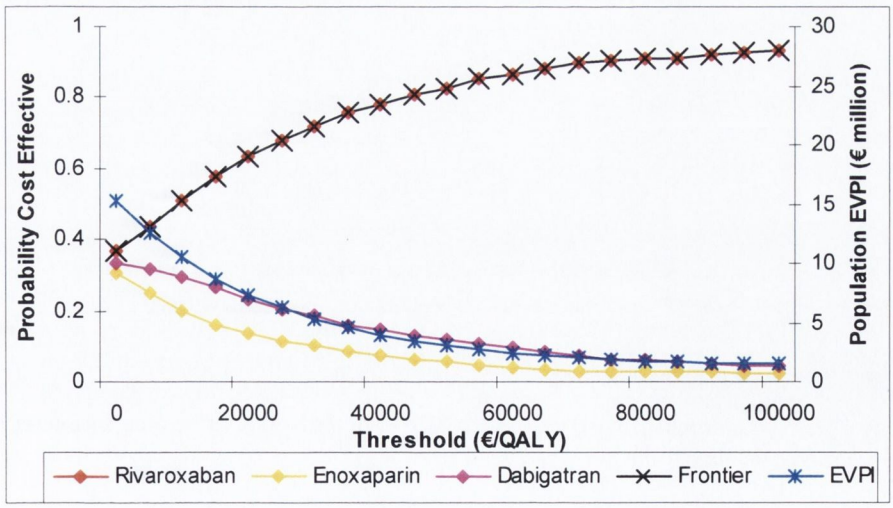
λ = cost-effectiveness threshold; **EVPI**=expected value of perfect information; **EVPPI**=expected value of perfect parameter information; **THR**=total hip replacement.

Figure 21: Total hip replacement lifetime model. Cost-effectiveness acceptability curves with EVPI curves for the original and revisited analyses.
(**a**) original cost data analysis (costs are in €, year 2008 values) and (**b**) revisited cost data analysis (costs are in €, year 2010 values). EVPI curves are depicted as a function of λ (€0 - €100,000/QALY), assuming a 10 year time horizon for the decision.

(a): Original analysis



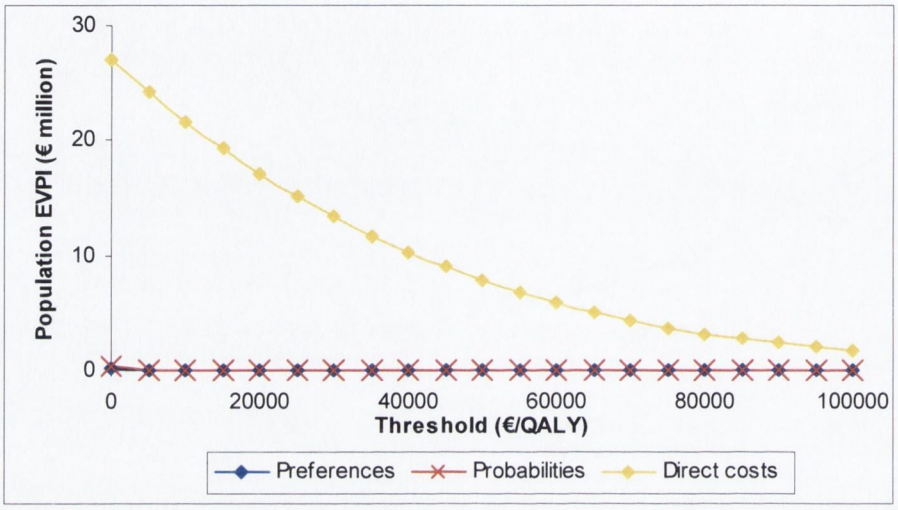
(b): Revisited analysis



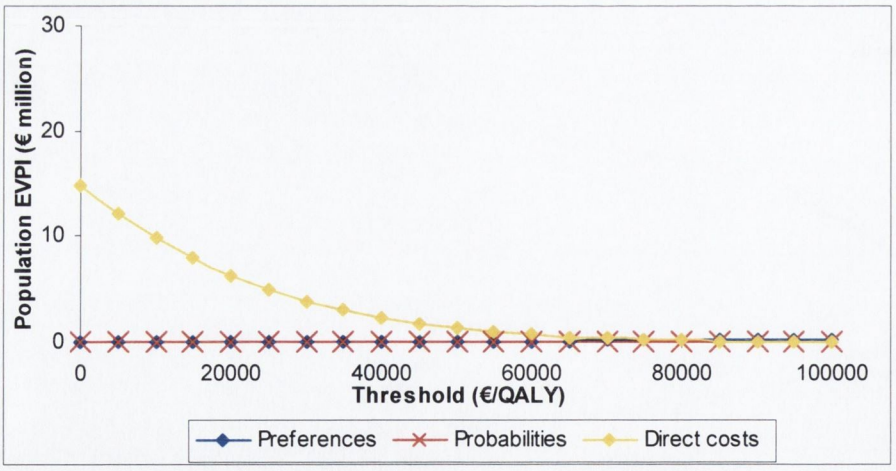
EVPI=expected value of perfect information; **λ**=cost-effectiveness threshold.

Figure 22: Total hip replacement lifetime model. Population level EVPPI estimates for original and revisited analyses.
Population level EVPPI estimates associated with each parameter subset as a function of λ (€0 - €100,000/QALY) are shown (**a**) original cost data analysis (costs are in €, year 2008 values) and (**b**) revisited cost data analysis (costs are in €, year 2010 values). A 10 year decision time horizon is assumed.

(a): Original analysis



(b): Revisited analysis



EVPI=expected value of perfect parameter information; **EVPPI**=expected value of perfect parameter information; λ=cost-effectiveness threshold

6.6 Discussion

This is the first VOI analysis which has attempted to quantify and decrease decision uncertainty within the context of the Irish healthcare payer. Here, VOI techniques were employed to establish the level of decision uncertainty associated with the choice of thromboprophylaxis after elective THR and TKR. The benefit of using VOI methods to decrease decision uncertainty was subsequently demonstrated.

Table 34 describes the VOI estimates, at €45,000 per QALY, for each thromboprophylaxis model. Patient level EVPI estimates associated with the lifetime models are less than those associated with the respective 180 day models. This decreased decision uncertainty reflects the decreased uncertainty previously seen in the cost-effectiveness analyses, where the lifetime models are associated with a higher probability of rivaroxaban being the most cost-effective strategy (see section 5.7)

Table 34 also illustrates how the size of the eligible population impacts on population estimates. The larger population EVPI values associated with THR compared to TKR are, in part, a reflection of the greater number of THR procedures preformed in acute public hospitals in Ireland [372].

The effective lifetime of a decision problem is unknown. As has been suggested in the literature [367], an arbitrary time horizon of 10 years was chosen here as the basecase. The impact of changing the horizon on the population EVPI is depicted in Figure 19, indicating a considerable range in estimates between those based upon assumptions of 5 and 15 year decision time horizons.

Figure 20 (a-d) illustrates the effect of the cost-effectiveness threshold on the EVPI estimates associated with each economic model. In all instances, the EVPI value is at its highest at €0 per QALY. This is the point where there is the lowest probability that rivaroxaban is the most cost-effective agent and the choice between all strategies is the most uncertain. As the threshold increases, rivaroxaban is expected to have a higher probability of cost-effectiveness, additional information is therefore less likely to change the decision and the EVPI consequently falls. In the current economic climate it is possible that the decision maker would consider a lower or even a zero

threshold. Crucially, the potential opportunity loss to the HSE would be increased in these circumstances.

The EVPI estimates fall more dramatically with increasing payer threshold in the lifetime- compared to the 180 day- models. This more prominent decrease in uncertainty, with increased threshold, is reflected in the respective CEACs. A more appreciable increase in the probability of rivaroxaban being cost-effective is seen in the lifetime models with threshold increase.

The EVPI values associated with each of the four thromboprophylaxis models are appreciable. Since EVPI analysis indicated that further research could be cost-effective, EVPPI analysis was performed. Table 34 highlights that, consistently across the four models (at €45,000 per QALY) further research should be directed towards the direct medical costs subset. Taking the THR lifetime model as an example (EVPI of €11.96 million), resolution of the uncertainty associated with the direct medical costs parameter subset is worth €9.00 million to the HSE. The EVPPI associated with the preferences was low, at €0.01 million, and the probabilities subset had no associated value. This does not mean that the uncertainty surrounding their values is unimportant, but it does mean that gathering more information about these parameter subsets would be unlikely to be valuable. It is noted that in this analysis, the sum of the parameter EVPPI estimates was less than the whole decision EVPI. This is likely to be due to correlations between parameters within the model [364].

The EVPPI associated with the direct medical costs was subsequently calculated across the entire threshold range (€0- €100,000 per QALY). Figure 20 (a-d) illustrates that consistently across all models the majority of the decision uncertainty is associated with the direct medical cost subset across the threshold range.

The THR lifetime model was chosen for further investigations.

Once it was determined that model uncertainty was associated with the direct medical costs, these were revisited. The revised costs included a number of Irish costing studies and updated Casemix data. The revisited costs were granted a narrower CoV on the log-Normal distribution, based on an elicitation exercise [309].

In the revisited analysis, the decision regarding which treatment to adopt does not change. In the basecase, rivaroxaban continues to dominate. The PSA results (over the threshold €0 - €100,000 per QALY) of the original and revisited analyses are presented in Figure 21 (a-b). In the revisited analysis, rivaroxaban continues to exhibit the highest probability of being cost-effective and the highest expected NMB over the entire threshold range. At €45,000 per QALY, the probability that rivaroxaban is the most cost-effective strategy increased from 69% (in the original analysis) to 81%. Figure 21 (a-b) also illustrate that at €45,000 per QALY, assuming a decision time horizon of 10 years, the population value of the decision uncertainty fell from €11.96 million to €3.43 million.

Vitally, in EVPI analysis, the costs of the proposed future research should not exceed the EVPI value if the research is to be considered cost-effective. In this study, the updated estimates of costs were collected in a timely manner at very little additional expense. The value of the uncertainty associated with the model fell from €11.96 million to €3.43 million. This investigation was therefore cost-effective.

Table 36 indicates that, at €45,000 per QALY, the EVPPI associated with the preferences subset increased from €0.01 million (in the original analysis) to €0.06 million (in the revisited analysis). This suggests that the uncertainty associated with the model decision becomes more driven by this parameter subset, as the uncertainty associated with the direct medical costs is decreased. This updated estimate however is still relatively low, indicating that further research on preferences is unlikely to be useful.

Figure 22 (a-b) illustrates EVPPI estimates for all three parameter subsets against the threshold (€0 - €100,000) for the original and revisited analysis. The values associated with probabilities and preferences remain low across the entire threshold range. This indicates that further research on these subsets is unlikely to be valuable, at any chosen threshold.

It is noted that this case study was not based upon a high budget impact area. In situations of high budget impact, the potential opportunity loss to the payer is likely to be greater, should the wrong decision be made.

This work has raised a number of important issues regarding the introduction of VOI analysis as part of the formal decision making processes within the Irish Healthcare System.

At present, in Ireland, the decision maker's judgement is based upon cost-effectiveness analysis and budget impact analysis. The decision is often swayed by the budget impact. There is uncertainty regarding all such decisions. VOI analyses will however place a tangible monetary value on the uncertainty associated with a cost-effectiveness analysis. It essentially combines the budget impact of the decision with a measure of uncertainty. The decision maker, who is responsible for holding budgets, is likely to find a decision, based at least partly on a monetary measure somewhat easier to make than one primarily based on probability.

Decision rules that also consider the value of evidence forgone would reduce the number of new technologies approved. The decision to reject technologies with ICERs higher than the threshold would be unaffected, but some technologies with ICERs below the threshold would also be rejected (particularly those priced such that the ICER is close to the threshold). Such decisions would provide clear incentives to manufacturers to either invest in further research or reduce the price of the new technology. Reducing the price will also reduce the EVPI if there is uncertainty regarding whether the new technology is sufficiently more effective to justify the additional cost. However, if the incremental effectiveness of the new technology is also uncertain then price reductions will be limited and will not continually reduce EVPI [378].

In this case study, revisiting the estimates of the direct medical costs resulted in a very minor delay in presenting the final analyses to the decision maker with negligible additional expense. However, for each new technology there will be a different type or amount of evidence that will be required to decrease uncertainty. In some circumstances, this research could be lengthy and expensive. In Ireland, the decision maker involved in reimbursement decisions is not directly charged with the identification of future research priorities and so it is not immediately obvious who would be responsible for prioritising and carrying out this research.

Resources are unlikely to be available within the HSE to fund the required research. It is likely to be directed back to the drug company. However, it has previously been highlighted that companies who are second- (or subsequent-) to-market within a new class of drug are likely to free-ride on the research undertaken by the company which was first-to-market [315].

Currently in Ireland, there is no formal framework in place whereby the reimbursement authority has the power to reverse a decision. As it stands therefore, VOI analysis could not easily be used to reverse a positive reimbursement decision should further research indicate that the product is not cost-effective. It could be used however, in the issuing of a positive or negative reimbursement decision or in a delay in this decision being made.

The results of this analysis (the original and revisited THR lifetime analyses) have been discussed with the HSE decision maker. It is believed that the increase in probability of cost-effectiveness, coupled with the substantially reduced potential opportunity loss could influence the decision maker's confidence in making a reimbursement decision. The decision maker has expressed an interest in the incorporation of the techniques into the decision process, particularly in areas of high budget impact, given the current economic climate. It is envisaged that, in particular, where a CEA had shown a reasonable probability of cost-effectiveness, but VOI analysis has shown a potentially high opportunity loss, VOI analysis may facilitate the issuing of a negative reimbursement decision [379].

A large number of reimbursement decisions made within Ireland are based upon economic models submitted by manufacturers. VOI analysis on such models will depend upon the adequacy of the model and, in particular, on how fully all forms of uncertainty have been characterised [315]. The VOI skills that I have acquired in the course of this study will now allow the NCPE to incorporate VOI analysis into our critique of the manufacturer's model. In the first instance we intend to routinely perform EVPI analysis on the manufacturer's model ourselves. The time and effort required to calculate EVPI is negligible. We will only consider the use of the computationally challenging EVPPI analysis where the PEVPI value is substantial.

Claxton and Sculpher report on two UK pilot studies which applied VOI analysis to directly inform policy decisions [254]. In neither was there a significant impact on the decisions taken. It was suggested that this was because those responsible for research prioritisation were unfamiliar with cost-effectiveness analysis, decision modelling and PSA. This resulted in a reluctance to accept and base decisions on such methods. The separation of research prioritisation and commissioning decisions from adoption and reimbursement was also considered to be a significant problem [254].

Subsequent to this analysis, Kunnskapssenteret (The Norwegian Knowledge Centre for the Health Services) [223] evaluated dabigatran etexilate and rivaroxaban compared to enoxaparin sodium after THR or TKR. Contrary to our study, their EVPI analysis indicated that it was the efficacy parameters which had the greatest impact on the decision uncertainty. In order to obtain efficacy parameters, they combined all relevant RCTs, across all doses of medications and treatment lengths, in meta-analyses. They used the 'GRADE' (Grading of Recommendations, Assessment, Development and Evaluation) [380] tool to assess the quality of the RCTs; PSA probability distributions on efficacy parameters were then awarded depending on the quality grade awarded. The quality of the evidence ranged from moderate to very low; for moderate, low or very low quality results, CIs of 90%, 80% and 70% respectively were applied. These PSA distributions are wider than those used in our analysis and this appears to be the cause of the disparity between their results and those obtained here.

There are a number of limitations to this study.

In an ideal setting, once it had been established that further research should be directed towards the direct medical costs parameter subset, the EVPPI associated with each individual cost would have been estimated and examined graphically. However, the THR lifetime model contained a total of 31 disaggregated costs and therefore the substantial computational overhead that this would have involved was a limiting factor. Estimation of the VOI associated with each cost would have taken about 100 hours per cost. With the advent of more powerful computers, it is likely to become feasible in the future to perform such analyses.

All VOI analyses are themselves associated with uncertainty. An EVPI analysis only provides information about the values of eliminating uncertainty around the parameters in the model. PEVPI is dependent on estimates of the size of the population, the time horizon over which technologies are relevant and the discount rate, all of which are themselves associated with uncertainty. Indeed, the effect of the assumption made about the decision problem time horizon has been illustrated here in Figure 19. Furthermore, EVPI is dependent on the specification of the decision model and the characterisation of uncertainty. Estimates are also altered by structural changes in the model [363], as illustrated by the difference in the EVPI estimates associated with the 180 day- and lifetime- models here.

The EVPPI values were estimated using the two-level Monte Carlo Simulation algorithm. EVPPI on the 180 day models was calculated on 30,000 inner loops and 1000 outer loops. The running time per parameter group was approximately four computational hours. Computational expense resulted in a reduction to 1000 inner- and 1000 outer-loops in the lifetime model investigations. This analysis took approximately 100 computational hours per parameter group. This low number of runs in the inner loops may have introduced an upward biased estimate of the EVPPI [66]. The relatively low number of runs in the outer loop for the analysis on all economic models may also have resulted in a lack of precision [381]. Oakley *et al* have recently presented an algorithm to estimate the EVPI bias and CI width for a specified number of inner and outer samples [382]. Further work here should involve an estimation of this bias. Elsewhere, the computational expense of the EVPPI calculation has recently been challenged with the use of the meta-modelling techniques (Multiple Linear Regression and Gaussian Processing), to significantly reduce the computing time. It has been proposed that, in the future, the use of meta-models will increase the accessibility of the extensive VOI analysis for computationally expensive health economic models [64].

When an economic model is perfectly linear and no correlation exists between input parameters, a less computationally expensive one-level algorithm, which does not require an outer loop, will provide estimates of the EVPPI that are equal to the two-level sampling algorithms [66]. In this study, the Dirichlet distribution will have introduced correlation in the probabilities and an inherent characteristic of a Markov

simulation is the multiplication of matrices with transition probabilities over subsequent cycles, causing the transitions to be nonlinear [371]. It would have been inappropriate therefore to use the one-level algorithm here.

Estimating total EVPI and EVPPI are only initial steps in guiding future research [365]. Complete elimination of uncertainty can be achieved only by an infinitely large sample. The practical task is therefore to calculate the expected value of sample information (EVSI), in order to find an optimum sample size for a future study [362, 364, 383]. In health economics, VOI methods are used in SA and in quantifying the potential value of research, whilst EVSI is promoted for determining optimum sample sizes and allocation rates in health and clinical studies [384].

Table 35 indicates that a number of the revisited costs were obtained from updated Casemix data and from an updated hospital database. It could be argued that the revisited costs are not associated with a true decrease in uncertainty as compared to the original costs. It was the analyst's personal belief about this degree of uncertainty that was examined in the elicitation exercise. The subjectivity of this analysis should be emphasised.

6.7 Conclusions

This study has shown the benefits of performing VOI analyses in quantifying and decreasing decision uncertainty.

Following discussions with the HSE decision maker, the NCPE now routinely incorporate VOI analysis into the HTA process of company submissions. The NCPE calculate population EVPI estimates alongside the PSA. EVPPI analysis will also be considered in the future where the population EVPI value is large. Consequently manufacturers could review model parameter estimates in an attempt to reduce uncertainty.

Chapter 7

Atrial Fibrillation - Incorporating a Review of the National Primary Care Prescribing Trends for Dabigatran etexilate and Rivaroxaban

7 ATRIAL FIBRILLATION - INCORPORATING A REVIEW OF THE NATIONAL PRIMARY CARE PRESCRIBING TRENDS FOR DABIGATRAN ETEXILATE AND RIVAROXABAN 219

7 Atrial Fibrillation - Incorporating a Review of the National Primary Care Prescribing Trends for Dabigatran etexilate and Rivaroxaban

7.1 Introduction

In 2009, the 'Randomized Evaluation of Long Term Anticoagulation Therapy' (RE-LY) trial which compared dabigatran etexilate to warfarin for stroke prevention in atrial fibrillation (SPAF) was published [385]. The 'Rivaroxaban-Once daily, oral, direct factor Xa inhibition Compared with vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation' (Rocket AF) trial was published in 2011 [386].

This chapter has four aims:

- First, to provide an overview of AF, including epidemiology, the associated risk of stroke and the use of anticoagulation for SPAF;
- Second, to introduce the pivotal clinical trials (RE-LY and ROCKET AF);
- Third, to discuss the current licensing status of rivaroxaban and dabigatran etexilate for SPAF;
- Fourth, to analyse the national primary care prescribing trends for these drugs in Ireland.

7.2 Atrial Fibrillation

7.2.1 Epidemiology

AF is the most common sustained cardiac arrhythmia, occurring in 1 to 2% of the general population [387]. Over 6 million Europeans suffer from AF and its prevalence is estimated to at least double in the next 50 years [388]. It is estimated that approximately 25% of all individuals aged 40 years or older will develop AF during their lifetime [389].

In 10 to 15% of cases, AF occurs in the absence of comorbidities. However, it is often associated with other cardiovascular diseases, including hypertension, heart failure, diabetes-related heart disease, ischemic heart disease and cardiomyopathies

[389]. In the large population-based ARIC Study, reduced kidney function and the presence of albuminuria were strongly associated with the incidence of AF [390].

A systematic literature search has located a number of AF epidemiological studies [387, 391-394]. These have been summarised in Table 37. It is difficult to compare prevalence/incidence rates from epidemiological studies pertaining to different jurisdictions. The age ranges and ethnicity of the reference population differ. Likewise, methods of diagnosis may vary. The first general population figures came from studies in the US [391, 395], followed by figures from Western Europe [387, 393, 396]. The ageing populations in Western Europe and the US, coupled with better diagnosis, management and survival of patients with AF might lead to higher estimates in more recent studies. Indeed, a rising prevalence, even independent of age, has been suggested [393, 397].

Irish epidemiological data is limited.

Mahmud *et al* [398] used digoxin as a surrogate for AF in a retrospective review of the Irish National GMS Prescription Database (2003). In total, 27,971 patients (over 45 years of age) were identified. Applying Irish population data, a higher prevalence of use was noted in men than women (5.2% vs. 4.3%, $p<0.001$). Less than 1% of people aged 45 to 64 years and over 10% of those 75 years and over received digoxin [398].

A 2004 Irish study which recruited 100 AF patients admitted to hospital over a 12 week period, reported an average age of 76.6 years with 53% of patients over 75 years [399].

More recently, Finucane *et al* [400] (2011) determined the prevalence of ECG documented AF in a nationally representative sample of Irish adults over 50 years (n = 4154) to be 3.2% (95%CI 2.5%, 4.0%). It was more common in older males (0.8% in the 50 to 59 years group vs. 10.8% in the 80 years and over group). Overall 38.2% were unaware of the diagnosis.

To summarise the studies in Table 37 and the Irish data, AF is the most common sustained cardiac arrhythmia [387]. Its prevalence increases substantially with age [387,

[391-394, 400-403]. Men are more often affected than women [387, 388, 391, 392, 394]. It has been shown to be less prevalent in older non-white individuals than in whites [392, 404]. It is often associated with other cardiovascular diseases [387, 389, 391, 393]. Limited Irish epidemiological data is available, but it has been suggested that the prevalence in adults over 50 years, in 2011 is 3.2% (95%CI 2.5%, 4.0%) [400].

Table 37: Incidence and prevalence of atrial fibrillation in North America and Europe

Author	Study Setting	Study Population	Prevalence	Incidence per 1000 person-years	Comment
US					
Psaty *et al* 1997 [391] The CHS	Population longitudinal study	4844 adults (≥ 65yrs) examined annually, on 4 occasions (1989 -1993)	Not investigated	19.2 **Varied with age/gender** **Men:** 65-74 yrs= 17.6 75-84 yrs= 42.7 **Women:** 65-74 yrs= 10.1 75-84 yrs= 21.6	**Independent predictors:** Valvular heart disease, coronary disease, higher systolic blood pressure, glucose, left atrial size
Go *et al* 2001 [392]	Retrospective study	17,974 patients diagnosed with AF (July 1996 - Dec 1997) (45% ≥75 years)	0.95% (95%CI 0.94%, 0.96%) **Varied with Age:** < 55yrs=0.1% ≥ 80 years=9.0% **Varied with Gender:** Men=1.1% Women=0.8%; p<0.001 **In > 50 yrs cohort:** White people=2.2% Black people=1.5%; p<0.001	Not investigated	
Europe					
Lip *et al* 1997 [393] The West Birmingham AF Project UK	Cross-sectional survey of General Practice population	16,519 adults (>50 yrs)	2.4% (36.9% of AF cohort were >80 yrs)	Not investigated	**Co-morbidities** Hypertension in 36.9% Ischaemic heart disease in 28.8%
Stewart *et al* 2001 [387] The Renfrew/Paisley Population Cohort Study Scotland	Population cohort study	15,406 adults (45-64 yrs) screened 1972 - 1976	0.65% (95%CI 0.53, 0.79%) **Varied with Age:** OR= 2.1 (95%CI 1.1, 10.2 per decade; p<0.05). **Varied with Gender** Male vs. female OR=1.8 (95%CI 1.2, 2.8; p<0.01)	4 yr incidence = 0.54 in 8,532 rescreened (1977-1979) 20 yr follow-up of 15,306: incident AF hospitalisation = 1.9	**Independent predictors:** Radiological cardiomegaly, raised systolic blood pressure

Table 35 continued

Author	Study Setting	Study Population	Prevalence	Incidence per 1000 person-years	Comment
Schmutz *et al* 2010 [394] Geneva	Prospective population study	3285 adults (≥ 50 yrs) followed Jan 2005 - Dec 2007	0.88% (95%CI 0.86, 0.90) **Varied with Age:** 50-54yrs=0.15% to 80-84yrs=2.75% **Varied with Gender** Men=1.30% (95%CI 1.26, 1.34) Women=0.44% (95%CI 0.41, 0.47)	Not investigated	It has been postulated that the low prevalence rates seen in this study might, in part, have been due to diagnoses being based upon a single ECG reading only [405].

Where: **CHS**= Cardiovascular Health Study; **US**=United States; **yrs**=years; **AF**=atrial fibrillation; **CI**=confidence interval; **OR**=odds ratio; **ECG**=electrocardiogram

7.2.2 The Risk of Stroke Associated with AF

AF is associated with a prothrombotic state which predisposes to stroke and thromboembolism [406]. It has been reported that approximately one in five of all strokes are attributed to AF [388, 407]. A systematic literature search has revealed several studies which have investigated the risk of stroke in patients with AF [408-417]. These are summarised in Table 38.

To summarise the studies in Table 38, the presence of AF is associated with an increased risk of stroke [409, 410] and of stroke recurrence [417]. The risk of stroke increases progressively with age [411, 415]. Prior stroke/TIA, hypertension, diabetes mellitus, and structural heart disease are also independent risk factors [413, 414]. Paroxysmal AF carries a similar stroke risk as permanent AF [412]. Strokes associated with AF are chiefly of cardioembolic origin, causing occlusion of larger cerebral arteries and are subsequently more severe in nature [415]. Even in the absence of manifest stroke, AF is a risk factor for cognitive impairment [416].

Table 38: The risk of stroke associated with atrial fibrillation

Author	Study Setting	Study Conclusions
Wolf *et al* 1991[409] part of US Framingham Study	Prospective cohort of 5070 participants (free from AF) examined every 2 years	572 pts had a 1st stroke during 34 year follow-up AF associated with a 5-fold excess in risk of stroke vs. no AF ($p < 0.001$).
Rodgers *et al* 2004 [410] UK	Prospective study of 4351 GP pts (>65 yrs) recruited 1995-1997	7.6% had a 1st stroke during 5 year follow-up AF associated with an increased risk of stroke vs. no AF (HR = 2.03, 95% CI 1.31, 3.16)
Hannon *et al* 2010 [408] Ireland	Prospective cohort study of 568 pts with new stroke events (Dec 2005 - Nov 2006)	Stroke associated with AF seen in 177 (31.2%) High AF prevalence might have been due, in part, to inclusion of • stroke occurring with prior AF diagnosis • new AF detected at stroke onset • paroxysmal AF detected within 3 months of stroke
Hillen *et al* 2003 [417] from the South London Community Stroke Register	Prospective community cohort of 1626 1st stroke pts (Jan 1995-Aug 2000)	At 5 years, cumulative risk of 1st stroke recurrence was 16.6% (95%CI 3.5, 20.4) AF reached significance in multivariable models of: • stroke recurrence (HR=1.95: 95%CI 1.27, 3.00; $p<0.01$) • death/stroke recurrence (HR=2.00: 95%CI 1.70, 2.36; $p<0.01$).
Stöllberger *et al* [411] Europe	Prospective study of European cohort of 409 AF pts followed for 101±2 months	Rate for stroke/SE was 3% per year Only • age (RR=1.05: 95% CI 1.02, 1.09; $p = 0.0006$) • previous stroke (RR= 2.14: 95% CI 1.02, 4.51; $p = 0.0454$) were independent predictors
The Stroke Risk in AF Working Group 2007 [413] US	Meta-analysis on studies that had determined independent factors associated with stroke in nonvalvular AF (Jan 1985 -Oct 2005)	Strongest, most consistent independent stroke risk factors: • prior stroke/TIA (RR= 2.5: 95%CI 1.8, 3.5) • age (RR=1.5 per decade: 95%CI 1.3, 1.7) • hypertension (RR= 2.0: 95% CI 1.6, 2.5) • diabetes mellitus (RR=1.7: 95% CI 1.4, 2.0) Further to this: • Female sex inconsistently associated with stroke • Evidence that heart failure or coronary artery disease is independently predictive was inconclusive

Table 36 continued		
Author	**Study Setting**	**Study Conclusions**
Jorgensen *et al* 1996 [415] The Copenhagen Stroke Study	Prospective community cohort of 1197 acute stroke pts treated on a stroke unit from time of acute admission to end of rehabilitation	AF was diagnosed in 18%: • 2% in <50 yrs • 15% in 71-79yrs • 28% in 81-89yrs • 40% in ≥ 90 yrs Pts with AF had a • higher mortality rate (OR=1.7: 95%CI 1.2, 2.5) • longer LOS (50 vs. 40 days, p<0.001) • lower discharge rate to own home (OR=0.60: 95%CI 0.44, 0.85) vs. those without AF Poorer neurological/functional outcomes with AF exclusively explained by initially more-severe strokes
Knecht *et al* 2008 [416] Germany	Stroke-free individuals (122 with- and 563 without- AF) recruited from the same community	AF pts performed significantly worse in • tasks of learning and memory (p< 0.01) • attention and executive functions (p< 0.01) Trend (p=0.062) towards worse performance in learning and memory tasks in pts with permanent vs. paroxysmal AF Corresponding to the memory impairment, hippocampal volume was reduced in AF pts

Where: **AF**=atrial fibrillation; **GP**=General Practice; **pts**=patients; **HR**=hazard ratio; **SE**=systemic embolism; **TIA**=transient ischaemic attack; **RR**=relative risk; **LOS**=length of stay.

7.2.3 The Cost Burden for Stroke in Ireland

Stroke is the third leading cause of death and disability worldwide [374]. It is estimated that over 30,000 people in Ireland are survivors of stroke, many of whom have significant residual disability [374]. It represents a large financial burden for the Irish HSE. According to Irish HIPE data there were 4549 discharges for stroke (DRG codes B70A, B70B, B70C) from acute hospitals in 2008; the weighted average LOS was 30.1 days [376]. The estimated per-patient cost, in 2011, of hospitalisation for the acute care of stroke is €12,860 [193, 376]. The estimated burden of illness in Ireland, for 2011, for the acute care of stroke is €66.7 million [193, 376].

DRG codes are not available for the long-term care costs of post stroke care. The Irish Heart Foundation COSI Report has estimated that the total direct and indirect acute and long-term cost burden for stroke in Ireland, in 2007, was between €489 million (assuming a low prevalence) and €805 million (assuming a high prevalence) [374] . The low stroke prevalence estimate combines data from the Health Module of the Quarterly National Household Survey (2001) and estimates of numbers of strokes in nursing home patients, while the high estimate is adopted from the World Health Organisation (WHO) [374].

7.2.4 Assessment of Stroke Risk in AF Patients

As previously discussed, patients with AF have a substantial risk of stroke, which is modified by the presence or absence of several risk factors [388]. The identification of various stroke clinical risk factors has led to the publication of various stroke risk schemes.

The $CHADS_2$ (cardiac failure, hypertension, age, diabetes, stroke (doubled)) stroke risk assessment index can be used as an initial, rapid means of assessing stroke risk in AF patients [388]. The scheme evolved from the AF Investigators and SPAF Investigators criteria [418]. It is based on a point system in which two points are assigned for a history of stroke or transient ischaemic attack (TIA) and one point each is assigned for age ≥75 years, a history of hypertension, diabetes, or recent cardiac failure. The original validation of this scheme classified a $CHADS_2$ score of '0' as

low risk, '1-2' as moderate risk, and '>2' as high risk [388]. A revised scoring scheme classifies a score of '0' as low-, '1' as moderate- and '≥ 2' as high-risk [419].

The CHA_2DS_2-VASc score is a refinement of $CHADS_2$ score, which is extended by including additional common non-major stroke risk factors; age 65-74 years, female gender and vascular disease (all assigned one point). Age ≥ 75 is assigned 2 points [419]. With a score of '0', patients are deemed to be at a low risk for stroke. With scores of '1' and '≥2', they are deemed to be at moderate and high risk respectively.

7.2.5 Anticoagulation in Patients with AF

At the time of writing (December 2011), European and US guidelines recommend a VKA (INR 2-3) for SPAF in patients at high risk of stroke and either aspirin or a VKA for those who are at moderate risk [388, 420-422]. Some experts would favour a VKA for all AF patients except those estimated to be at low risk [420]. Warfarin is the most commonly prescribed VKA in Ireland [142].

A systematic literature search has revealed a number of prospective, retrospective and meta-analytic studies which provide an evidence base for the use of warfarin in SPAF [402, 423-429]. Warfarin has been compared to aspirin for this indication [430-432]. These studies are summarised in Table 39.

On review of the studies in Table 39, evidence indicates that warfarin has a protective effect against ischemic stroke in patients with AF [402, 423, 424, 432]. The use of warfarin has been shown to reduce medical costs in patients with AF [429]. There is an increased propensity to stroke with an INR <2.0 [428]. Increasing age and higher INRs are associated with increased risk of haemorrhage [427]. Therapeutic anticoagulation may also provide important long-term benefits for patients who have had a stroke [423, 425]. Adjusted-dose warfarin is significantly more efficacious in stroke prevention than aspirin [430-432]. Aspirin appears to primarily reduce noncardioembolic strokes [432].

Table 39: Studies which examine the use of warfarin and/or aspirin for stroke prevention in atrial fibrillation

Author	Study Setting	Study Conclusions
Warfarin for SPAF		
Meta-analysis		
Hart *et al* 2007 [423]	Meta-analysis of RCTs published 1966-2007	Adjusted-dose warfarin (vs. control) associated with: • 64% (95%CI 49, 74) reduction in all strokes • 67% (95%CI 54, 77) reduction in ischaemic strokes • Significant reduction in all-cause mortality significantly; relative risk reduction =26% (95% CI 3, 43)
Cooper *et al* 2006 [424]	Meta-analysis of RCTs published 2000- 2005	Adjusted standard-dose warfarin (RR=0.35: 95% CrI 0.24, 0.52) and adjusted low-dose warfarin (RR=0.35: 95%CrI 0.19, 0.60) associated with significantly lower rates of ischemic stroke vs. control.
Prospective Studies		
Hannon *et al* 2011 [425] Ireland	159 pts with AF & ischaemic stroke (Dec 2005-Nov 2006) 17% on warfarin before stroke	Therapeutic INR at stroke onset associated with: • better early (72 hrs-28 days) functional improvement (p=0.04) • good functional outcome at 1 yr (adjusted OR=4.8: 95% CI 1.45, 23.8; p=0.04) • better late survival after stroke (adjusted 2-year OR for death=0.08: 95% CI 0.01, 0.78; p=0.03)
Gladstone *et al* 2009 [426] Canada	Sub-study of Registry of the Canadian Stroke Network (2003 - 2007) AF pts admitted with acute ischemic stroke	First Ischemic Stroke (n=597): • strokes were disabling in 60% & fatal in 20% • preadmission meds were warfarin (40%), antiplatelets (30%) and no antithrombotics (29%) • 74.2% of those taking warfarin had sub-therapeutic INR (<2) Recurrent Ischaemic Stroke (n=323): • 18% were on warfarin with therapeutic INR • 39% were on warfarin with sub-therapeutic INR • 15% were on no antithrombotics
Hylek *et al* 2007 [427] US	472 consecutive patients (≥ 65 yrs) who started warfarin for AF (Jan 2001-Jun 2003); followed for 1 yr	The cumulative incidence (per 100 person-years) of major haemorrhage: • < 80 yrs = 4.7 • ≥ 80 yrs = 13.1 (p <0.009) Associated with increased risk of haemorrhage: • first 90 days of warfarin • age ≥ 80 yrs • INR ≥ 4.0
Lakshmnarayan *et al* 2006 [402] US	Medicare pts (≥ 65 yrs)	From 1992 to 2006: • AF prevalence increased from 3.2% to 6.0% • warfarin use in AF increased significantly from 24.5% to 56.3% • ischaemic stroke rates declined from 46.7 to 19.5 per 1000 patient-years Cox proportional hazards regression confirmed protective association of warfarin against stroke in AF

Table 37 continued		
Author	**Study Setting**	**Study Conclusions**
Hylek *et al* 2003 [433] US	74 pts on warfarin with AF & ischemic stroke (1989-1994)	Risk of stroke increased at INR < 2.0. Compared to INR=2 adjusted OR for stroke at: • INR (1.7) = 2.0 (95%CI 1.6, 2.4) • INR (1.5) = 3.3 (95%CI 2.4, 4.6) • INR (1.3) = 6.0 (95%CI 3.6, 9.8) Other independent risk factors: prior stroke, diabetes mellitus, hypertension and smoking
Retrospective studies		
Mercaldi *et al* 2011 [429] US	119,764 Medicare pts with AF (2004-2005) • Mean age=79.3yrs • 58.5% on warfarin • Average follow-up-2.1yrs	On multivariate adjustment warfarin (vs. no warfarin) associated with: • decreased risk of ischaemic stroke (HR=0.73: 95%CI 0.70, 0.76; p<0.0001) • no increase in haemorrhagic stroke (HR=0.81: 95%CI 0.72, 0.90) • a small increased risk of major bleed (HR=1.04: 95%CI 1.01, 1.07) Per pt medical costs per yr were $9,836 lower in pts on warfarin (p<0.0001)

Warfarin versus Aspirin for SPAF		
Hart at el 2007 [431]	Meta-analysis of RCTs published 1966-2007	Adjusted-dose warfarin substantially more efficacious in stroke prevention than aspirin (relative risk reduction = 39% (95%CI 19, 53)
Hart *et al* 2000 [432] US	Retrospective review of ischemic strokes occurring in AF pts in the SPAF I-III clinical trials: SPAF I (1985-1987) SPAF II (1989-1992) SPAF III (1993-1997)	Of the 217 ischemic strokes in 3950 AF pts: • 52% were cardioembolic • 24% were noncardioembolic • 24% were of uncertain cause Cardioembolic strokes were more disabling (p=0.05) Adjusted-dose warfarin reduced cardioembolic strokes by 83% (p < 0.001) vs. aspirin Compared to placebo/no antithrombotics: • proportion of cardioembolic stroke was lower with warfarin (p=0.02) • proportion of noncardioembolic stroke was lower with aspirin (p=0.06)
Mant *et al* 2007 [430] BAFTA study UK	RCT: 973 primary care AF pts (≥75 yrs); warfarin (INR 2-3) vs. aspirin Average follow-up= 2.7 yrs	Fewer primary events (fatal/disabling stroke, intracranial haemorrhage, or clinically significant arterial embolism) in pts on warfarin vs. aspirin (24, (1.8% per yr) vs. 48, (3.8% per yr), RR=0.48: 95%CI 0.28, 0.80). No difference in the risk of major haemorrhage

Where: **SPAF**= stroke prevention in atrial fibrillation; **RCT**=randomised controlled trial; **CI**=confidence interval; **CrI**=credible interval; **AF**=atrial fibrillation; **pt(s)**=patient(s); **yr**=year; **OR**=odds ratio; **HR**=hazard ratio; **BAFTA**=Birmingham Atrial Fibrillation Treatment of the Aged; **RR**=relative risk.

7.2.6 The Cost of Anticoagulation Monitoring Services

The limitations of warfarin have been well documented. It has significant drug, food and alcohol interactions. It has a narrow therapeutic index and a high inter- and intra-individual variation in the dose-response relationship requiring INR monitoring. [388].

A systematic search of published literature has revealed a number of studies which have investigated the cost of INR monitoring services [434-438]. A number of these pertain specifically to monitoring warfarin in AF patients [435-438].

The direct costs (2000 US$) to the health-payer of providing an outpatient pharmacy anticoagulation service were investigated in a cohort of 97 patients on warfarin for AF [438]. Utilising the ACCP risk stratification criteria, 80.4% were deemed to be at high risk for ischemic stroke. The percentage of INR values within the target range (2-3) was 60.4%; the percentage within or near the target range was 74.6%. The per-patient-per-month cost of the monitoring service was $51.25; comprising 27% for staff costs, 36% for laboratory tests and 37% for drug costs (warfarin plus LMWH bridging therapy). These costs did not significantly differ among patient groups with various risks for ischemic stroke.

Bjorholt *et al* [435] estimated the direct medical cost (2003) to the health payer of monitoring warfarin in primary care AF patients in Sweden. The type and number of resources consumed at monitoring visits were investigated in the main by Delphi-panel studies. Total cost of INR monitoring was obtained by multiplying the monitoring costs with monitoring frequencies derived from published studies. The mean cost of one INR monitoring visit was €60.50. The mean costs of monitoring for the first three months, the first year and the second year of treatment were €749, €1,787 and €979 respectively.

Menzin *et al* [436] reviewed the quality of anticoagulation control and the associated direct medical costs (2003 US$) to the health-payer in AF patients (n=600; identified 1996-1998) across structured anticoagulant clinics. The mean percentage of time spent within the target INR (2-3) was 62%. Mean per-patient annual costs varied from $216 to $339.

A 2006 Costing Report by the UK National Health Services (NICE Clinical Guideline 36) estimated the direct cost to the health payer of providing anticoagulation treatment to AF patients [437]. It was assumed that an annual course of warfarin for an AF patient requires 20 INR monitoring appointments and that anticoagulation is started in hospital in 91% of cases with 74% of follow-up appointments conducted outside hospital. A weighted annual unit cost per patient was estimated to be about €569 [437] (STG £1= €1.487, Dec 2006 exchange rate) [439].

Schulman *et al* [434] investigated the costs of warfarin-based anticoagulation monitoring models. All costs (2010 Can$) were calculated for a three month period. The cost from the health payer perspective ranged from $108-$199, patient costs were $40-$80 and the total societal costs ranged from $188-$244. When reimbursement for unemployed caregivers was also considered the total cost increased to $308-$503 per three months.

A 2009 micro-costing study of patient attendance at an anticoagulation clinic in an Irish GP practice was identified [373]. This study was based on 10 randomly selected patients in the practice who had been on warfarin for AF for at least 12 months. Costs included staff, overhead and equipment. Direct costs per patient visit were estimated to be €28.97.

Warfarin has regularly been in the top 15 most frequently prescribed medicines in Ireland. More than 32,400 patients in Ireland are currently receiving the drug [440]. It is evident from the costing studies pertaining to Ireland and other jurisdictions [373, 434-438] that the management of patients receiving warfarin places a large financial burden on services within the Irish health service.

7.2.7 Cardiac Rate and Rhythm Management in AF

Therapy after onset of AF should include adequate antithrombotic treatment and also control of the ventricular rate. Adequate control of the ventricular rate may reduce symptoms of AF (including palpitations, dyspnoea, fatigue, and dizziness) and improve haemodynamics. The main determinants of ventricular rate during AF are the conduction characteristics and refractoriness of the atrioventricular node and the

sympathetic and parasympathetic tone. Drugs commonly used are β-blockers, non-dihydropyridine calcium channel antagonists, and digitalis glycosides. Amiodarone may be suitable for some patients with otherwise refractory rate control [388]. Of note, digoxin is the most commonly prescribed digitalis glycoside compound in Ireland [209].

7.2.8 Summary on Atrial Fibrillation

AF is the most common sustained cardiac arrhythmia [387]. The prevalence in Ireland in 2011 is estimated to be 3.2% (95%CI 2.5%, 4.0%) [400]. AF is associated with a prothrombotic state which predisposes to stroke and thromboembolism [406]. Strokes associated with AF are chiefly cardioembolic in origin and subsequently can be severe in nature [415]. Stroke represents a large financial burden for the Irish HSE.
Warfarin has a protective effect against stroke in patients with AF [402, 423, 424, 432]. Despite its clinical efficacy, warfarin has multiple, well-known limitations, including numerous interactions with drugs, food and alcohol and the need for regular INR monitoring [388]. The management of AF patients receiving warfarin places a large financial burden on services within the Irish health service.

Therapy after onset of AF should include adequate anticoagulation and also control of the ventricular rate [388].

It is recognised internationally that clinicians and patients are eager to embrace alternative oral anticoagulants that are equally efficacious to warfarin for SPAF but are easier to administer [441].

7.3 Efficacy Data Pertaining to Dabigatran etexilate and Rivaroxaban for use in SPAF

7.3.1 Dabigatran etexilate Pivotal Clinical Trial

RE-LY is a multicentre, PROBE (prospective, randomised, open-label with blinded endpoint evaluation) trial, which involved over 18,000 patients with AF and at least one stroke risk factor [385]. It evaluated the non-inferiority of dabigatran etexilate 110 mg BD or 150 mg BD (double blind dose comparison) compared with open label

adjusted dose warfarin (INR 2-3). All analyses were based on the intention to treat (ITT) principle.

The primary outcome was stroke (ischemic and haemorrhagic) or systemic embolism (SE). The primary safety endpoint was major bleeding [385]. After database lock on August 15th 2009, several additional primary efficacy and safety outcome events were identified [442]; these are reported here.

After a median of 2.0 years follow-up, 21% of participants had discontinued dabigatran etexilate, 16.6% had discontinued warfarin [385].

Stroke or SE occurred in 134 of 6076 patients (1.11% per year) in the 150 mg dose group and in 202 of 6022 patients (1.71% per year) in the warfarin group (RR= 0.65; 95%CI 0.52, 0.81). No significant difference in the same outcomes was found between the 110 mg dose (183 of 6015; 1.53% per year) and warfarin (RR= 0.90; 95%CI 0.74, 1.10). Both doses were noninferior to warfarin ($p<0.001$). The 150 mg dose was superior to warfarin ($p<0.001$) [442].

Compared to warfarin, the 110mg dose significantly reduced the rate of major bleeding (RR=0.80; 95%CI 0.70, 0.93). No significant difference was found between the 150 mg dose and warfarin [442]. Both doses were associated with significantly fewer ICHs than warfarin. The 110mg dose was associated with significantly fewer life threatening bleeds; no significant difference was found between the 150mg dose and warfarin for life threatening bleeds. The 150 mg dose significantly increased GI bleeding compared with both warfarin and the 110mg dose [385].

Both doses were associated with a non-significantly increased risk of MI compared with warfarin [442].

Rates of dyspepsia were elevated with dabigatran etexilate (11.8% in the 110 mg group and 11.3% in the 150mg group) as compared with warfarin (5.8%) [385]. There was a borderline reduction in the risk of death from any cause with the 150mg dose compared to warfarin (HR=0.88; 95%CI 0.77, 1.00; p= 0.051) [442].

7.3.2 Rivaroxaban Pivotal Clinical Trial

Rocket AF is a multicentre, randomised, double-blind, double-dummy trial which involved over 14,000 patients with nonvalvular AF and a history of stroke or at least two additional independent risk factors [386]. Patients were randomised in a double-blind fashion to receive either rivaroxaban, 20 mg OD (15 mg OD in moderate renal impairment), or dose-adjusted warfarin with target INR of 2.5 (range 2-3) using point-of-care INR devices to receive true or sham INR values, depending on drug allocation [386]. The primary hypothesis was that rivaroxaban would be non-inferior to warfarin for the primary outcome in the per-protocol population. Testing for noninferiority and superiority was also performed in the ITT population [443].

The primary outcome was stroke (ischemic and haemorrhagic) or SE. The primary safety end point was the composite of major and clinically relevant non-major bleeding events.

After a median follow-up of 707 days, 23.7% and 22.2% of participants had discontinued rivaroxaban and warfarin respectively.

In the per-protocol population, stroke or SE occurred in 188 of 6968 patients (1.7% per year) in the rivaroxaban group and in 241 of 7004 in the warfarin group (2.2% per year) (HR=0.79; 95%CI 0.66, 0.96; $p<0.001$ for noninferiority). In the ITT analysis, the primary endpoint occurred in 269 of 7081 patients (2.1% per year) and in 306 of 7090 patients (2.4% per year) in the rivaroxaban and warfarin groups respectively (HR= 0.88; 95%CI 0.74, 1.03; $p<0.001$ for noninferiority; $p = 0.12$ for superiority).

No significant difference was found in the rates of major and non-major clinically relevant bleeding with rivaroxaban (14.9% per year) vs. warfarin (14.5% per year) (HR=1.03; 95%CI 0.96, 1.11; p=0.44). There were significant reductions in ICH (0.5% vs. 0.7%; $p =0.02$) and fatal bleeding (0.2% vs. 0.5%; $p = 0.003$) in the rivaroxaban group.

In the ITT analysis the risk of death from any cause in the rivaroxaban and warfarin groups were 4.5% and 4.9% per year respectively (HR=0.92; 95% CI 0.82, 1.03; p= 0.15) [386].

7.3.3 Comparison of the RE-LY and ROCKET AF Clinical Trials

A systematic literature search has not revealed any head-to-head studies which compare dabigatran etexilate and rivaroxaban for SPAF. The RE-LY and ROCKET AF trials however have a number of similar conclusions [385, 386]:

- When compared to warfarin, both rivaroxaban and dabigatran etexilate (110mg and 150mg) significantly reduce the risk of haemorrhagic stroke [385, 386]. Indeed, the reduction in the risk of the composite primary efficacy end-point in both studies was driven by the reduction in the risk of haemorrhagic stroke. Only dabigatran etexilate 150 mg also significantly reduced the risk of ischemic stroke, albeit to a lesser extent than the reduction in haemorrhagic stroke.

- As compared to warfarin, both doses of dabigatran etexilate and rivaroxaban significantly reduced the risk of ICH and were associated with a non-significant decrease in all cause mortality [385, 386].

Despite these similarities in conclusions, there are important differences in the design of the studies:

- Of those enrolled in ROCKET-AF, 90% had a $CHADS_2$ score of ≥ 3; the mean score was 3.5 [386]. RE-LY had a lower risk population, fewer than 50% had a $CHADS_2$ score of ≥ 3; the mean score was 2.1 [385].

- A double blind design was successfully achieved in ROCKET AF [386]. In RE-LY, assignments to dabigatran etexilate or warfarin were not blinded [385].

- The mean percentage of the study period during which the INR was within the therapeutic range (2-3) in the warfarin cohort was 64% in RE-LY [385] and 55% in ROCKET AF [386].

- Statistical analyses were handled differently in the studies. RE-LY used ITT for both noninferiority and superiority testing [385]; ROCKET AF used the per-protocol population for the first tests of noninferiority and superiority [386].

It is noted that (owing to the potential for confounding and bias in analyses based on selected follow-up times) the CONSORT statement favours the use of an ITT analysis when testing for superiority. The difference with regard to the number of primary events that were excluded in the per-protocol analysis, as compared with the ITT analysis, could indicate a nonrandom loss in the per-protocol analysis. It would therefore be safer to rely on the results of the ITT analysis in ROCKET AF [444].

- The US Food and Drug Administration (FDA) have identified a number of important issues affecting interpretation of the ROCKET AF results. They state that in noninferiority trials, the constancy assumption must be satisfied (i.e. the control treatment must have the same magnitude of benefit relative to placebo as it had in the reference trials used to estimate its effect). Concerns about nonconstancy in ROCKET-AF relate to [(a)] the high risk patients enrolled, [(b)] over 5% of patients discontinued due to withdrawal of consent, [(iii)] the INR was in the therapeutic range only 55% of the time in the warfarin group.

  The uncertainty about the validity of the constancy assumption raise concerns that rivaroxaban could be inferior to either dabigatran etexilate or warfarin, particularly when the latter is 'used skillfully' [445].

These differences in trial design highlight some of the challenges which would be encountered in performing an indirect comparison between dabigatran etexilate and rivaroxaban in the absence of head-to-head studies.

7.4 Current Licensing Status of Rivaroxaban and Dabigatran etexilate

Since 2008, dabigatran etexilate and rivaroxaban have been licensed in Ireland for the prevention of VTE after THR or TKR [73, 74]. In 2008, both drugs received a positive reimbursement status under the CD Schemes for this indication.

7.4.1 North America, Australia and Japan

Dabigatran etexilate: The FDA and Health Canada licensed dabigatran etexilate 150mg but not 110mg for the prevention of stroke and SE in adult patients with nonvalvular AF (and one or more stroke risk factors) in October and November 2010

respectively [153, 155]. The FDA made the decision to only approve the higher dose because they could not find any subgroup in which use of the lower dose would represent an advantage over warfarin [446]. It was also licensed in Japan and Australia for SPAF in the first quarter of 2011 [447, 448]. In a press release, issued on the 26th August 2011, Boehringer Ingelheim Ltd stated that over 350,000 patients were taking dabigatran etexilate for SPAF in the US, Canada and Japan within 10 months of its approval. It also stated that nine out of ten cardiologists (n=14,019) in the US had prescribed the drug [449].

Rivaroxaban: On the 13th September 2011, the FDA-Cardiovascular and Renal Drugs Advisory Committee recommended the approval of rivaroxaban for SPAF [450]. The FDA approved rivaroxaban for this indication on 04 November 2011 [451].

7.4.2 Europe

Dabigatran etexilate: On the 18th April 2011, the European Medicines Agency (EMA)'s Committee for Medicinal Products for Human Use (CHMP) recommended the approval for dabigatran etexilate for SPAF in adult patients with nonvalvular AF (and one or more stroke risk factors). The EC approved the extension of the EU label to include this indication on the 4th August 2011 [452]. On the 26th August 2011, the Irish Summary of Product Characteristics (SPC) was updated with the extension of the license to include this indication [74].

On the 5th August 2011, the Scottish Medicines Consortium (SMC) accepted dabigatran etexilate for SPAF according to the license, for use within the NHS-Scotland [453]. NICE released their Final Appraisal Determination, in October 2011, recommending the use of the drug for this indication [454]. The drug does not meet criteria for appraisal set by the All Wales Medicines Strategy (AWMSG) since NICE guidance is expected within 12 months of the projected receipt of the submission [455].

Rivaroxaban: The EMA-CHMP recommended the approval of rivaroxaban for SPAF on the 22nd September 2011; at the time of writing (December 2011), the EC decision is pending [456]. NICE guidance on rivaroxaban for SPAF is expected in May 2012 [457].

7.5 Economic Evaluation and Reimbursement Status in Ireland

The NCPE has assessed Boehringer Ingelheim Ltd.'s economic evaluation of dabigatran etexilate, compared to warfarin for SPAF. From the HSE's perspective, the ICERs are €6,311/QALY and €20,654/QALY for patients < 80 years and patients ≥ 80 years respectively. PSA indicates a probability of cost-effectiveness of 94% and 98%, at thresholds of €20,000/QALY and €30,000/QALY respectively, in patients < 80 years. For those patients ≥ 80 years, the respective probabilities are 52% and 63%. The NCPE estimate that the gross budget impact (includes the annual drug cost only) has the potential to exceed €17.1 million by 2015. The net impact (which also includes event costs, long term disability costs and INR monitoring costs) has the potential to exceed €6.9 million by 2015. The NCPE advised that dabigatran etexilate could be considered cost effective for this indication; however concern was raised regarding uncertainties associated with some of the clinical input data and the model assumptions. In addition the NCPE estimate the PEVPI to be about €13 million at a threshold of €20,000/QALY (assuming a 10 year decision time horizon). In view of this and the price/ICER relationship the NCPE recommend a reimbursement price significantly below €2.80 per day to ensure value for money for the HSE [458].

The HSE subsequently released their reimbursement decision on 23 November 2011. This HSE Statement advised GPs, pharmacists and other prescribing clinicians that no new patients should be prescribed dabigatran etexilate for SPAF under the CD Schemes. Only those patients who are already receiving the drug, under the Schemes, for this indication can continue to receive it and their pharmacists will be reimbursed [459]. It is unclear if the HSE are currently monitoring the prescribing of the drug to ensure that it is only being prescribed as decreed.

The NCPE will assess Bayer Ltd's economic evaluation on rivaroxaban for this indication in the near future.

7.6 The GMS Prescribing Database

The GMS is the largest of the CD Schemes. In 2010 the number of persons eligible was 1,615,809 (about 40% of the population) [6]. This study population may not be truly representative of the general population across the whole of Ireland, but the

HSE-PCRS GMS prescribing database captures more than 65% of all drugs prescribed at the primary care level [460].

The HSE-PCRS GMS database provides details on monthly dispensed medications for each individual within the scheme. The strength, quantity, method and unit of administration of each drug dispensed, ingredient costs, pharmacist dispensing fee and prescriber information are available. Gender, age group and health board region of each claimant is also recorded, but no diagnosis or outcomes are reported.

Within the database, the medicines are coded using the international WHO Anatomical Therapeutic Chemical (ATC) classification system. In the ATC classification system, the drugs are divided into different groups according to the organ or system on which they act and their chemical, pharmacological and therapeutic properties. Drugs are classified in groups at five different levels [461]. The complete classification of dabigatran etexilate illustrates the code structure:

B (1st level):	blood and blood forming
B01 (2nd level):	antithrombotic agents
B01A (3rd level):	antithrombotic agents
B01AE (4th level):	direct thrombin inhibitors
B01AE07 (5th level):	dabigatran etexilate

The monthly GMS database files are made available to the NCPE with a lag time of about three months.

7.7 Analysis of Primary Care Prescribing Trends of Dabigatran etexilate and Rivaroxaban in Ireland

Since 2008, dabigatran etexilate and rivaroxaban have been licensed and reimbursed, in Ireland, for the prevention of VTE after THR or TKR [73, 74]. Treatment with rivaroxaban should be continued for five weeks after THR and for two weeks after TKR [73]. Treatment with dabigatran etexilate should be continued for 28 to 35 days after THR and for ten days after TKR [74].

The study period for this analysis was January 2010 to June 2011 inclusive. At this time neither drug was licensed for SPAF; as such, the maximum licensed duration of treatment was 35 days. Likewise, the HSE had not reached a reimbursement decision regarding the use of either drug for SPAF (the HSE decision on dabigatran etexilate was reached subsequent to this study period, in November 2011).

Currently in Ireland, no formal system exists whereby reimbursement is halted if a drug is supplied for longer than an agreed duration. As such, it is possible that both drugs may have been supplied and reimbursed for longer than the maximum licensed duration.

7.7.1 Objective

The objective of this study was to analyse national and health-board primary care prescribing trends for dabigatran etexilate and rivaroxaban; to determine the number of patients who had been prescribed either drug, the volume of drug dispensed and the HSE expenditure.

A further aim was to review the duration of oral anticoagulant prescribed. A subsequent objective was to investigate the co-prescription of recommended AF rate/rhythm control agents [388] in patients who had received long courses of the oral anticoagulant. For the purposes of this analysis, such rate/rhythm control agents were considered a surrogate for AF.

7.7.2 Methods

A retrospective analysis (January 2010-June 2011 inclusive) of the HSE-PCRS-GMS pharmacy claims database of dispensed medications identified the study population.

All analyses were performed using SAS (v9.1, SAS Institute Inc. Cary, US) and Microsoft Excel 2010.

7.7.2.1 The National Rate of Prescribing of Rivaroxaban and Dabigatran etexilate on the GMS Scheme

The total number of GMS patients who had received at least one prescription for rivaroxaban (ATC code B01AX06) or dabigatran etexilate (ATC code B01AE07) throughout Ireland from January 2010 to June 2011 inclusive was determined. The age and gender of these patients were ascertained.

For the purposes of this analysis, the minimum age-group was assumed if more than one age-group had been recorded for a patient. The results were adjusted for the distribution of age groups within the GMS population.

7.7.2.2 Gross GMS Expenditure on Rivaroxaban and Dabigatran etexilate

The gross national and per-health board GMS expenditure on both dabigatran etexilate and rivaroxaban over the study period was established. Gross expenditure includes the net ingredient cost of the dispensed drug, the value added tax (VAT) and the pharmacist dispensing fee. (It should be noted here that, in Ireland, oral medications are not subject to VAT) [462].

7.7.2.3 Primary Care Prescribing Trends for Rivaroxaban and Dabigatran etexilate

The monthly number of GMS prescriptions for rivaroxaban or dabigatran etexilate dispensed throughout Ireland and in each health board (January 2010 to June 2011 inclusive) was established.

7.7.2.4 Duration of Therapy

The duration of therapy with either dabigatran etexilate or rivaroxaban during the study period (January 2010 to June 2011 inclusive) was analysed. The HSE-PCRS GMS database only contains information on strength and quantity of preparations dispensed and there is no information on dosage. The dose of dabigatran etexilate for the only licensed indication at the time of the study period (thromboprophylaxis after THR or TKR) is 220mg OD or 150mg OD. During the study period, the drug was available only as 110mg and 75mg hard capsules [74]. A 150mg hard capsule was introduced, after this time, in August 2011 [463]. The dose of rivaroxaban for this indication is 10mg OD; rivaroxaban is available as 10mg film coated tablets [73].

Thus, by analysing the total quantity of units dispensed during the study period, the duration of therapy was estimated. Two units of dabigatran etexilate and one unit of rivaroxaban was considered equivalent to a daily dose.

For the purposes of this analysis, it was considered pragmatic to direct further research towards those who had received treatment for longer than 90 days of treatment (at the VTE prophylaxis dose). This allowed for the situation where there had been inadvertent supply of more than 35 days (up to 90) of VTE prophylaxis due to the prescribing and dispensing of full packs, with subsequent wastage of the over-supply. Importantly, it also acknowledges the fact that the dose of rivaroxaban and dabigatran etexilate for SPAF is different from the dose used in VTE prophylaxis. The dose of dabigatran etexilate for SPAF is 150mg BD or 110mg BD [385]. The dose of rivaroxaban for SPAF is 20mg OD or 15mg OD [386].

7.7.2.5 Co-prescription of AF Rate/Rhythm Control Agents

Since the HSE PCRS GMS database is not linked to diagnosis no information on the actual indication for which the anticoagulant was prescribed was available. In this analysis the prescription of a rate/rhythm control agent was used as a surrogate for AF.

The cohort of patients who had received more than 90 days of oral anticoagulation was initially identified. Of this cohort, the number of patients who had been co-prescribed one of the following rate/rhythm control agents: a β-blocker (ATC code C07AB), a non-dihydropyridine calcium channel antagonist (ATC code C08D), digoxin (ATC code C01AA05) or amiodarone (ATC code C01BD01) was then established. Only patients who had received the oral anticoagulant and the rate/rhythm control agent at the same time (i.e. there was at least one month where both drugs had been co-supplied) were included in the analysis.

The odds ratio (OR) and 95%CI for the prescription of long term oral anticoagulant in patients on a rate/rhythm control agent compared to patients not on a rate/rhythm control agent can be calculated as [258]:

1. The OR of long term anticoagulation being prescribed in a patient on rate/rhythm control therapy vs. a patient not on rate/rhythm therapy is:

$$OR = (A/B) / (C/D)$$

Where: A=number of patients on oral anticoagulant and on rate-rhythm therapy
B=number of patients not on oral anticoagulant but on rate-rhythm therapy
C=number of patients on oral anticoagulant but not on rate-rhythm therapy
D=number of patients not on oral anticoagulant and not on rate-rhythm therapy

2. The 95%CI is then calculated as:

$$SE(\log_e OR) = \sqrt{(1/A + 1/B + 1/C + 1/D)}$$

Where: SE=standard error

3. So that a 95%CI for the log OR is obtained as:

$$\log_e OR - 1.96 \times SE(\log_e OR) \quad \text{to} \quad \log_e OR + 1.96 \times SE(\log_e OR)$$

7.7.3 Results

7.7.3.1 The National Rate of Prescribing of Rivaroxaban and Dabigatran etexilate on the GMS Scheme

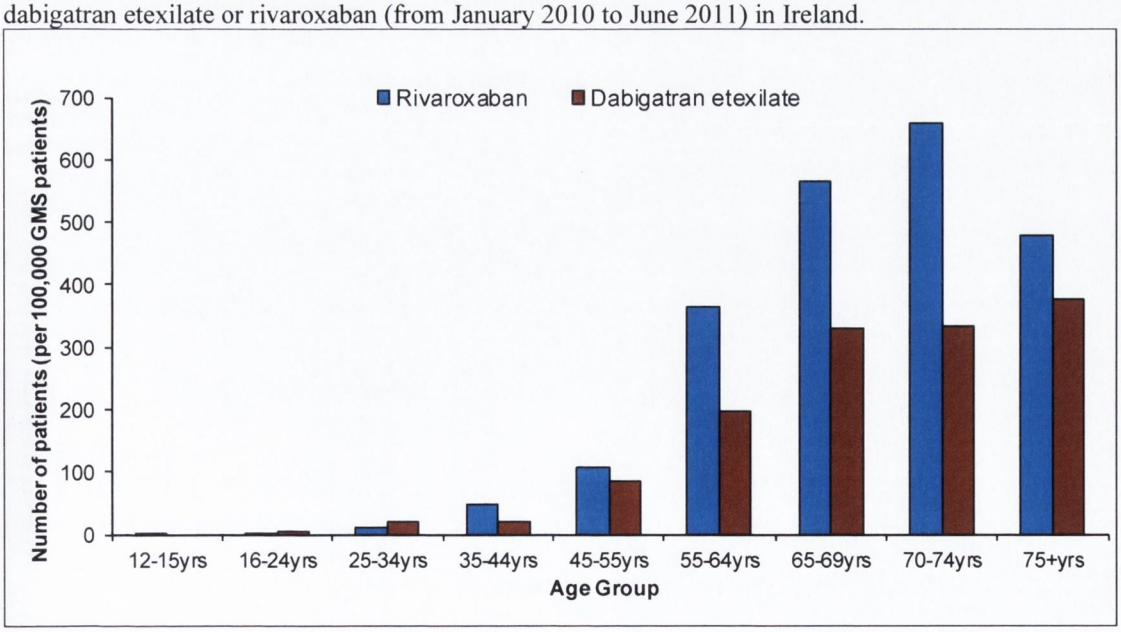
Rivaroxaban

From January 2010 to June 2011 inclusive, 3003 GMS patients (female 56%) in Ireland had received at least one prescription for rivaroxaban. The number of patients (per 100,000 GMS eligible patients), who received the drug, in each age-group, is shown in Figure 23; 51% were 70 years and over. Of note, one person in the 12-15 years age group had received the drug.

Dabigatran etexilate

Over the same period, 1929 GMS patients (female 51%) had received at least one prescription for dabigatran etexilate. The number of patients (per 100,000 GMS eligible patients), who received dabigatran etexilate, in each age-group is shown in Figure 23; 52% were 70 years and over.

Figure 23: The number of patients (per 100,000 eligible GMS patients) in each age-group who received dabigatran etexilate or rivaroxaban (from January 2010 to June 2011) in Ireland.



7.7.3.2 Gross GMS Expenditure on Rivaroxaban and Dabigatran etexilate

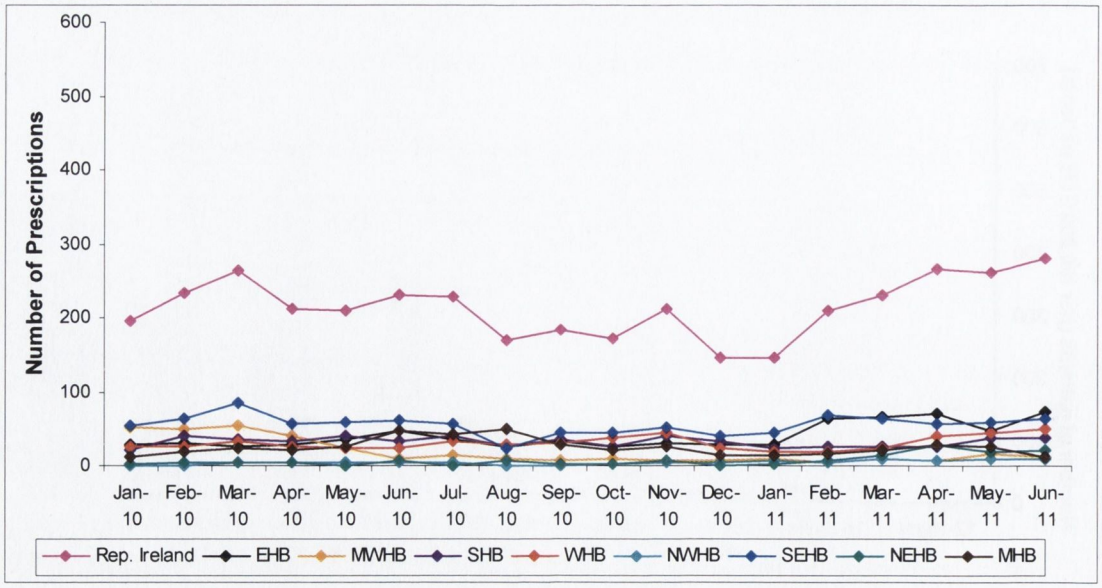
The gross national GMS expenditure on rivaroxaban from January 2010 to June 2011 inclusive was €575,348. Over the study period, the gross national GMS expenditure on dabigatran etexilate was €773,995.

7.7.3.3 Primary Care Prescribing Trends for Rivaroxaban and Dabigatran etexilate

Rivaroxaban

The total number of prescriptions dispensed over the study period was 3844. The disaggregated monthly analysis, shown in Figure 24, reveals that, although there was some degree of fluctuation, the number of prescriptions for rivaroxaban dispensed throughout Ireland every month did not increase substantially over the study period. Likewise, prescribing rates in each health board remained relatively constant throughout the study period; the largest number of prescriptions was dispensed in the SEHB.

Figure 24: The number prescriptions for rivaroxaban dispensed on the GMS scheme each month from January 2010 to June 2011.

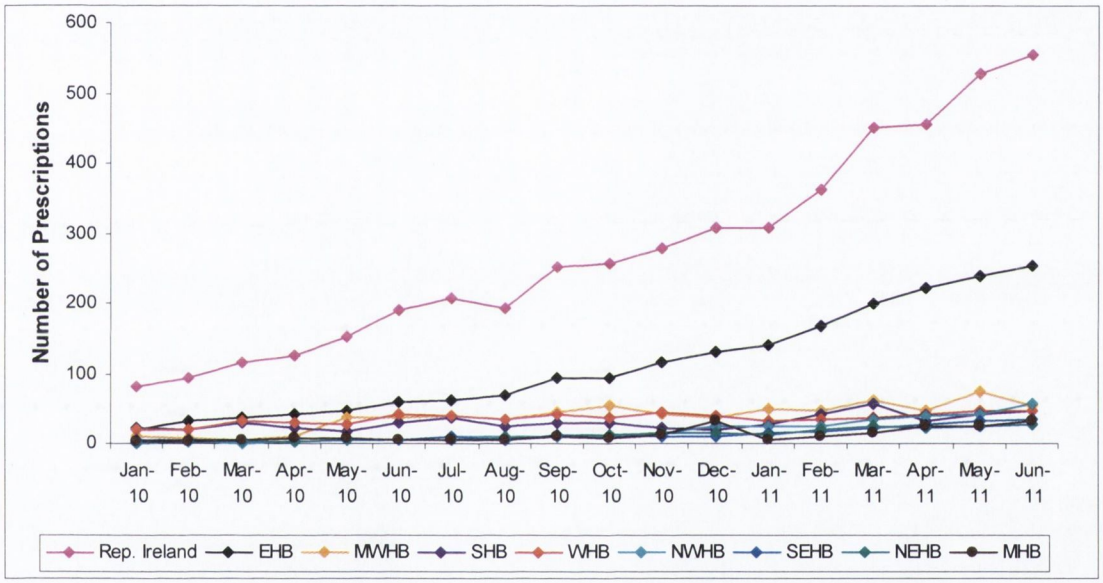


GMS=General Medical Services; **EHB**=Eastern health board; **MWHB**=Mid-western health board; **SHB**=Southern health board; **WHB**=Western health board; **NWHB**=North-western health board; **SEHB**=South-eastern health board; **NEHB**=North-eastern health board; **MHB**=Midlands health board.

Dabigatran etexilate

The total number of prescriptions dispensed was 4920. The monthly analysis, shown in Figure 25, illustrates that the number of prescriptions for dabigatran etexilate dispensed throughout Ireland increased steadily from 82 in January 2010 to 555 in June 2011 (6.8 fold increase). Prescribing patterns in the eight health boards indicate that the increasing monthly volume of prescriptions seen in Ireland was driven by the EHB.

Figure 25: The number of prescriptions for dabigatran etexilate dispensed on the GMS scheme each month from January 2010 to June 2011.



GMS=General Medical Services; **EHB**=Eastern health board; **MWHB**=Mid-western health board; **SHB**=Southern health board; **WHB**=Western health board; **NWHB**=North-western health board; **SEHB**=South-eastern health board; **NEHB**=North-eastern health board; **MHB**=Midlands health board.

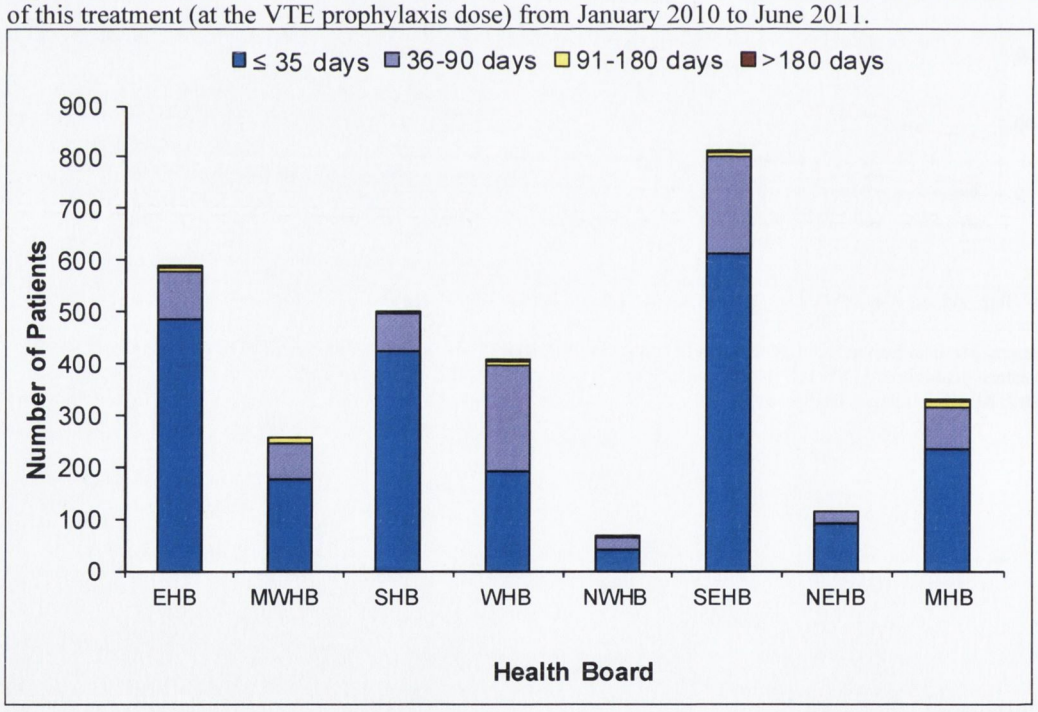
7.7.3.4 Duration of Therapy

The duration in therapy here is described in terms of the number of days of oral anticoagulant (at the VTE prophylaxis dose) received.

Rivaroxaban

Nationally, 73% of the patients who had received rivaroxaban had received 35 days or less of treatment (the maximum licensed duration), 25% had received between 36 and 90 days, 1.5% had 91 to 180 days and 0.5% received more than 180 days of treatment. Figure 26 indicates that the drug was prescribed for longer than the maximum licensed duration (of 35 days) across all health boards. The percentage of patients, who received more than 35 days ranged from 15% of the Southern- to 53% of the Western-health board.

Figure 26: The number of patients who received rivaroxaban in each HSE health board and the duration of this treatment (at the VTE prophylaxis dose) from January 2010 to June 2011.

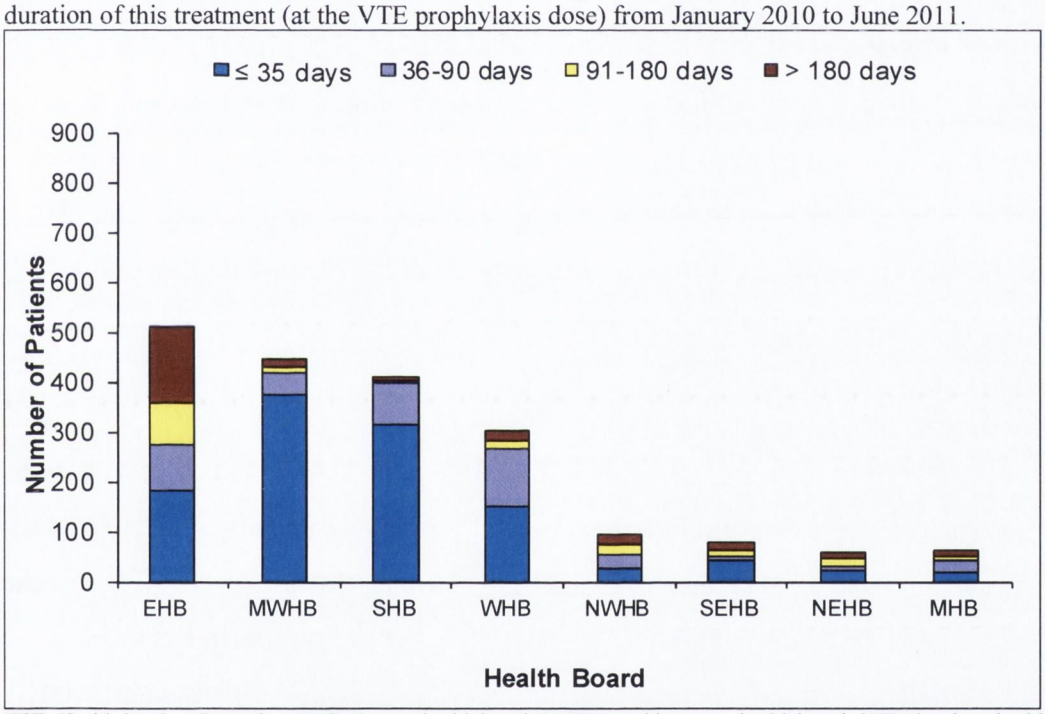


HSE=Health Services Executive; **EHB**=Eastern health board; **MWHB**=Mid-western health board; **SHB**=Southern health board; **WHB**=Western health board; **NWHB**=North-western health board; **SEHB**=South-eastern health board; **NEHB**=North-eastern health board; **MHB**=Midlands health board.

Dabigatran etexilate

Nationally, 58% of the patients who had received dabigatran etexilate had received 35 days or less of treatment, 21% had received between 36 and 90 days, 8% had 91 to180 days and 13% had received more than 180 days. Figure 27 shows that the drug was prescribed for longer than the maximum licensed duration in all health boards. The percentage of patients who received more than 35 days ranged from 16% of the Mid-Western to 70.5% of the North-Western health board. A number of patients in all health boards had received the drug for more than 180 days.

Figure 27: The number of patients who received dabigatran etexilate in each HSE health board and the duration of this treatment (at the VTE prophylaxis dose) from January 2010 to June 2011.



HSE=Health Services Executive; **EHB**=Eastern health board; **MWHB**=Mid-western health board; **SHB**=Southern health board; **WHB**=Western health board; **NWHB**=North-western health board; **SEHB**=South-eastern health board; **NEHB**=North-eastern health board; **MHB**=Midlands health board.

It is further noted that 76% of patients in the EHB cohort who had received more than 90 days of dabigatran etexilate were still receiving this drug in June 2011.

7.7.3.5 Co-prescription of AF Rate/Rhythm Control Agents

The EHB dabigatran etexilate cohort was chosen for further analysis because of the relatively high number of patients who had received long-term dabigatran etexilate.

A total of 540,221 GMS patients were identified in the EHB cohort. Of these, 14,496 patients had received at least one prescription for a rate/rhythm control agent. A total of 510 patients had received at least one prescription for dabigatran etexilate; of these 329 patients (64.5%) had received it for longer than the maximum licensed duration of 35 days (at the VTE prophylaxis dose).

In total, 76 (32.5%) of the 234 patients who had received more than 90 days of dabigatran etexilate had concurrently received rate/rhythm control therapy. Patients on rate/rhythm control therapy were significantly more likely to receive more than 90 days of dabigatran etexilate compared to patients not receiving rate/rhythm control therapy (OR= 17.9; 95%CI 13.6, 23.5).

Likewise, 47 (31%) of the 152 patients who had received more than 180 days of dabigatran etexilate had been co-prescribed rate/rhythm control therapy. Patients on rate/rhythm control therapy were significantly more likely to receive more than 180 days of dabigatran etexilate compared to patients not receiving rate/rhythm control therapy (OR= 16.3; 95%CI 11.5, 23.0).

7.7.4 Discussion

The prevalence of AF in Ireland in 2011 has been estimated to be about 3.2% [400]. In an Irish cohort study, AF was associated with 31.2% of new stroke events [408]. Stroke represents a large financial burden for the Irish HSE [193, 376]. Warfarin has a protective effect against stroke in patients with AF [402, 423, 424, 432]. It has significant drug, food and alcohol interactions and requires intensive INR monitoring [388]. The management of patients receiving warfarin for SPAF places a large financial burden on services within the Irish health service [373, 440]. Dabigatran etexilate and rivaroxaban do not require anticoagulation monitoring and have fewer drug and food interactions than warfarin [73, 74].

During the study period (January 2010 to June 2011 inclusive), rivaroxaban and dabigatran etexilate were only licensed in Ireland for VTE prophylaxis after THR or TKR (maximum treatment duration of 35 days). Both drugs had received a positive

decision regarding their CD Scheme reimbursement status for this indication only. Neither drug was licensed or approved for reimbursement for SPAF, in Ireland.

This is the first analysis of the primary care prescribing patterns of rivaroxaban or dabigatran etexilate in Ireland.

From January 2010 to June 2011, 3003 GMS patients had received at least one prescription for rivaroxaban; 1929 had received at least one prescription for dabigatran etexilate. Thus, less patients nationally had received dabigatran etexilate, however the national gross GMS expenditure on dabigatran etexilate (€773,995) was higher than that on rivaroxaban (€575,348) (despite comparable drug cost [305]). This suggests that more patients on dabigatran etexilate had received treatment of longer duration.

Figure 24 highlights that the monthly number of prescriptions for rivaroxaban has remained reasonably stable over the study period. Figure 25 indicates that the progressive increase in the month-on-month prescriptions for dabigatran etexilate is driven by the EHB. The larger national number of prescriptions for dabigatran etexilate over the study period, despite less patients receiving dabigatran etexilate again suggests longer treatment durations being prescribed with this drug.

Further investigations were thus directed towards the duration of treatment. Figure 26 and Figure 27 indicate that there were a considerable number of patients who received anticoagulation for longer than 35 days across all health boards. In this study, it was considered pragmatic to direct further research towards those who had received treatment for longer than 90 days. Nationally, 2% and 21% of those who had been prescribed rivaroxaban and dabigatran etexilate respectively had received treatment for longer than 90 days. Figure 27 indicates that, although dabigatran etexilate had been prescribed for more than 90 days in all health boards, the EHB cohort had the largest number of such patients (n= 234).

The EHB cohort was thus chosen for further analysis. For the purposes of this analysis, rate/rhythm control agents were considered to be a surrogate for AF. In the EHB, patients on rate/rhythm control therapy were significantly more likely to receive

more than 90 days of dabigatran etexilate compared to patients not receiving rate/rhythm control therapy (OR= 17.9; 95%CI 13.6, 23.5). Likewise, patients on rate/rhythm control therapy were significantly more likely to receive more than 180 days of dabigatran etexilate compared to patients not receiving rate/rhythm control therapy (OR= 16.3; 95%CI 11.5, 23.0).

There is no antidote to the anticoagulant effect of either dabigatran etexilate [74] or rivaroxaban [73]. It is a concern that this analysis has revealed that over 50% of all prescriptions for dabigatran etexilate and rivaroxaban were dispensed to patients 70 years and over. It has been recognised that elderly patients are at a higher risk of bleeding secondary to anticoagulant therapy [464]. On October 2011, Boehringer Ingelheim Ltd. issued new recommendations following an evaluation of reports of cases of fatal bleeding in Japan (some cases had occurred in elderly patients with severe renal impairment, which constitutes a contraindication for the drug). Renal function should now be assessed in all patients prior to initiating dabigatran etexilate. While on treatment, renal function should be assessed if a decline in function is suspected. Also renal function should now be assessed at least once a year in those over 75 years or in those with renal impairment [465]. On 12 November 2011, it was announced that dabigatran etexilate had been linked to about 260 deaths from bleeding across the world. Boehringer Ingelheim Ltd stress that the risk of death from these figures is still below the rate seen in RE-LY [466].

This analysis has revealed that rivaroxaban has been prescribed in one patient in the 12-15 years age-group. The safety and efficacy of rivaroxaban in those less than 18 years have not been established; as such it is not recommended for use in this group [73].

This study suggests that national use of rivaroxaban may be more reflective of the licensed indication for this drug and that dabigatran etexilate has been more commonly prescribed for indications outside its license. It is possible that such indications might include VTE treatment [467], acute coronary syndrome [468] and SPAF. Analysis of co-prescription of rate/rhythm control agents (considered to be a surrogate for AF) within the EHB cohort suggests that, contrary to its license and reimbursement status, dabigatran etexilate may have been prescribed for SPAF in

some. This might reflect the dates of publication of RE-LY and ROCKET AF. RE-LY was published in 2009 [385], whilst ROCKET AF was published in September 2011 [386] (i.e. subsequent to the analysis period here (January 2010 to June 2011 inclusive)).

There are safety implications associated with the prescribing of drugs outside their license. In contrast to the short course of anticoagulant required for the primary prevention of VTE events secondary to THR and TKR, SPAF requires chronic therapy [388]. The median follow-up duration in ROCKET AF was 707 days [386], in RE-LY it was 2.0 years [385]. Those patients receiving dabigatran etexilate in RE-LY however, were permitted to continue receiving it after trial completion as part of the on-going rollover study, RELY-ABLE [469]. As such the long term safety of these new oral anticoagulants is, as yet, unclear. On the contrary, after nearly six decades in clinical practice, much is known about long term treatment with warfarin [470].

Pertinent long term safety issues include the non-significantly increased risk of MI with dabigatran etexilate compared to warfarin seen in RE-LY [385, 442]. In RE-LY, MI occurred in 75 patients on warfarin (0.64% per year), 98 patients on dabigatran etexilate 110mg (0.82% per year) and 97 patients on the 150mg dose (0.81% per year) [442]. The mechanism of increased MI is unclear [385]. It has been postulated that it might be due to a superior effect of warfarin in MI prevention [471, 472].

There are financial implications associated with prescribing drugs for purposes for which the cost-effectiveness from the HSE perspective has not yet been established. These implications are particularly important given the current economic climate. It is noted here that at the time of this analysis no formal system existed within the HSE-PCRS to monitor the prescribing of medicines and to limit their reimbursement, the extended durations of oral anticoagulants seen here will therefore have been fully reimbursed.

In August 2011, subsequent to the study period in this analysis, the NCPE assessed Boehringer Ingelheim Ltd's economic evaluation of dabigatran etexilate for SPAF from the HSE's perspective. The basecase and sensitivity analyses indicate that the drug can be considered to be cost-effective. However, the budget impact and

population EVPI estimates are high [458]. At the time of writing (December 2011), the HSE had confirmed that only those patients already receiving dabigatran etexilate for SPAF will be permitted to receive the drug under the CD Schemes. No new patients should be prescribed dabigatran etexilate for SPAF under the Schemes [459]. At this time, the HSE has not confirmed a reimbursement decision regarding the use of rivaroxaban for this indication.

Pink *et al* (2011) [473] used a DES model (for a cohort of 50,000 simulated patients with a mean baseline $CHADS_2$ score of 2.1) to extrapolate the findings of RE-LY to a lifetime horizon. From the UK NHS perspective, when compared with warfarin, 110mg and 150 mg BD dabigatran etexilate were associated with positive incremental net health benefits of 0.094 (95% central range -0.083 to 0.267) and 0.146 (-0.029 to 0.322) QALYs respectively. In the economic analysis, the 150mg dose dominated the 110mg dose, had an ICER of £23,082 (€26,700) per QALY gained versus warfarin, and was more cost-effective in patients with a baseline $CHADS_2$ score of 3 or above. In centres that achieved good control of INR (TTR $\geq$ 65.5%), dabigatran 150 mg was not cost-effective (£42 386 (€49,030) per QALY). No subgroup for which dabigatran 110 mg offered any clinical or economic advantage over 150 mg was identified.

There are a number of limitations to this study.

This study demonstrates that the HSE PCRS GMS database is a valuable tool for evaluating the prescribing of reimbursable medicines on the GMS scheme in Ireland. However, since the database is not linked to diagnosis, no information on the actual indication for which the anticoagulants were prescribed was available. The possible indications can only be speculated. Also, in using rate/rhythm control agents as a surrogate for AF, patients with AF not receiving such therapy will have been missed. Likewise, these drugs may have been prescribed for alternative indications.

It is likely that estimates of the percentage of patients who received long term anticoagulant treatment are conservative; those individuals who continued on treatment beyond June 2011 will not have been captured. Indeed, analysis here revealed that 76% of patients in the EHB cohort who had received more than 90 days of dabigatran etexilate were still receiving this drug in June 2011.

It is noted that about 40% of the Irish population are eligible for the GMS Scheme [9]. This study population may not be truly representative of the general population across the whole of Ireland. However the HSE-PCRS GMS prescribing database captures more than 65% of all drugs prescribed at the primary care level [460].

7.7.5 Conclusions

During the study period (January 2010 to June 2011 inclusive), rivaroxaban and dabigatran etexilate were only licensed in Ireland for VTE prophylaxis after THR or TKR. Over this time period, there has been a steady increase in the uptake of dabigatran etexilate on the GMS scheme. Such an increase in uptake has not been seen with rivaroxaban. Both drugs have frequently been prescribed for longer than the maximum licensed duration of 35 days. It is evident that, in particular, dabigatran etexilate has routinely been prescribed for long durations. Analysis of co-prescription of rate/rhythm control agents within the EHB cohort suggests that, contrary to its license and reimbursement status, dabigatran etexilate may have been prescribed for SPAF in some.

There are efficacy and safety concerns surrounding the use of drugs for unlicensed indications. There are budget impact concerns surrounding the use of drugs for indications which do not have a positive HSE-PCRS reimbursement status. Given the current economic climate, it would appear appropriate that medicines are only reimbursed for those indications which have received such a positive status.

This study demonstrates the GMS database as a useful tool for evaluating the prescribing of reimbursable medicines on the GMS scheme in Ireland. This information could be more widely used in planning, monitoring and assessing the effectiveness of drug licensing and reimbursement decisions in the future.
The database analytical skills that I have developed in the course of this study will be useful in the future. It is envisaged that these skills will be used in conjunction to those skills gained in the area of economic analyses when performing HTAs in other therapeutic areas.

Chapter 8

Recommendations Arising from the Work in this Thesis

8 Recommendations Arising from the Work in this Thesis

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

8.1 Development of Irish Data Sources

All evaluations require comprehensive, accurate data sources. The probability, cost and preference parameters input into the economic evaluations, in this thesis, were derived, in the main, from systematic literature searches. These searches highlighted a lack of good quality Irish epidemiological, cost and preference data. As such, values from disparate sources from a range of jurisdictions have been used in the economic evaluations. It is recommended that Irish epidemiological, cost and preference data be developed further.

VOI analysis on the economic models indicated that the majority of the decision uncertainty associated with choice of thromboprophylaxis after THR and TKR was associated with the direct medical costs. A pragmatic starting point would thus be the further development of national cost databases and Irish costing studies.

It is equally noted that VOI on other economic models might indicate that further research should be directed towards other model parameter subgroups. In this thesis, preference weights for the general population were taken from a less than ideal source (self reported time-trade-off QoL values in a US adult population). It would seem appropriate that, in the first instance, the development of a database containing Irish-specific preference weights for the general population would be also be a sensible endeavour.

The development of such national databases would represent obvious challenges. Database Governance is the set of policies, procedures and practices which ensure that the database provides the user with convenient access to up-to-date accurate information, is easy to manage, is security protected and contains a minimum amount of redundant data [474, 475]. Issues of who should fund and who should coordinate the

database would need to be resolved. The requirements of all stakeholders should be considered.

8.2 Handling Uncertainty in Economic Models

The 'Guidelines for the Economic Evaluation of Health Technologies in Ireland' state that the results of the PSA should be presented as a scatter plot and a CEAC. The Guidelines make no mention of the CEAF and EVPI analysis.

The CEAC can represent decision uncertainty, but should not be used to determine the optimal decision. Instead, the CEAF shows the decision uncertainty surrounding the optimal strategy. It has been argued that the CEAF presents uncertainty in a format that is more relevant to decision making [56]. This thesis has demonstrated the usefulness of the CEAF as a decision making tool. It is recommended that the CEAF therefore been integrated into the HSE decision making process; the 'Guidelines for the Economic Evaluation of Health Technologies in Ireland' should be amended accordingly.

The CEAF can be augmented by VOI analysis to show the potential gains to further research. Indeed the results of the VOI analysis undertaken in this thesis have been discussed with the decision maker and the NCPE now routinely perform EVPI analysis on company model based submissions. Currently in Ireland, there is no formal framework in place whereby the reimbursement authority has the power to reverse a decision. As it stands therefore, VOI analysis could not easily be used to reverse a positive reimbursement decision should further research indicate that the product is not cost-effective. It could be used however, in the issuing of a positive or negative reimbursement decision or in a delay in this decision being made.

As has been illustrated in this thesis, population-EVPI estimates are dependent on estimates of the size of the population (as illustrated in Table 34), the time horizon for the decision problem (as illustrated in Figure 19) and the discount rate. In order to fully integrate VOI analysis into the decision making process, the 'Guidelines for the Economic Evaluation of Health Technologies in Ireland'should discuss the handling of these parameters in order to standardise VOI calculations.

8.3 Evaluation of the Prescribing of Reimbursable Medicines

Work within this thesis has demonstrated that the GMS database is a useful tool for evaluating the prescribing of reimbursable medicines. This study has suggested that both rivaroxaban and (in particular) dabigatran etexilate, have routinely been prescribed for durations outside their license and reimbursement status. Since no formal system exists within the HSE-PCRS to monitor the prescribing of medicines and to limit their reimbursement, these extended treatment durations will have been fully reimbursed. The associated financial implications are particularly important given the current economic climate. It is thus recommended that a formal system is set in place whereby the prescribing and reimbursement of medicines within the CD Schemes are routinely monitored.

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List of Publications

Peer Reviewed Publications

1. **A cost-effectiveness model comparing rivaroxaban and dabigatran etexilate with enoxaparin sodium as thromboprophylaxis after total hip and total knee replacement in the Irish healthcare setting**
   McCullagh L, Tilson L, Walsh C, Barry M.
   Pharmacoeconomics 2009; 27(10): 829-846

2. **The author's reply**
   McCullagh L, Tilson L. Walsh C, Barry M
   Pharmacoeconomics 2010; 28(9): 784-785

3. **Value of Information analysis to reduce decision uncertainty associated with the choice of thromboprophylaxis after total hip replacement in the Irish healthcare setting**
   McCullagh L, Walsh C, Barry M.
   Pharmacoeconomics *in press*

4. **Prescribing trends for dabigatran etexilate in primary care in Ireland**
   McCullagh L, Barry M.
   Irish Medical Journal *in press May 2012*

Conference Proceedings-Poster Presentations

5. **Cost-effectiveness of rivaroxaban and dabigatran etexilate for the prophylaxis of venous thromboembolism and associated long term complications after total hip replacement in Ireland**
   McCullagh L, Tilson L, Walsh C, Barry M
   ISPOR. 12th Annual European Congress, 24-27 October 2009, Paris, France.

   Also presented at the 4th School of Medicine Postgraduate Research Day, 19 September 2011, Trinity College Dublin.

6. **An application of Value of Information analysis to decrease uncertainty**
   McCullagh L, Walsh C, Barry M
   HTAi. 7th Annual Meeting, 6–9th June 2010, Dublin, Ireland.

7. **Prioritising further research using the expected value of perfect information: Application to venous thromboembolism prophylaxis after total hip replacement**

   McCullagh L, Walsh C, Barry M

   ISPOR. 13th Annual European Congress 7-10 November 2010. Prague, Czech Republic.

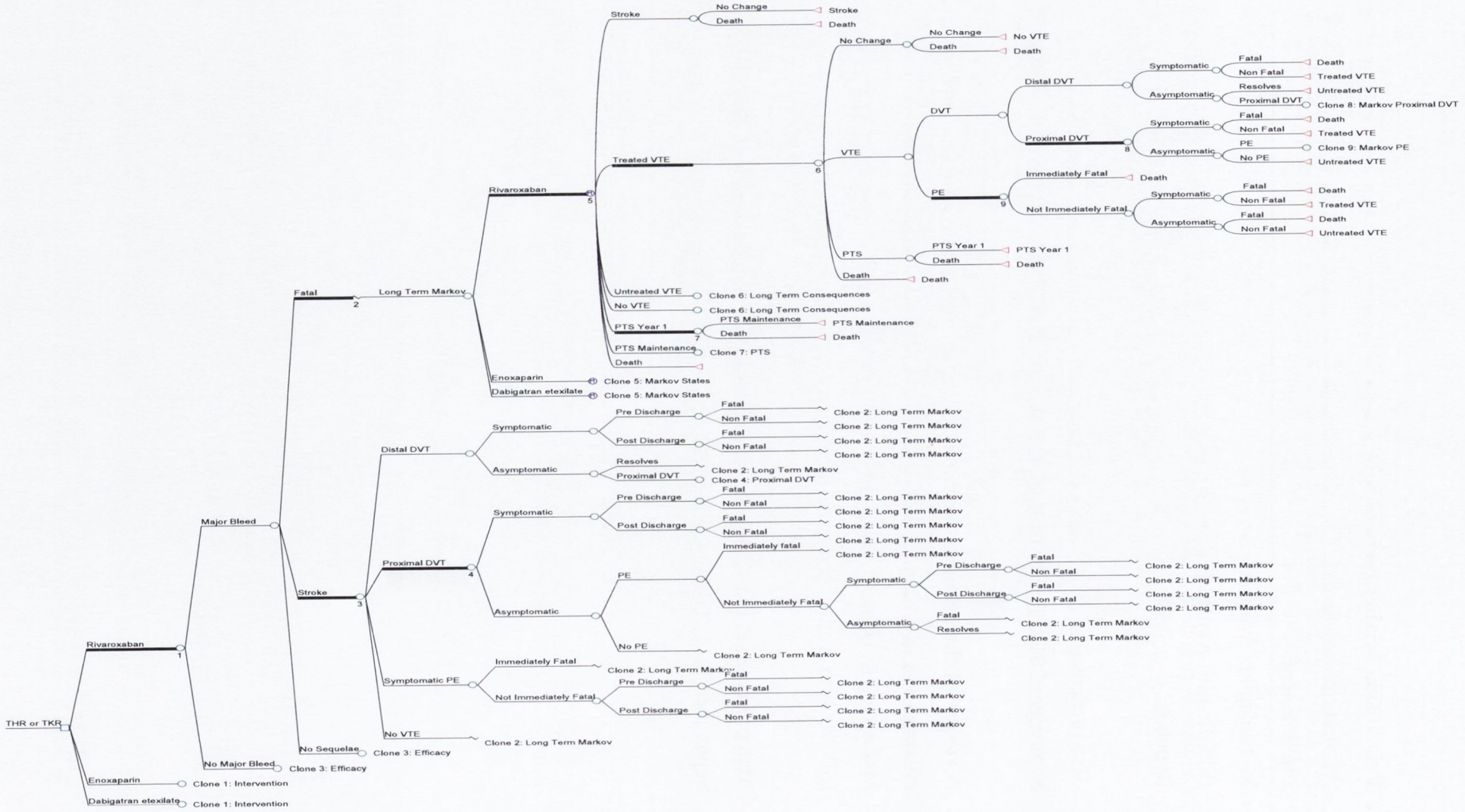
   Also presented at the 4th School of Medicine Postgraduate Research Day, 19 September 2011, Trinity College Dublin.

8. **A review of the primary care prescribing of dabigatran etexilate and rivaroxaban in Ireland**

   McCullagh L, Usher C, Barry M

   ISPOR. 14th Annual European Congress, 5-8 November 2011, Madrid, Spain.

   Also presented at the 4th School of Medicine Postgraduate Research Day, 19 September 2011, Trinity College Dublin.



Appendix 1: Lifetime Thromboprophylaxis Model. **THR**=total hip replacement; **TKR**=total knee replacement; **DVT**=deep vein thrombosis; **PE**=pulmonary embolism; **PTS**=post thrombotic syndrome

Appendix 2: The full WinBUGS code for Mixed Treatment Comparison (Section 5.5)

```
model{
for(i in 1:ns){
        delta[i,bi[i]] <- 0
        mu[i] ~ dnorm(0,0.0001)
                for (k in 1:na[i]){
                        r[i,k] ~ dbin(p[i,t[i,k]],n[i,k])
                        log(p[i,t[i,k]]) <- mu[i] + min(delta[i,t[i,k]],-mu[i]/1.00000001)
                        }
                for (k in 2:na[i]){
                        delta[i,si[i,k]] <- d[si[i,k]] - d[bi[i]]
                        }
        }
d[1]<-0
for (k in 2:nt){d[k] ~ dnorm(0,0.0001) }
## Indirect Comparisons ##
for (c in 1:nt){
        for (k in 1:nt){
                lrr[c,k] <- d[c] - d[k]}}
}
```

Input Data for Distal DVT*

```
list(
r= structure(.Data= c(22, 11, 27, 9, 24, 22, 1, 10), .Dim=c(4, 2)), ## Number of PEs per arm
n= structure(.Data= c(1558, 1595, 869, 864, 894, 874, 90, 89), .Dim=c(4, 2)), ## Number of patients per arm
t= structure(.Data= c(1, 3, 2, 3, 1, 4, 1, 2), .Dim=c(4, 2)), ## Treatment (1=Enoxaparin Long, 2=Enoxaparin
Short, 3=Rivaroxaban, 4=Dabigatran)
na=c(2, 2, 2, 2), ## Number of arms per trial
nt=4, ## Number of Treatments
ns=4, ## Number of Studies
bi=c(1, 2, 1, 1), ## Baseline treatment in each study
si= structure(.Data= c(NA, 3, NA, 3,NA, 4, NA, 2), .Dim=c(4, 2)) ## Treatment non-baseline
)
```

*r and n inputs change for proximal DVT and symptomatic PE.